ISSN: 1987-6521; E-ISSN:2346-7541, DOI:10.36962/GBSSJAR
JANUARY-MARCH 2020 VOLUME 52 ISSUE 01

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ISSN: 1987-6521; E-ISSN:2346-7541, DOI:10.36962/GBSSJAR
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Index Copernicus Value (ICV) for 2018 – 76.92
IPI Value: 2.42
IARC Impact Factor 2017 – 2.110
Catalogue of Russian Journals Impact Factor (2016) – 0.171
Impact factor РИНЦ 2017-0.041

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SCIENTIFIC JOURNAL OF ACADEMIC RESEARCH

ISSN: 1987 - 6521, E – ISSN: 2346 – 7541; DOI PREFIX: 10.36962
BLACK SEA SCIENTIFIC JOURNAL OF ACADEMIC RESEARCH
MULTIDISCIPLINARY JOURNAL

EDITORIAL BOARD LIST SEE PAGE 44

ISSN: 1987-6521; E-ISSN: 2346 – 7541; UDC: 551.46 (051.4) / B-64

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ISSN: 1987 - 6521, E – ISSN: 2346 – 7541
JANUARY-MARCH 2020 VOLUME 52 ISSUE 01
THE BALTIC SCIENTIFIC JOURNALS
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CELL CLASSES AND TYPES WHICH ARE ESSENTIAL DURING SKIN REGENERATION

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ABSTRACT

The Skin has the natural ability to heal and replace damaged and dead cells regulated by a network of complex immune processes. This ability is conferred by the population of resident immune cells that act in coordination with other players to provide a homeostatic environment under constant challenge. In this article we conclude that near future discoveries using such innovative strategies will not only help us achieve better therapeutic products for skin-related immune disorders but will also foster ideas toward novel cosmetic formulations and topical applications for improving skin's regenerative potential.
Keywords: damaged and dead cells, resident immune cells, therapeutic products.

The stem cells are involved in the renewal and regeneration of the epithelium of various organs. The largest reservoir of epithelial stem cells in the human body is the skin. This organ is a specialized interior barrier protecting the body from the influence of physical, chemical, environmental and biological factors[1], ensuring at the same time the reception of signals from the external environment. Skin is also involved in numerous physiological processes which determine the homeostasis of the body.

Renewal and regeneration of the epidermis which is the outer layer of the skin, is possible by the presence of different populations of stem cells that reside in microenvironments (niches),that creates specific conditions to preserve the biological properties of these cells. Because divisions of cells in niches are quite rare, it became possible to distinguish them from other rapidly proliferating cells of the skin. On this basis, the stem cells in the interfollicular epidermis, bulge region of the hair follicles, and within the sebaceous glands were located.

Tissues have a natural capacity to replace dying cells and to heal wounds. This ability resides in resident stem cells, which self-renew, preserve, and repair their tissue during homeostasis and following injury. The skin epidermis and its appendages are subjected to daily assaults from the external environment [2.3]. A high demand is placed on renewal and regeneration of the skin's barrier in order to protect the body from infection and dehydration and to heal wounds. This review focuses on the epithelial stem cells of skin, where they come from, where they reside, and how they function in normal homeostasis and wound repair.

Moreover hair follicles are suggested to be a niche for melanocyte progenitor cells and other multipotent stem cells derived from the neural crest, as well as mesenchymal stem cells. The presence of stem cells that are characterized by high proliferative potential and the ability to self-renew allow maintaing homeostasis and regeneration of epidermis. Identification [4], isolation and characterization of epithelial stem cells is necessary to understand skin diseases background, develop effective methods for their treatment and for wider use of stem cells in regenerative medicine, gene therapy or cosmetology.

The stem cells variations and types represent a novel hope for regenerative medicine. In adult life, stem cell deposits are kept in organ niches; the need for tissue or organ regeneration mobilizes stem cells via the SDF-1-CXCR4 regulation axis. Constant regeneration of the skin is achieved due to stem cell differentiation within the epidermis and the hair follicle; thus, skin may serve as an excellent source of stem cells. This is of paramount importance in the treatment of chronic skin wounds and burns

The enormous interest in the biology of stem cells (SC) is related to their capacity for self-renewal, replication and differentiation to other cells that build different tissues and organs. SCs replenish lost cells throughout an organism's lifespan. SCs have the capacity for unlimited replication that gives a population of 'sister' SCs. These cells are responsible for self-renewal and differentiate into tissue-specific cells[5].

This process maintains the constant number of aging somatic cells, which become apoptotic. In the future, SCs could be used in the treatment and regeneration of organs and tissues. The implantation of SCs could be applied instead of the transplantation of tissue and organs [6.7]. This would be a huge step in regenerative medicine.

There are several types of SCs, which differ one from another in their proliferation and differentiation capacity. The less mature SCs have greater possibilities of differentiation and replication. Previous research suggested that tissue-committed stem cells (TCSCs) showed plasticity i.e. the possibility of these cells transdifferentiating into other TCSCs under the control of environmental factors. For example, hematopoietic stem cells (HSCs) could differentiate into heart stem cells,

hepatic stem cells or pancreas stem cells. The new hypothesis on this subject is that stem cell niches are not only colonized by TCSCs but also contain pluripotent stem cells (PSCs)[8.9], which can differentiate into specific tissue. PSCs express embryonic markers such as Oct4, Nanong and Rex-1 and give rise to SCs specific for various tissues and organs; some of them are deposited during embryogenesis in organs and can survive in these localizations to adulthood. Kucia and Ratajczak confirmed that bone marrow (BM) and other tissue of adults is equipped with PSCs — the very small embryonic-like stem cells (VSELs). The morphology of these cells and their immunohistochemical features are similar to those of early embryonic SCs. They were initially isolated from murine BM as a homogenic lineage Sca-1+lin- -CD45– which demonstrates coexpression of PSCs markers such as SSEA-1, Oct-4, Nanog and Rex-1.

Direct electron microscopy showed cells with a large nucleus with euchromatin and narrow cytoplasm. The cells are isolated from human BM, circulating blood and umbilical cord blood as CD34+CD133+CXCR4+lin-CD45– , small size cells (7 μm in diameter) [19–21]. In vitro, they differentiate into all three germ layers [16]. These cells are enriched for mRNA for skin epidermis like Trp63, Krt2-5, BNC. During ontogenesis, VSELs are deposited in BM and in other organs (tissues) and are mobilized in cases of organ and tissue damage for their regeneration. Their number is higher in young individuals and decreases with age. The stem cells migration, which is the key process in their development and regeneration, is regulated by the axis CXCR4-SDF-1. CXCR4 receptor has been described in many types of tissue-specific SCs including nervous tissue, skeletal muscles, heart, liver, endothelium, tubules of nephron, pigment cells of retina and embryonic PSC. SCs follow the SDF-1 gradient. The SDF-1 is expressed in stromal, endothelial, cardiac, skeletal muscle, liver, brain and renal cells. Recently, the alternative receptor for SDF-1, CXCR7, was described.

The damage of tissue increases expression of SDF-1 that attracts CXCR4+ SCs, which are necessary for organ reparation. The expression of SDF-1 can be up-regulated by HIF-1a and down-regulated by steroids, granulocytes colony stimulating factor (G-CSF) and transforming growth factor (TGF-b1) [10]. Investigators have found SCs in the niches of the epidermis. PSCs as Oct4+ embryonic cells or as non-epidermal non-melanocyte Oct4+Nanog+ cells have been identified in the same niche. The association of these cells with VSELs requires further investigation. Dyce et al. determined that SCs isolated from the skin include a population capable of differentiating into oocyte-like cells expressing Oct4 and other markers characteristic for oocytes. The hypothesis on the migration of cells of epiblast — primordial germ cells (PGCs) — into nongonadal niches during early embryogenesis may explain their presence in the skin. Obtaining PSCs from the skin may potentially give us new uses for these cells in terms of treatment, and become a new experimental model for in vitro studies.

Cells are the main component of the tissue-engineered skin used for burn therapies. They include both stem and somatic cells and can be divided into three main groups: autologous, allogeneic and xenogeneic. One of the main trends in choosing a cell type for patient treatment is the use of autologous cells as they do not cause immune rejection and their tumorigenicity is low due to the absence of epigenetic manipulations. Nowadays, animal cells are not widely used for skin tissue regeneration, only ECM or its components that they synthesize. Plant stem cells, which are commonly applied in cosmetics, can be interesting as they have no use limitations when compared to animal and human cells. Of course, they cannot be used in skin substitute development as a cell component; but they can provide bioactive substances, which can improve the wound healing processes.

Fibroblasts and keratinocytes are common cells used in products for wound and burn healing. Keratinocytes are the major cell component of the epidermis and responsible for its stratified structure and form numerous tight intercellular junctions. Fibroblasts are the main cell type of the dermis and produce ECM components and secrete various growth factors (TGF-β), cytokines (TNF-α), and matrix metalloproteinases, which ensure the ECM formation and keratinocyte proliferation and differentiation. Commercial products such as Epicel, Cryoskin, and BioSeed-S contain keratinocytes; Dermagraft, TransCyte and Hyalograft 3D—fibroblasts; and Apligraf, Theraskin, and OrCell—a combination. The use of these cells enables the large-scale production of standardized product batches. However, these materials are mostly non-permanent bioactive dressings, which provide cytokines, ECM, and growth factors for the successful skin reparation [11]. Immune rejection is commonly reported with allogeneic fibroblasts and keratinocytes, but this is mostly shown for allogeneic keratinocytes that can be explained by the difference in HLA expression and cytokine production.

Progenitors of mast cells, myeloid cells and lymphoid DC travel through the bloodstream and migrate to the dermis where they mature as a result of resident elements. The predominant tissues in the bone marrow are MSCs and fibroblasts. MSCs from hair follicles arising from the neural crest are the closest to this sort judging by their properties.[12] It Is worth a mention to state that the quantity of platelets increases during an immune response due to their special properties. The dermis is the structural and functional backbone of the epidermis. It provides access to cells within circulation which are strictly regulated. These selective cells can practically only be found within this area. This is primarily keratinocytes, LC and γδ T lymphocytes. The last two function as part of the innate as well as the adaptive immunity, which links both the skin compartments with the entire body. This is required to present antigens traveling through the lymphatic path in the dermis followed by the lymphatic follicle. γδ T lymphocytes support keratinocytes and promote their regeneration.

Fetal fibroblasts are of particular interest because they can significantly improve skin repair due to the high expansion ability, low immunogenicity, and intense secretion of bioactive substances such as basic fibroblast growth factor, vascular

ISSN: 1987 - 6521, E – ISSN: 2346 – 7541
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endothelial growth factor, and keratinocyte growth factor. However, ethical issues limit their application.Epidermal stem cells (ESC) are of particular interest for skin tissue regeneration as they have favorable features such as high proliferation rate and easy access and keep their potency and differentiation potential for long periods. They are one of the skin stem cell types, either heterogeneous or autogenous origins. ESC are mostly connected to the process of skin regeneration. They are rare, infrequently divide and generate short-lived and rapidly dividing cells, which are involved in the regeneration process. Their main population, responsible for skin repair, is located in the basal layer of the epidermis; however, they can also be revealed in the base of sebaceous glands and the bulge region of hair follicles. Moreover, as they can be easily derived from the patient's skin and transplanted to the same patient, ESC are not restricted by ethical issues. Grafts containing autologous holoclones ESC have proven to be effective in treating vast skin defects: epidermolysis, skin and ocular burns [13].

Mesenchymal stromal cells (MSC) have similar (not identical) features as ESC and can be derived from various tissues, even the skin as mentioned previously. They have a high differentiation potential and a certain degree of plasticity and may generate cells of mesodermal, ectodermal, and endodermal lineages. Moreover, paracrine, trophic, and immunomodulatory MSC properties enable their clinical use. MSC can migrate to the injured tissues, differentiate, and regulate the tissue regeneration by the production of growth factors, cytokines, and chemokines. Their immunomodulatory activity is based on the release of anti-inflammatory cytokines and the inhibition of proliferation of CD4+ and CD8+ natural killer cells, T cells, and B cells. MSC are considered to be hypoimmunogenic because they do not express class I and II molecules of the major histocompatibility complex (MHC) and co-stimulatory proteins (e.g., CD40, CD80, CD86)[14]. Therefore, the transplantation of allogenic MSC has a low risk of the immune rejection. In burn therapy, adipose-derived stromal cells refined from the stromal vascular fraction are widely applied because of their easy access and isolation procedure and inspiring improvement of the healing processes. They are showed to preserve their therapeutic effects after freezing that ensures their multiple use. It is worth mentioning that even the freshly isolated stromal vascular fraction is showed to be effective in burn therapy, but compared to adipose-derived stromal cells, it can release high concentrations of inflammatory mediators. However, the number of randomized controlled preclinical and clinical trials remains insufficient.Among the MSC derived from other tissues (adipose tissue, umbilical cord, etc.) the MSC derived from bone marrow (BMSC) requires special attention.

They also possess plasticity and can differentiate into tissues of mesodermal, ectodermal, and endodermal origin. BMSC are considered to participate in the skin development. It has been reported that bone marrow can generate not only hematopoietic and mesenchymal cells but also fibroblast-like cells that are located in the dermis and actively proliferate in the skin during the regeneration processes.

The possible disadvantages of BMSC are that the tumor microenvironment may induce changes in the angiogenesis ability and anti-tumor response[15]. Moreover, they may generate tumor-associated fibroblasts and shift a normal immune cell phenotype to an immunosuppressive and tumor promoting one.Nowadays, the greatest interest in tissue regeneration belongs to induced pluripotent stem cells (iPSC); using somatic cell reprogramming like a magic wand, we can develop patient-specific cells with a tailored phenotype and apply them in clinics.

The most commonly used cells for cell reprogramming are dermal fibroblasts, melanocytes, and keratinocytes since they can be easily accessed and isolated from punch biopsies[16]. Research has shown that both murine and human iPSC can be differentiated into dermal fibroblasts, keratinocytes, and melanocytes, opening a door for iPSC technology into dermatology applications.

The interesting fact is that fibroblasts achieved via this technique may show increased properties compared to those of the parental fibroblasts, e.g., the exceeded ECM production. This might be related to the changed epigenetic signature that occurs during iPSC differentiation and is critical for their use in skin tissue regeneration [17]. However, when cells are reprogrammed with tumorigenic c-Myc and this transgene remains in iPSC, the risk of tumor formation increases, because c-Myc might be reactivated. Since modern methods for cell purification cannot ensure the full separation of differentiated cells from iPSC, undifferentiated and partly differentiated cells may be implanted into a patient and increase the possibility of tumor formation. Further, use of lineage-tracing concepts in such regenerative experimental model systems will enhance our understanding of molecular events and trigger factors that are responsible for immune cell trafficking to sites of regeneration, post skin injury.

Taken together, we conclude that near future discoveries using such innovative strategies will not only help us achieve better therapeutic products for skin-related immune disorders but will also foster ideas toward novel cosmetic formulations and topical applications for improving skin's regenerative potential.

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ISSN: 1987 - 6521, E – ISSN: 2346 – 7541
JANUARY-MARCH 2020 VOLUME 53 ISSUE 02

FEW IMPORTANT ASPECTS OF USAGE OF BIOLOGIC AGENTS IN THE DERMATOLOGY

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ABSTRACT
The Biologic therapy has dramatically changed the way medicine, and specifically dermatology, is practiced today. The use of biologic agents in dermatology is evolving, with psoriasis being the most common indication for which biologics are used currently. However, several other dermatologic diseases seem to be responsive to biologic therapy, and continuing research and development efforts are elucidating the benefit-risk profiles of various biologic medications in these dermatologic conditions. Understanding their mechanisms of action, labeled and off-label uses in dermatology, and common adverse effects helps to inform clinical decision making and improve patient outcomes.
Keywords: biologic agents in dermatology, dermatologic diseases, various biologic medications.

Biologics currently represent a new hope for managing psoriasis. Dermatologists might find themselves faced with an opportunity to experience a novel step in therapy.
Biologics are medications made from human or animal proteins. They are designed to specifically target biologic pathways that cause inflammation in the skin and other organs.Biologics have been used in many people worldwide to treat severe psoriasis [1], psoriatic arthritis, other types of arthritis and inflammatory bowel diseases (e.g. Crohn's disease). Biologic medications are given as injections.Acondition such as psoriasis develops in people who are genetically predisposed.
Immune cells are triggered and become overactive, creating inflammation in the skin (which we recognise as psoriasis) and, in some cases, the joints (psoriatic arthritis). Biologics work in different ways to traditional treatments by blocking the activation and behaviour of immune cells that play a role in a disease such as psoriasis. Examples of biologic drugs currently used in Australia to treat psoriasis include etanercept (enbrel), adalimumab (humira), infliximab (remicade), ustekinumab (stelara) and secukinumab (cosentyx) [2].
Biologics are associated with an increased risk of new infections or reactivation of old infections. With long-term treatment there may be an increased risk of lymphoma.
Prior to starting on a biologic drug, your dermatologist will carefully review your medical history and examine or test you for evidence of tuberculosis, HIV and other chronic infections, significant heart disease or significant evidence of atherosclerosis and past history of cancer.
It may be necessary to have a booster for some childhood diseases such as whooping cough, diphtheria or polio. You should be immunised against hepatitis A and B as well. Necessary live vaccines will be given prior to commencing treatment.
A number of blood tests, a chest X-ray and other investigations will be required. Biologic drugs are rated category B or C in pregnancy, and planned pregnancy needs to be discussed with the treating doctor.
Live or attenuated vaccines should not be given while taking biologics. These include vaccines such as herpes zoster, influenza (including nasal form), measles, mumps, rubella rotavirus, oral polio vaccine, smallpox, varicella, yellow fever, typhoid (oral form) and BCG injection.
It is important to remember that all systemic medications, whether traditional or the newer biologics, have broad effects and people undergoing treatment have to be carefully monitored.
The target-specific mediators of inflammation have become an important and useful part of the dermatologists' treatment armamentarium. They modulate the immune system through stimulatory or inhibitory actions, acting at only specific parts of the immune system; hence, their safety profile is generally considered to be more favorable than that of traditional systemic immuno-suppressive agents. Nevertheless, they are not devoid of adverse reactions, a few of which are associated with significant morbidity[3].
The initial over enthusiasm though has been replaced by a guarded and cautious approach now, with increasing years of experience with these drugs. The following account focuses attention to the biologics, which are/or may become useful in dermatological diseases. Broadly, these include agents acting against tumor necrosis factor-α (TNF-α), those acting on cell surface receptors, fuspion proteins and intravenous immunoglobulins (IVIG).
The tumour necrosis factor-alpha (TNF-α) is a potent proinflammatory cytokine exerting pleiotropic effects on various cell types and plays a critical role in the pathogenesis of chronic inflammatory diseases, such as psoriasis. Accumulating evidence suggests that not only soluble TNF-α (sTNF, a homotrimer of 17 kDa monomers), but also its precursor form

(transmembrane TNF [tTNF], a homotrimer of 26 kDa monomers) is involved in the inflammatory response. sTNF is released as a soluble cytokine after being enzymatically cleaved from its cell-surface-bound form (tTNF) by TNF-α-converting enzyme, TNF is produced by numerous cell types, including immune cells (B cells and T cells, basophils, eosinophils, dendritic cells, natural killer cells, neutrophils and mast cells), nonimmune cells (astrocytes, fibroblasts, glial cells, granuloma cells and keratinocytes) and many kinds of tumor cells[4].

The biological activity of TNF-α is triggered by binding to one of two structurally distinct receptors: TNF receptor type I (TNFRI [or p55 or CD120a]) and TNF receptor type II (TNFRII [or p75 or CD120b]). TNFRI and TNFRII are present in all cell types except erythrocytes. Upon binding to TNF receptors, both transmembrane and soluble TNF-α mediate pleiotropic effects (apoptosis, cell proliferation and cytokine production). Three anti-TNF agents, Infliximab (INF), Adalimumab (ADA) and Etanercept (ETN) are approved worldwide for the treatment of psoriasis. INF and ADA are anti-TNF monoclonal antibodies. INF is a human-murine chimeric monoclonal antibody with a constant human region (Fc) and a variable mouse region and ADA is a fully human IgG1 monoclonal anti-TNF antibody[5].

Both have two binding sites for TNF-α and present high specificity, affinity and avidity for the citokyne. ETN is composed of the extracellular portion of two human TNFRII linked to a Fc portion (CH2 and CH3 domains) of human IgG1. ETN is supposed to form 1:1 complex with the TNF-α trimer. INF and ADA form stable complexes with TNF-α, while ETN forms relatively unstable complexes. The TNF-α-producing cells temporarily express TNF-α in their plasma membranes (tTNF). INF, ADA and ETN bind to transmembrane TNF-α with similar affinities that are lower (weaker) than for soluble TNF-α. Since INF and ADA are IgG1 antibodies, binding to tTNF, they are capable of complement fixation and also can produce the destruction of the TNF-α-bearing cell by antibody dependent cell cytotoxicity (ADCC).

ETN possess the Fc portion of IgG1 that can induce ADCC, but it does not carry the CH1 domain of IgG1 which is important for the activation of C3. Thus, differential clinical efficacies of anti-TNF agents may be explained by their different action on transmembrane TNF-α-bearing cells. The two main sources of TNF-α in the body are lymphocytes and macrophages (cells which form the granulomas) and the sTNF is essential for the maintenance of granulomas architecture[6]. ADA and INF induce complement-dependent cytotoxicity, ADCC and outside-to-inside signalling through transmembrane TNF-α and seem to be more potent than ETN in the elimination of transmembrane TNF-α-bearing macrophages and transmembrane TNF-α-bearing T cells. Therefore, they are very effective in disrupting granulomas, being indicated in the treatment of granulomatous diseases such as Crohn's disease.

However, the occurrence of reactivation of latent TB is more common in patients receiving ADA and INF than in patients treated with ETN or with other biologics that do not directly inhibit the TNF-α (for example, the interleukin inhibitors). ADA and INF are more effective than the ETN in the treatment of plaque psoriasis. The most common adverse effects of ADA and ETN (subcutaneous use) are reactions in application sites while the most common adverse effects related to INF (intravenous use) are infusion reactions. Another common side effect of anti-TNF agents are common infections (especially of the upper respiratory tract).

As a result of the immunological alterations provoked by TNF-α inhibitors, the use of these drugs has been associated with severe infections of viral, bacterial and fungal etiology so it is essential to properly monitor the patients using these drugs and to know all their common and rare possible adverse effects. The inhibitors of interleukins (ustekinumab - UST and secukinumab - SEC) are more effective in the treatment of plaque psoriasis than the anti-TNF agents as they act directly on the Interleukin (IL) -23/17 axis (the protagonist of the immunopathogenesis of psoriasis)[7].

By the way, the main mechanism of action of the anti-TNF agents in plaque psoriasis appears to be the inhibition of sTNF involved in the activation of dermal dendritic cells (which are potent sources of IL-23). Thus, the anti-TNF agents would also inhibit the IL-23/17 axis. Ustekinumab is a fully human IgG1-k monoclonal antibody that binds specifically to the p40 subunit of the cytokines interleukin (IL)-12 (p40+p35) and IL-23 (p40+p19). It binds to the same epitope within the D1 domain of the p40 subunit of each cytokine. Binding of ustekinumab to IL-12 and IL-23 prevents their association with IL-12Rβ1, which is expressed on the surface of a variety of immune cells such as natural killer and T cells. By directly neutralizing their biological activity, ustekinumab attenuates the immune cell activation properties of IL-12 and IL-23.

Ustekinumab is unable to bind to IL-12 or IL-23 that is already bound to IL12Rβ1; therefore, it is unlikely to contribute to complement- or antibody-mediated cytotoxicity. By inhibiting the soluble IL12 and IL-23, UST inhibits, respectively, the differentiation in the lymph node of naive T-helper lymphocytes (LThθ) into Th1 and Th17. In psoriasis patients, these activated Th17 and Th1 cells fall in circulation and are captured by the activated endothelial cells on the skin. In the dermis, Th17 and Th1 interact with the antigen-presenting cells - APC (i.e, macrophage and dermal dendritic cells) and under the influence of IL-12 and IL-23 (produced by the APC), they proliferate and release their specific repertoire of cytokines (TNF-α, INFγ, IL-17, IL-22 and others).

By inhibiting IL-23 and IL-12, UST does not allow the prolif eration of the Th1 and Th17 in the dermis. Besides, UST may also act in skin lesions preventing IL-17 release by various cells of the innate immune system (neutrophils, mast cells, LTYδ cells and innate lymphoid cells).

ISSN: 1987 - 6521, E – ISSN: 2346 – 7541
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Finally, it is a very effective drug and has an excellent safety profile for the treatment of plaque psoriasis. Nasopharyngitis, upper respiratory tract infection and headache are reported as the most common adverse effect of UST. IL-17 (or IL-17A) is a key cytokine in the immunopathogenesis of psoriasis[8].
It acts on keratinocytes altering their differentiation and proliferation, and stimulating them to produce various proteins (cytokines, chemokines and antimicrobial peptides), which attracts more immune cells to the skin. IL-17A acts on keratinocytes individually and together with the TNF-α and IL-22. The inhibition of IL-17 by SEC (human IgG1κ monoclonal antibody that binds to soluble interleukin IL-17A) reduces the production of various chemokines by keratinocytes including the ones responsible for the arrival of neutrophils in the skin. SEC causes rapid disappearance of neutrophils (potent sources of IL17A) in psoriasis lesions. The disappearance of neutrophils correlates with the decrease in proliferation of keratinocytes, demonstrating a strong interaction between these cells in the immune response.
IL-17A is important in defense against extracellular pathogens and candidiasis has been reported in patients using SEC (cases controlled with classical treatments without systemic infection report). The effectiveness of SEC is greater than the UST in the treatment of plaque psoriasis, but rare adverse effects of SEC include neutropenia and isolated reports of Crohn's disease activation. For conclusion, it is important to know the immunopathogenesis of psoriasis and the mechanisms of action of the biologics in order to understand better their indications and possible adverse effects. In this way, we can individualize the treatment of those patients who need this type of medication.
Usage of biologics represents a novel therapeutic approach in dermatology. It has been used for a few years in other specialties, like rheumatology. Dermatologists must nonetheless be vigilant regarding the toxicity of biologics, whether it be renal, hepatic or on the bone marrow, in addition to immunosuppression, teratogenicity and carcinogenesis. Clinical studies with biologic agents indicate a net improvement of the clinical condition of psoriasis, referred to as PASI 75, to the effect of 40% to 60%.Since psoriasis is a chronic disease and the medications for treating it are expensive, the traditional medications, like methotrexate (MTX), cyclosporine, retinoids and phototherapy, will probably keep being used.
In this situation, the effects of each drug will have been potentialized, and their toxic effects and the cost of treatment reduced. Nonetheless, the toxic effects of the traditional drugs-which are well known-must be recalled when performing a combination with biologics. It is also known that they are not nephrotoxic or hepatotoxic and that they seem to be useful in associations with MTX or cyclosporine[8].
Another aspect to be considered is increased immunosuppression when in combination with traditional drugs, like with azathioprine, hydroxyurea and mycophenolatemofetil.
Current studies had shown that, biologics have less impact on immunosuppression compared to traditional drugs, because they act in accordance with specific steps of the immune process. Still, the carcinogenic potential must considered mainly with prolonged use, or in patients with an increased risk of cutaneous neoplasia, like in those who have already been using phototherapy for a long time. In rheumatology, infliximab is used in association with MTX in an attempt to prevent the formation of anti-chimeric antibodies[9].
There were no reports of increased carcinogenesis with this association or with etanercept and MTX.60 More studies are required, though, as is more time for these drugs to obtain definitive conclusions. Apart from these associations, sequential therapy must be considered as well. They are the drugs of choice for treating psoriasis. On the other hand, etanercept has proved to keep its effects for up to six months after the end of therapy. Alefacept also induces periods of greater remission and better efficacy in subsequent therapeutic cycles. Therefore, it seems as though they will be useful in a second phase of sequential therapy[10].
More complete comparative and long-lasting studies must be performed in order to upgrade the best indication for this new class of medications in dermatology. Biologics currently represent a new hope for managing psoriasis. Dermatologists might find themselves faced with an opportunity to experience a novel step in therapy. Indeed, this step might be as important as the introduction of corticosteroids was in its time-or more.
It is important and necessary for dermatologists to upgrade their knowledge for this new era, whose signs can already be glimpsed. This is how dermatologists will ensure their place in further research and not be left on the side-lines from other medical and scientific specialties.

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BLACK SEA
SCIENTIFIC JOURNAL OF ACADEMIC RESEARCH
ISSN: 1987 - 6521, E – ISSN: 2346 – 7541
JANUARY-MARCH 2020 VOLUME 53 ISSUE 02

IMPORTANT SPECIFICATIONS ON THE THERAUPETIC SPECTRUM OF SKIN STEM CELL POPULATIONS

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ABSTRACT

Stem cell therapy has become a very promising and advanced scientific research topic. The development of treatment methods has evoked great expectations. This review focused on the discovery of different stem cells and the potential therapies based on these cells. The genesis of stem cells is followed by laboratory steps of controlled stem cell culturing and derivation. Quality control and teratoma formation assays are important procedures in assessing the properties of the stem cells tested. Among many types of stem tissue applications, the use of graphene scaffolds and the potential of extracellular vesicle-based therapies require attention due to their versatility. The review is summarized by challenges that stem cell therapy must overcome to be accepted worldwide. A wide variety of possibilities makes this cutting edge therapy a turning point in modern medicine, providing hope for untreatable diseases.
Keywords: different stem cells, extracellular vesicle-based therapies.

1) Epidermal stem cells (EpSC). Advantages of using EpSC for research, diagnostic and therapeutic purposes include their readily accessibility and relatively simple isolation from (bioptic) skin tissues in comparison to ESCs. EpSC are further considered to be less “artificial” than iPSCs. Immune rejection following autologous transplantation is not expected and the tumorigenicity of these cells is considered to be low, due to their lesser degree of potency and absence of (epi-)genetic manipulations. In contrast, iPSCs reprogramming with tumorigenic c-Myc increases the frequency of transformed cells during iPSC generation [1]. Tumor formation risk increases when the c-Myc transgene remains in establishediPSCs and becomes reactivated.

EpSCs demonstrate further favorable features, such as their high proliferation rate with the ability to double their number within 3~4 days of culture. At the same time they are able to keep their potency and differentiation potential for longer periods, although progressive aneuploidy (a state in which cells have abnormal numbers of chromosomes) and polyploidy (a state in which cells have one or more extra fully duplicated sets of chromosomes) as well as accumulation of mutations occur after several passages in cell culture. Notably, ethical issues do not restrict their use. This is in contrast to the serious ethical concerns that arise in ESCs research when referring to human dignity and ideas of personhood along the creation as well as destruction of embryos as the earliest forms of human life specifically for research purposes [2]. All these characteristics make skin derived adult SCs an ideal population for the use in SC-based therapies. Grafts generated from autologous epithelial cultures that encase an appropriate number of EpSCs as holoclones were shown to permanently recover massive epithelial defects (e.g., in skin and ocular burns or epidermolysisbullosa). Therewith, EpSCs also prove to provide both, a cellular environment and normal ECM to mediate restoration of a normal dermal-epidermal junction.

2) Multipotent mesenchymal stromal cells (MSCs). Since their first identification as fibroblast precursors in bone marrow in the 1950s, mesenchymal (stem) stromal cells (MSCs) have been obtained from several tissues, including adipose tissue, skin, umbilical cord blood, placenta, peripheral blood, endometrium, dental pulp, dermis, amniotic fluid, as well as from tumors. MSC of different origin share similar features but are not identical. Even in the skin several MSC subtypes exist. Regardless of their origin, MSCs possess a broad differentiating potential and some degree of plasticity, since they generate cells of not only mesodermal origin (i.e., osteocytes, adipocytes, chondrocytes, myoblasts, and tenocytes) but also of ectodermal (e.g., neurocytes, melanocytes) and endodermal lineages (e.g., hepatocytes, thyroid cells)[3].

In 2006, the International Society for Cellular Therapy established guidelines for MSC characterization to counteract controversies concerning its name, definition, isolation and characterization criteria. The name “multipotentmesenchymal stromal cells” was favoured and three minimal criteria were delineated: i) adherence to plastic in culture; ii) expressing a combination of surface antigens (CD73+, CD90+, CD105+, CD34−, CD45−, CD11b−, CD14−, CD19−, CD79a− and HLA-DR−); and iii) in vitro differentiation-capability into adipocytes, osteoblasts and chondrocytes. However, MSC populations isolated from different tissues significantly differ in their proliferation, differentiation and molecular phenotype.

Besides the differentiation-capability in vitro, the trophic, paracrine and immunomodulatory functions of MSCs are those that hitherto may have the biggest therapeutic implication in vivo.
One of the main functions of MSCs is to support repair of damaged tissues. In response to inflammation MSCs migrate towards injured sites, differentiate into cells (mainly fibroblasts) and operate through the release of molecules participating in tissue regeneration such as cytokines (i.e., PGE2, GM-CSF, interleukin [IL]-1, RA, IL-7, IL-8, IL-10, and IL-11), growth factors and chemokines. In addition, MSCs modify tissue healing through pro-angiogenic, anti-fibrotic, and anti-apoptotic pathways. In stromal vascularized tissues, their perivascular amount correlates with the blood vessel density and the number of pericytes as mesenchymal progeny. The immunomodulatory abilities of MSCs reside on the secretion of anti-inflammatory cytokines and the inhibition of CD4+ and CD8+ T cell, B-cell, and natural killer (NK) cell proliferation. These features depend on the microenvironmental milieu that MSCs encounter after their application[4]. Thus, MSCs have been shown to exert even opposite effects in response to different inflammatory cues. Although it is not fully determined whether MSCs are immunoprivileged or immunoevasive, they are specified as hypo-immunogenic due to their menial expression of major histocompatibility complex (MHC) class I molecules, as well as lack of MHC class II and co-stimulatory molecules, inclusive CD80, CD86, and CD40. These characteristics reduce the risk of immune rejection so that MSCs are considered to be safe when used in an allogeneic environment. Various methods have been applied to generate “optimized” MSCs, including genetic modification through viral and non-viral modifications, bioengineering of surface receptors, and priming with biological agents. For example, MSCs activated by nucleotide oligomerization domain 2 (NOD2; involved in the regulation of differentiation of umbilical cord derived MSCs and able to modulate inflammatory responses) or MSCs overexpressing SOD3 (a powerful antioxidant molecule) have been shown to exert much higher therapeutic efficacy than naïve MSCs in experimental immune modulatory models of atopic eczema and psoriasis, respectively. Although a confirmation of these results in the clinic is still missing, development of exceedingly efficient MSCs with augmented benefit and minimum risk along genetic modifications gives promising therapeutic perspectives[5].

3) Bone marrow stem cells. Bone marrow comprises at least two different lineages of cells: hematopoietic and associated supporting stroma with mesenchymal cells. Hematopoietic cells are produced by hematopoietic stem cells (HSCs), which are situated in the bone marrow SC niche. The mesenchymal compartment contains a subset of cells (1 in 107 to 108) with probably (pluri-)multipotent differentiation capacity, referred to as MSCs.

4) Bone marrow derived mesenchymal stromal cells (BM-MSCs). The BM-MSCs are similar but somewhat different to mesenchymal stromal cells isolated from other tissues. The former can be isolated, enriched and transfused into allogeneic or autologous recipients along bone marrow transplantation (BMT) and exert a substantial role in producing erythrocytes, leukocytes, and platelets. They show also plasticity with their ability to differentiate into tissues of mesodermal, endodermal, and ectodermal origin, including skin and have been implicated to contribute to skin development. Nevertheless, the nature and function of these cells is still beeing controversial discussed[6].
In addition, BM SCs may also serve as a reservoir for skin epithelial cells. After BMT, donor cells differentiating into keratinocytes were detected in human epidermis of recipients for at least 3 years before vanishing. However, such BM-derived keratinocytes seem to be an extremely rare finding, perhaps contributing to only ~0.0001%~0.0003% of all epidermal cells in this setting. Since BM-derived epithelial cells are sparse, the physiological role of BM cells in regeneration of the skin has been called into question. Potential drawbacks of BM-MSC therapy refer to immune modulating abilities in context of a tumor microenvironment leading to an unfavourably alteration of anti-tumor response and angiogenesis[7]. Furthermor MSCs may serve as precursors of tumor-associated fibroblasts and possess the capability to skew neutrophils and inflammatory monocytes or tissue macrophages into an immunosuppressive and tumor-promoting phenotype.

5) Induced pluripotent stem cells. Reprogramming of somatic cells to iPSCs provides an important (and ex vivo infinitely expandable) cell source to develop customized, patient-specific cells with a broad spectrum of cellular phenotypes for potential therapeutic applications. Skin cells like dermal fibroblasts, keratinocytes, dermal papilla cells or melanocytes are preferentially used for this technique, since they are easily accessible in the patient via isolation from punch biopsies. Especially fibroblasts further have plain culture conditions. Adult adipose SCs, yielded via lipoaspiration, pose another source for iPSCs. The differentiation of both, mouse and human iPSCs into keratinocytes, melanocytes, and fibroblasts has already been successfully shown [8]. This thus opens the possibility of extending iPSC technology into the field of dermatology.
Interestingly, fibroblasts differentiated from iPSCs may display specific properties that exceed those of the parental fibroblasts from which these iPSCs were originally reprogrammed, such as an increased production and assembly of ECM. Acquisition of an augmented biological potency of modified cells when compared to their parental origin is probably related to a modified epigenetic signature following differentiation of iPSCs and is an important functional feature for using these cells in regenerative therapies. Fibroblasts are essential in maintaining normal tissue homeostasis and wound repair

ISSN: 1987 - 6521, E – ISSN: 2346 – 7541
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through their synthesis of ECM proteins and secretion of growth factors. Their incorporation into tissue-engineered biomaterials seems promising for the use in repairing damaged or diseased tissues by fabricating dermal substitutes. In this context, iPSC-derived fibroblasts offer a novel source of autologous cells for dermal regeneration. Although iPSCs have enormous potential for cell-based drug designs, cell therapy, and disease modeling, their transition into the clinic is still hindered by the missing evidence of safety and reliability of the reprogramming technology. Although cell identity can be modified by the exogenous expression of transcription factors, the efficiency of nuclear reprogramming remains low (0.1% to 3%). This low outcome is probably associated with residual epigenetic memory of the tissue from which iPSCs were derived, detected via gene profiling studies in iPSCs. It is known that differentiated somatic cells have distinctive epigenetic patterns to maintain their cell identity. Cellular reprogramming works to change this epigenetic status of differentiated cells back to an undifferentiated state. Further, there is evidence that through the reprogramming process a restructuring of the existing somatic epigenetic memory takes place, followed by the generation of a new “epigenetic signature” adapted to the type of cell to be differentiated. In addition, currently available cell purification technologies may not fully succeed in separating the differentiated cells from undifferentiated iPSCs[9].
Undifferentiated or partly differentiated iPSC could consequently be transplanted into the patient, carrying an increased risk of tumor/teratoma formation. Furthermore, it remains unclear to what extent the reprogramming process affects the genomic integrity of a cell. Several recent genomic analyses have signified that genomic abnormalities such as the accumulation of mutations and aberrant DNA methylation of distinct single bases emerge in iPSCs, either by the reprogramming process or following culture conditions[10].
To address this issue, genome integration-free approaches are already widely used aiming at the reduction of the tumorigenic risk of insertion mutagenesis. However, it is necessary to perform more extensive and thorough genomic and epigenetic studies before using iPSCs in the clinic. Interestingly not only iPSCs but also dermal fibroblasts themselves were demonstrated to have features of in vitro pluripotency without the necessity to be reprogrammed back to immaturity via activation of embryonic stage genes. Again, more studies will be needed to definitively exclude aiPSC-mediated immune response in patients. Immune rejection related to iPSC-based genetic correction is another problematic aspect, especially in skin diseases with homozygous null mutations of relevant genes.

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ISSN: 1987 - 6521, E – ISSN: 2346 – 7541
JANUARY-MARCH 2020 VOLUME 52 ISSUE 01
THE BALTIC SCIENTIFIC JOURNALS
BLACK SEA
SCIENTIFIC JOURNAL OF ACADEMIC RESEARCH

CELLULAR THERAPY AND STEM CELL USAGE DURING HAIR LOSS: FUTURE PERSPECTIVES

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ABSTRACT
Stem cells may have potential as a treatment for regenerating hair. Initially, methods to obtain stem cells have concentrated on isolating the primary cells from the tissue of interest through biopsy and growing these cells outside the body to be transplanted into the patient. Stem cell treatment of nonautoimmune hair loss like androgenetic alopecia is promising. Although an autologous transplant is viewed as the standard, its use is limited because of a lack of data and the diminished viability of cells that are made available using this method. Adipose-derived stem cells are a promising alternative because of their limited immunogenicity. They are easy to obtain, are multipotent, and can differentiate into different cell lines. They also have significant potential for angiogenesis. More studies are needed to establish the efficacy of the various types of stem cell-based treatments for people with hair loss.
Keywords: treatment for regenerating hair, autologous transplant, adipose-derived stem cells.

Alopecia is a common hair loss disorder that may be due to hereditary factors, medical conditions, hormonal imbalances, autoimmune disorders, nutritional problems, environmental factors, psychological stress, and aging. All these damaging factors affect the hair cycle and reduce stem cell activity and the regeneration of hair follicles.[1] Alopecia is not painful or life-threatening; however, there can be skin irritation and physical problems brought about by the loss of hair, not only on the scalp but also in the eyelashes and eyebrows.[3] Alopecia that is due to chemotherapy, though having a different etiology, can also bring about anxiety and identity issues.Hair follicles have mature epithelial and melanocyte stem cells, also known as hair follicular stem cells (HFSCs), contained in a bulge in the attachment area of arrectorpilimuscles [2]. In addition, HFSCs are likewise located inside the outer root sheath inside the area of the proximal end of the isthmus. HFSCs are involved in the regeneration of epidermal cells and the structure of hair follicles and sebaceous glands.[4] In the scalp of those with hair loss, the numbers of hair follicle stem cells remain unaltered, although there is a decrease in actively proliferating progenitor cells.[5] Thus, hair stem cell treatments are promising new treatments for hair loss. Hair stem cell treatments include the advancement of new autologous advances to include hair regrowth in vitro and in vivo through regeneration and stimulation. Stem cells may have potential as a treatment for regenerating hair. Initially, methods have concentrated on isolating the primary cells from the tissue of interest through biopsy and growing these cells outside the body to be transplanted back into the patient. Stem cells are a promising approach for the treatment of nonautoimmune hair loss like androgenetic alopecia. First, hair follicles are easily accessible and observable. Next, the anatomy and physiology of hair follicles are well studied. In addition, hair follicles and its derived cells have been cultured in vivo and autologous transplantation of hair follicles is widely done. The hair follicle is a self-renewing miniorgan with numerous stem cells at the bulge area and dermal sheath. Due to this, pluripotent, multipotent, and adipose-derived stem cells (ADSCs) have potential as cell-based treatments for hair loss.[6] The regeneration of hair follicles relies upon well-organized interactions between epithelial receptors and mesenchymal parts. In the past, various epithelial and mesenchymal parts were consolidated and grafted in vivo to enhance interactions between them. Hypothetically, hair follicle stem cells could effectively yield hair follicles in typical assays. Thus, hair follicle stem cells were demonstrated to be beneficial materials for the regeneration of hair follicles. This article aims to review the use and potential of hair follicle stem cell treatment in alopecia.
Only free full-text articles were included. The author narratively described the major findings and conclusions from individual studies. Out of the 849 studies reviewed, only 24 studies fit the criteria.

Stem cells types for hair renegeneration
Stem cells are classified according to their plasticity. The classes into which they fall include: the multipotent stem cells, pluripotent stem cells, totipotent stem cells, and the adult stem cells which are a certain type of multipotent stem cell. Studies on hair regeneration as of present have dwelt more on the use of pluripotent and multipotent stem cells and adipose tissue-derived stem cells.

Autologous stem cells: Cellular therapy is being studied for alopecia in the form of autologous dermal papillae (DP) cells to induce hair follicular regeneration. Pluripotent stem cells may be coaxed into hair follicle lineages to promote hair

ISSN: 1987 - 6521, E – ISSN: 2346 – 7541
JANUARY-MARCH 2020 VOLUME 53 ISSUE 02

growth.[8],[10] Although an autologous transplant is viewed as the standard, its use is limited because of a lack of data and the diminished viability of cells that are made available using this method. As of now, techniques are being improved which improve the viability of autologous stem cells of the hair follicle.[1]Cells can retain phenotypes and the ability to create hair follicles even after passing through bioreactors. The potential for regeneration of cultured dermal papilla to encourage the growth of a hair follicle was studied in the skin of mice. At first, dermal papilla cells (DPCs) were seen to grow with the expression of CD200, and these fusiform cells formed colonies in three to 5 days. After 2 weeks, they gained a passaging capability and formed an extracellular matrix after the third passaging. Histopathological examination in rodents showed that structures changed into hair follicles at the areas of infusion in the dermis. Autologous-induced pluripotent stem cells (iPSCs) are engineered stem cells that have been created from mature body cells by way of transduction of four reprogramming transcription factors which are mostly found in embryonic stem cells (ESCs). These factors are cMYC, SOX2, OCT4, and KLF4. iPSCs have certain growth characteristics and can differentiate in a manner that is similar to those of ESCs. These stem cells can be genetically modified to treat hair loss and are able to provide an unlimited source of specific cells for hair regeneration.

Adipose-derived stem cells: ADSCs appear as an ideal cell population in regenerative medicine because there may be minimal immunogenic properties. They are also easy to obtain, are multipotent, and can easily differentiate into different cell lines. They also have significant potential for angiogenesis. These cells have appeared to be from mural cells situated in the perivascular areas, vascular smooth muscle cells, and pericytes. These cells are involved in the development of blood vessels and are receptive to vesicular endothelial growth factor (VEGF).

Embryonic stem cells: Human ESCs (hESCs) were activated to first create neural cells and then into hair-inducing DP-like cells in culture. hESC-derived DP-like cells express markers typically found in adult human DP cells and are able to encourage the growth of hair follicles when transplanted under the skin of mice. These hESC-derived dermal papilla-like cells were placed into the dermal papilla of newly formed hair follicles, and appropriate markers were expressed. Prior to the study, the knowledge that DP cells were proposed as the cell-based treatment for hair loss diseases initially struck the researchers; however, they are not suitable for this purpose because they cannot be obtained in needed amounts, and they can rapidly lose their ability to induce hair follicle formation when they are cultured. Functional hESC-DP cells are capable of inducing greater hair growth for the treatment of alopecia.

Cord blood stem cells: Wharton's jelly is a gel-like substance that is present inside the umbilical cord and in the vitreous humor. It has become a good source of stem cells because it is widely available from many donors, it is noninvasive and painless and offers no risk to the donor. There are also no ethical considerations, has a weak immunogenic potential, and can grow and differentiate easily. Furthermore, it carries a minimal risk for infections.
In 2013, two studies exhibited that it is possible to get cells with cytokeratin 19 (CK19) expression and hair-like structures from WJMSC in vitro. CK19 is a marker of bulge stem cells which reflects the regeneration capability of altered skin.[14],Yoo et al. analyzed the impact of human Wharton's jelly stem cell (hWJSC) on faster wound healing and the growth of hair follicles. Enriched hWJSC cells were able to create new hair follicles. Growth factors may be added to the culture medium, such as hepatocyte growth factor which enhances hair follicle growth, basic fibroblast growth factor (bFGF) which enhances DPC growth, and VEGF which also enhances hair follicle growth.
In addition, the effects of bone marrow and umbilical cord stem cells to dermal papilla-like tissue growth were examined. Cells of the outer sheath of the hair were utilized for incubation and infused into the skin of mice. The mice were then studied after 6 weeks. Accordingly, hair follicle development was observed.Wu et al. showed that the potential for hMSC from human embryos to DPCs in hMSC cultures utilizing DPCs acquired from patients. Versican, CD133, stem cell factor, endothelin-1, and fibroblast growth factor expressions were seen during differentiation. Li et al. in 2015 have previously described a new type of stem cell from human umbilical cord blood which is known as cord blood-derived multipotent stem cell (CB-SC). CB-SCs are different from other types of stem cells functionally and genetically such as monocyte-derived stem cells hematopoietic stem cells, endothelial progenitor cells (EPCs), and mesenchymal stem cells (MSCs). According to the authors, clinical data have demonstrated that a single treatment was able to provide balanced immune responses that allowed the regeneration of hair cells. Their study focused on the therapeutic potential of Stem Cell Educator therapy in alopecia areatapatients [15]. The authors created a Stem Cell Educator therapy, wherein patient's blood is circulated through a closed-loop system that could separate mononuclear cells from whole blood further allowing cells to briefly interact with human CB-SCs and to return the “educated” cells to the patient's blood circulation. The results showed that patients with severe alopecia areata achieved improved hair regrowth and quality of life after they received Stem Cell Educator therapy. Immunohistochemistry revealed the formation of a “ring of transforming growth factor-beta 1” around hair follicles, leading to the restoration of immune balance in the hair follicles and the protection of newly created hair follicles against destruction by the body's own cells. The hair follicle is an interesting organ. The application of stem cells in hair regeneration is promising because these stem cells can lead to follicle regeneration. Stem cell regeneration for the

treatment of nonautoimmune hair loss such as androgenetic alopecia or FPHL is very feasible for various reasons. Although an autologous transplant is viewed as the standard, its use is limited because of a lack of data and the diminished viability of cells that are made available using this method. ADSCs are easy to obtain, are multipotent, and can easily differentiate into different cell lines, along with their significant potential for angiogenesis. More studies are needed to establish the efficacy of the various types of stem cell-based treatments for people with hair loss.

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BLACK SEA
SCIENTIFIC JOURNAL OF ACADEMIC RESEARCH
ISSN: 1987 - 6521, E – ISSN: 2346 – 7541
JANUARY-MARCH 2020 VOLUME 53 ISSUE 02

CELL THERAPY AND DERMATOLOGY

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ABSTRACT

The stem cells are undifferentiated cells capable of generating, sustaining, and replacing terminally differentiated cells and tissues. They can be isolated from embryonic as well as almost all adult tissues including skin, but are also generated through genetic reprogramming of differentiated cells. Preclinical and clinical research has recently tremendously improved stem cell therapy, being a promising treatment option for various diseases in which current medical therapies fail to cure, prevent progression or relieve symptoms. This review summarizes general aspects as well as current and future perspectives of stem cell therapy in dermatology.
Keywords: cells capable, replacing terminally, differentiated cells.

Stem cells generally have two major characteristics that they can give rise to specialized cell lineages or cells and are capable of self-renewing for long periods. Traditionally, stem cells can be categorized into two different groups, embryonic stem cells and somatic stem cells. Embryonic stem cells are obtained from the inner cell mass of blastocyst in mammalian embryos. Embryonic stem cells are pluripotent; therefore, they have the potential to derive progeny cells belonged to all three germ layers including ectoderm, endoderm and mesoderm. Unlike embryonic stem cells, somatic stem cells are typically found in mature organs or tissues. Some somatic stem cells might be multipotent but majority of them are lineage limited, i.e. hematopoietic stem cells can only give rise to mature blood cells, whereas neural stem cells can only divide into neuronal and glial cells, differentiated, adult somatic cells can be reprogrammed to generate induced pluripotent stem cells (iPSCs), and now iPSCs become a new emerging group of stem cells[1]. The reprograming is achieved by exogenous addition of four transcription factors (Oct-3/4, Sox2, c-Myc, and Klf4) using retroviral transduction. IPSCs have been shown to be pluripotent and can give rise to a wide range of mature cell types.
Skin stem cells as well fall into the classification as somatic stem cells, however, due to the cellular heterogeneity of skin, various types of skin stem cells were found in past decades.
Recently, significant advances have been made in identifying different types of skin stem cells with the aid of molecular tools.

Subgroups of skin stem cells are listed as below:

Stem cell therapies are at the forefront of regenerative aesthetic medicine. Multipotent stem cells and induced pluripotent stem cells (iPSCs), progenitor cells that result from the dedifferentiation of specialized adult cells, have demonstrated promise in tissue regeneration for a wide range of dermatologic conditions and aesthetic applications. Herein, the potential of stem cells as a new frontier in aesthetic dermatology.
Regenerative medicine encompasses innovative therapies that allow the body to repair or regenerate aging cells, tissues, and organs. The skin is a particularly attractive organ for the application of novel regenerative therapies due to its easy accessibility [2]. Among these therapies, stem cells and platelet-rich plasma (PRP) have garnered interest based on their therapeutic potential in scar reduction, antiaging effects, and treatment of alopecia.
Stem cells possess the cardinal features of self-renewal and plasticity. Self-renewal refers to symmetric cell division generating daughter cells identical to the parent cell. Plasticity is the ability to generate cell types other than the germ line or tissue lineage from which stem cells derive [3]. Stem cells can be categorized according to their differentiation potential. Totipotent stem cells may develop into any primary germ cell layer (ectoderm, mesoderm, endoderm) of the embryo, as well as extraembryonic tissue such as the trophoblast, which gives rise to the placenta. Pluripotent stem cells such as embryonic stem cells have the capacity to differentiate into any derivative of the 3 germ cell layers but have lost their ability to differentiate into the trophoblast.
Adults lack totipotent or pluripotent cells; they have multipotent or unipotent cells. Multipotent stem cells are able to differentiate into multiple cell types from similar lineages; mesenchymal stem cells (MSCs), for example, can differentiate into adipogenic, osteogenic, chondrogenic, and myogenic cells. Unipotent stem cells have the lowest differentiation potential and can only self-regenerate. Herein, we review stem cell sources and their therapeutic potential in aesthetic dermatology.

Multipotent stem cells derived from the bone marrow, umbilical cord, adipose tissue, dermis, or hair follicle bulge have various clinical applications in dermatology [4]. Stem cells from these sources are primarily utilized in an autologous manner in which they are processed outside the body and reintroduced into the donor. Autologous multipotent hematopoietic bone marrow cells were first successfully used for the treatment of chronic wounds and show promise for the treatment of atrophic scars. However, due to the invasive nature of extracting bone marrow stem cells and their declining number with age, other sources of multipotent stem cells have fallen into favor.

Umbilical cord blood is a source of multipotent hematopoietic stem cells for which surgical intervention is not necessary because they are retrieved after umbilical cord clamping. Advantages of sourcing stem cells from umbilical cord blood includes high regenerative power compared to a newborn's skin and low immunogenicity given that the newborn is immunologically immature.

Another popular source for autologous stem cells is adipose tissue due to its ease of accessibility and relative abundance. Given that adipose tissue–derived stem cells (ASCs) are capable of differentiating into adipocytes that help maintain volume over time, they are being used for midface contouring, lip augmentation, facial rejuvenation, facial scarring, lipodystrophy, penile girth enhancement, and vaginal augmentation. Adipose tissue–derived stem cells also are capable of differentiating into other types of tissue, including cartilage and bone[5]. Thus, they have been successfully harnessed in the treatment of patients affected by systemic sclerosis and Parry-Romberg syndrome as well in the functional and aesthetic reconstruction of various military combat–related deformities.

Adipose tissue–derived stem cells are commonly harvested from lipoaspirate of the abdomen and are combined with supportive mechanical scaffolds such as hydrogels. Lipoaspirate itself can serve as a scaffold for ASCs. Accordingly, ASCs also are being utilized as a scaffold for autologous fat transfer procedures in an effort to increase the viability of transplanted donor tissue, a process known as cell-assisted lipotransfer (CAL). In CAL, a fraction of the aspirated fat is processed for isolation of ASCs, which are then recombined with the remainder of the aspirated fat prior to grafting. However, there is conflicting evidence as to whether CAL leads to improved graft success relative to conventional autologous fat transfer.

The skin also serves as an easily accessible and abundant autologous source of stem cells. A subtype of dermal fibroblasts has been proven to have multipotent potential. These dermal fibroblasts are harvested from one area of the skin using punch biopsy and are processed and reinjected into another desired area of the skin. Autologous human fibroblasts have proven to be effective for the treatment of wrinkles, rhytides, and acne scars[6].

In June 2011, the US Food and Drug Administration approved azficel-T, an autologous cellular product created by harvesting fibroblasts from a patient's own postauricular skin, culture-expanding them in vitro for 3 months, and reinjecting the cells into the desired area of dermis in a series of treatments. This product was the first personalized cell therapy approved by the US Food and Drug Administration for aesthetic uses, specifically for the improvement of nasolabial fold wrinkles[7].

In adults, hair follicles contain an area known as the bulge, which is a site rich in epithelial and melanocytic stem cells. Bulge stem cells have the ability to reproduce the interfollicular epidermis, hair follicle structures, and sebaceous glands, and they have been used to construct entirely new hair follicles in an artificial in vivo system.

Hair follicle epithelium and interfollicular epidermis can be regenerated using cultured bulge stem cells. The cultured bulge stem cells were mixed with dermal papilla cells from neonatal rat vibrissae and engrafted into a silicone chamber implanted on the backs of severe combined immune deficient (SCID) mice. The grafts exhibited tufts of hair as well as a complete interfollicular epidermis at 4 weeks after transplantation. Thus, these bulge stem cells have the potential to treat male androgenic alopecia and female pattern hair loss. Bulge stem cells also have been shown to accelerate wound healing [8]. Additionally, autologous melanocytic stem cells located at the hair follicle bulge are effective for treating vitiligo and are being investigated for the treatment of hair graying.

The regenerative capacity of keratinocytes and fibroblasts from human skin has created new opportunities to develop cell-based therapies for patients. Cultured cells and bioengineered skin products are being used to treat patients with inherited and acquired skin disorders associated with defective skin, and further clinical trials of new products are in progress.

The capacity of extracutaneous sources of cells such as bone marrow is also being investigated for its plasticity in regenerating skin, and new strategies, such as the derivation of inducible pluripotent stem cells, also hold great promise for future cell therapies in dermatology. The future directions relating to cell therapy in dermatology are dedicated particularly for inherited skin diseases associated with fragile skin and poor wound healing.

One of the key functions of skin is to provide a mechanical barrier against the external environment. In several inherited and acquired dermatological disorders, however, this resilience is broken. Loss of a functional epidermis can have profound biological and clinical consequences including loss of water and electrolytes, cutaneous and systemic infections, as well as impaired thermoregulation [9]. Epidermal failure can occur from burns, trauma, and adverse drug reactions. Several inherited diseases associated with inherent mechanical weaknesses in epidermal or dermal structural proteins can all be associated with extensive skin wounds and chronic erosions. Ulceration of the skin caused bycommon pathologies such as venous hypertension, arterial impairment, diabetes mellitus, or neuropathies creates an enormous

ISSN: 1987 - 6521, E – ISSN: 2346 – 7541
JANUARY-MARCH 2020 VOLUME 53 ISSUE 02

clinical and health economic burden. Therapeutic interventions to restore an intact epithelium and recover skin function have therefore been an important long-term focus of both traditional and translational medicine, and one in which a number of key advances and clinical benefits have occurred in recent years. The cellular therapy to repair or restore a defective epithelium and possibly deeper skin layers represents an attractive area of translational research that could have significant health benefits for many people. The development and application of cell therapy in dermatology, with a special focus on inherited skin disorders in which chronic ulceration has a major impact on quality of life. The main emphasis of the text is on recent clinical studies as well as new and emerging strategies that can exploit and harness the regenerative potential of human cells to restore skin tissue, although an overview of the clinical applications of cell therapy across a range of skin diseases is under study. With regard to the focus of this research topic, it is hoped that cell therapy lessons learned from studies on rare skin diseases will also be relevant to improving future healthcare of patients with more common disorders associated with different kind and type of skin diseases[10].

There remain some differences in skin composition between ethnic groups, e.g. the stratum corneum structure. Investigations on transepidermal water loss in patients of different types of skin have unfortunately reported conflicting results. However, when collectively interpreting all available data, most studies indicate differences between ntypes of the skin. The findings have important implications for the ability of different skin types to endure and recover from exogenous insults, absorb topical therapeutic agents and maintain moisture under various physiological conditions.

Topical dermatological formulations aim to deliver therapeutically effective concentration of drugs to the skin layers, which are also the target site. The barrier function of skin is mostly mediated by the stratum corneum. The stratum corneum consists of 15–20 layers of acutely flattened, metabolically inactive, polygonal cells. The process of drug or chemical absorption into the skin is influenced by several factors. These include molecular size, lipophilicity, pH of formulation, penetrant concentration, temperature and formulation compositions among others. Although differences in morphology and physiology do not fully determine differences in efficacy and safety, variability between ethnic groups warrants further study.

Besides, skin contains all the major enzymes found in the liver and other tissues capable of catalyzing a number of metabolic reactions.

Metabolism of topically applied compounds results in altered pharmacological and toxicological effects.

There are a number of chemical groups that are particularly susceptible to skin metabolism, including alcohols, acids, primary amines and esters, among others. Thus, the skin has unique and complicated dermatokinetics similar to pharmacokinetics in plasma.

Assessment of the dermatokinetics of topical dermatological formulations is of utmost importance in assessing the safety and efficacy of dermatological products. Numerous approaches are reportedly being used to determine the real-time measurement of molecules in the skin layers. Regulatory agencies, such as the U.S. FDA, are still exploring different techniques for characterizing drug dermatopharmacokinetics. Certain dermatological products applied to the skin surface may penetrate into deeper tissue layers and reach the systemic circulation. The issue of efficacy must also be considered.

RESULT

As to the stem cell therapy on skin, although initially most clinical trials were mainly designed as autologous engraftment, nowadays already some of them aimed for allogeneic indications. Similar to the topical formulations applied in the dermatological fields, reviewing policies should be more dedicated on potential safety concerns, especially on ethnic bridging issues as mentioned above. Based upon the differences in morphology and physiology between different types of the skin, the possible variation in efficacy and/or safety of allogeneic skin cell products should not be ignored

Therefore, both regulatory bodies and pharmaceutic companies should work together to set the standard bridging criterion for skin stem cell products, especially those of allogenic indications. The best solution will be always to enroll adequate numbers of non-Caucasian subjects into future clinical trials. For developing ideal medications, we definitely have to verify the characteristics of proposed skin stem cell products and clarify the differences in efficacy and safety across different races, hence to actually promote public health.

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BLACK SEA
SCIENTIFIC JOURNAL OF ACADEMIC RESEARCH
ISSN: 1987 - 6521, E – ISSN: 2346 – 7541
JANUARY-MARCH 2020 VOLUME 53 ISSUE 02

PHARMACEUTICAL AGENTS-MEDIATED LIVER TOXIC DAMAGE AND OBESITY

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ABSTRACT

Studies have shown that drug-induced liver injury, which involves the parent drug or a reactive metabolite generated through cytochromes P450, Microvesicular steatosis, a potentially severe liver lesion usually associated with liver failure and profound hypoglycemia, is due to a major inhibition of mitochondrial fatty acid oxidation (FAO). Moreover, recent investigations suggest that some drugs could favor lipid deposition in the liver through primary alterations of white adipose tissue (WAT) homeostasis. Numerous factors could favor drug-induced mitochondrial and metabolic toxicity, such as the structure of the parent molecule, genetic predispositions (in particular those involving mitochondrial enzymes), alcohol intoxication, hepatitis virus C infection, and obesity. In obese and diabetic patients, some drugs may induce acute liver injury more frequently.
World many countries are facing an epidemic of obesity that can be explained, at least in part, by a sedentary life style and calorie overconsumption. This poses a major issue for public health since obesity primarily enhances the risk of various illnesses such as type 2 diabetes, coronary heart disease, some cancers and non-alcoholic fatty liver disease (NAFLD). Consequently, obese patients are consuming on average more drugs than non-obese individuals, some medications in obese individuals can cause severe liver damage [1].
Keywords: microvesicular steatosis, profound hypoglycaemia, alcohol intoxication.

There is limited sensitivity of non-invasive testing in the diagnosis of NAFLD, and generally speaking, a liver biopsy is required for confirmation. Thus, the prevalence of NASH in a general population has been difficult to estimate. In a 1977 study, steatosis was noted in 24% of random patients who died in motor vehicle accidents, and NASH was present in 2.4%. In 1990, using histological guidelines, NASH was found on autopsy in 6.3% of 351 non-alcoholic, obese, and nonobese patients. In 2011, Williams et al noted an astounding prevalence of biopsy-proven NASH of 12.2% in a group of random volunteers at an army base.
Overall, the prevalence of NASH in Western populations appears to be between 3% and 10%. Initial studies had suggested a female predominance of NASH, with women accounting for 60%–83% of diagnoses. Subsequent study of morbidly obese patients pointed to a male predominance of NASH [2]. However, more recent data suggest that men and women may be affected equally Ethnicity has been noted to be a factor in the United States, with higher prevalence of NAFLD in Hispanics (45%) compared with whites (33%) and African Americans (24%).
The prevalence of NASH is also likely to be higher in Hispanics, assuming similar rates of progression from NAFLD to NASH across ethnic groups. Albeit obesity rates are highest in the Hispanic population, obesity does not explain the higher prevalence of NAFLD in the white population compared to African Americans.
Obesity has been documented to have a strong association with NASH and NAFLD. Some of the earliest reports of the two have been described in cohorts of obese patients [3]. NASH has been found in up to 36% of patients with morbid obesity undergoing weight loss surgery. The strongest association of NASH is with central and not overall obesity, and some individuals, labelled as “nonobese” NAFLD on the basis of BMI, have been found to have central obesity.
Accordingly, central obesity, determined by a waist-to-hip ratio, is strongly associated with insulin resistance and has been added to the diagnostic criteria of the metabolic syndrome (Adult Treatment Panel [ATP] III guidelines; . That said, obesity is by no means necessary for NAFLD/NASH to occur, as noted by Wanless and Lentz,**4** who found steatohepatitis in 2.7% of lean individuals.
Disorders of glucose metabolism, including type 2 diabetes mellitus (type 2 DM), hyperglycemia, and glucose intolerance, have a strong association with NAFLD and confer an independent risk for the development of steatohepatitis, a risk that is further amplified by the presence of obesity[4]. Diabetes mellitus, hyperglycemia, and insulin resistance have been described as ranging from 20%–75% of adults with NASH to as high as 91% in some study groups.
Central obesity, as outlined above, is an independent risk factor for insulin resistance and, as such, can be considered a contributing factor to the formation of NASH.
Dyslipidemia (hypertriglyceridemia, hypercholesterolemia, or both) has been reported in 20%–92% of patients with NAFLD.
Most of these patients had other components of the metabolic syndrome, highlighting the importance of diagnosing the metabolic syndrome and its effect on NASH.

NAFLD has been associated with multiple other conditions such as surgical interventions, medications, and metabolic diseases. NASH was observed in obese patients who underwent a jejunoileal bypass (J-I bypass), a once-popular weight loss surgery. This group of patients is particularly prone to progressive liver disease and cirrhosis. Subsequently, the procedure has been abandoned because of the association with liver failure, and reversal of the operation has been recommended. NAFLD has also been described in patients with other surgical procedures, including extensive small bowel resection, gastroplasty, and biliopancreatic diversion.

Small intestinal bacterial overgrowth and diverticulosis have been found in a higher prevalence in NASH patients.

Acute starvation, rapid weight loss, and hypothyroidism are associated with NASH. NASH also has been noted in patients with rare errors of metabolism such as abetalipoproteinemia and Wilson disease, and hepatic steatosis is a feature of Weber-Christian syndrome.

The liver, located between the absorptive surface of the gastrointestinal tract and drug targets throughout the body, is central to the metabolism of virtually every foreign substance. Most drugs and xenobiotics are lipophilic, enabling them to cross the membranes of intestinal cells. Drugs are rendered more hydrophilic by biochemical processes in the hepatocyte, yielding water-soluble products that are excreted in urine or bile.This hepatic biotransformation involves oxidative pathways, primarily by way of the cytochrome P-450 enzyme system.[6] After further metabolic steps, which usually include conjugation to a glucuronide or a sulfate or glutathione, the hydrophilic product is exported into plasma or bile by transport proteins located on the hepatocyte membrane, and it is subsequently excreted by the kidney or the gastrointestinal tract[2,4].

Mitochondrial dysfunction is a major mechanism of liver injury. A parent drug or its reactive metabolite can trigger outer mitochondrial membrane permeabilization or rupture due to mitochondrial permeability transition. The latter can severely deplete ATP and cause liver cell necrosis, or it can instead lead to apoptosis by releasing cytochrome *c*, which activates caspases in the cytosol.

Necrosis and apoptosis can trigger cytolytic hepatitis resulting in lethal fulminant hepatitis in some patients. Other drugs severely inhibit mitochondrial function and trigger extensive microvesicular steatosis, hypoglycaemia, coma, and death. Milder and more prolonged forms of drug-induced mitochondrial dysfunction can also cause macrovacuolar steatosis. Although this is a benign liver lesion in the short-term, it can progress to steatohepatitis and then to cirrhosis.

Patient susceptibility to drug-induced mitochondrial dysfunction and liver injury can sometimes be explained by genetic or acquired variations in drug metabolism and/or elimination that increase the concentration of the toxic species (parent drug or metabolite).

Susceptibility may also be increased by the presence of another condition, which also impairs mitochondrial function, such as an inborn mitochondrial cytopathy, β-oxidation defect, certain viral infections, pregnancy, or the obesity-associated metabolic syndrome.

Liver injury due to mitochondrial dysfunction can have important consequences for pharmaceutical companies. It has led to the interruption of clinical trials, the recall of several drugs after marketing, or the introduction of severe black box warnings by drug agencies.

Pharmaceutical companies should systematically investigate mitochondrial effects during lead selection or preclinical safety studies [5].

Nowdays sedentary life style, consumption of junk food and excessive caloric consumption is leading to one of the world health society challenges, to the Obesity [1]. This could pose another medical issue, in particular for hepatologists, since many drugs are able to induce liver injury.

Moreover, there is growing evidence that obesity and NAFLD can increase the risk of drug-induced liver injury (DILI), at least for some drugs. Thus, obese patients could be more prone to develop DILI as a consequence of drug overconsumption and an intrinsic susceptibility of their diseased liver to drug-induced hepatotoxicity.

Actually, DILI in obese patients could occur as two distinct clinical settings. Indeed, in the context of obesity and related metabolic diseases, some drugs seem to aggravate pre-existing NAFLD whereas others could induce more frequently an acute hepatitis.

Drugs that could aggravate NAFLD in obese patients are tamoxifen, irinotecan, methotrexate and nucleoside reverse transcriptase inhibitors (NRTIs) such as stavudine and didanosine.

Aggravation of NAFLD has also been documented in different animal models with rosiglitazone, tetracycline, phenobarbital and pentoxifylline.

Drugs that could induce acute liver injury more often in obese individuals are the volatile halogenated anesthetic halothane and isoflurane, acetaminophen(APAP), and other drugs such as losartan, ticlopidine and omeprazole. However, it is noteworthy that the list of drugs in temporary and should expand in the future as DILI in the context of obesity is gaining growing attention.

Since these mechanisms have mostly been discovered during experimental studies, any extrapolation to humans should be done with caution.

ISSN: 1987 - 6521, E – ISSN: 2346 – 7541
JANUARY-MARCH 2020 VOLUME 53 ISSUE 02

Drug-induced worsening of NAFLD could be explained by different mechanisms. Regarding fatty liver, some drugs could be able to stimulate lipogenesis in steatotic liver, but not in normal liver, by activating lipogenic transcription factors such as peroxisomeproliferator is activated receptor-γ (PPARγ) (e.g. rosiglitazone), pregnane X receptor (e.g. tamoxifen) and carbohydrate response element-binding protein (e.g. pentoxifylline). Because numerous drugs are able to alter mitochondrial function [2,5], it is conceivable that impaired mitochondrial fatty acid oxidation (mtFAO) could also be involved in drug-induced aggravation of fatty liver.

Importantly, increased FAO during NAFLD is a key adaptive mechanism in order to restrain fat accretion, and thus any impediment to this adaptation could significantly aggravate fatty liver. Reduced VLDL secretion could be involved, as several drugs were shown to interfere with VLDL synthesis by inhibiting microsomal triglyceride transfer protein (MTP) activity (e.g. amiodarone, tianeptine) or apolipoprotein B-100 synthesis (e.g. mipomersen). Some drugs are also able to induce oxidative stress, which can trigger the progression of simple steatosis to non-alcoholic steatohepatitis (NASH).

Drug-induced oxidative stress could have several origins, in particular through glutathione (GSH) depletion and inhibition of the mitochondrial respiratory chain (MRC).

The pre-existent reduction of GSH levels and MRC activity in NAFLD could prime drug-induced oxidative stress and accelerate the progression of fatty liver to NASH.

Unlike ethanol overconsumption, which is known to aggravate NAFLD, it is still unknown whether drugs able to aggravate NAFLD can stimulate the production of proinflammatory and fibrogenic cytokines such as TNFα and TGFβ, respectively.

It is worth mentioning that drug-induced aggravation of NAFLD can also be secondary to the worsening of insulin resistance (IR), a key mechanism leading to hepatic lipid deposition.

Indeed, worsening of IR exacerbates not only hepatic lipogenesis secondary to hyperinsulinemia but also the delivery of free fatty acids (FFA) to the liver due to adipose triacylglycerol hydrolysis.

Drugs known to trigger (or worsen) IR are, for instance, synthetic corticosteroids, antipsychotic drugs (e.g. clozapine, olanzapine), NRTIs, protease inhibitorsand thiazide diuretics (e.g. hydrochlorothiazide).

Higher risk of drug-induced acute hepatitis in obesity could be related to increased activity of several cytochromes P450 (CYPs), which could enhance the generation of toxic metabolites.

Indeed, increased activity of several CYPs such as CYP1A2, CYP2C9, CYP2D6and CYP2E1 has been documented in obese individuals. Higher CYP2E1 activity could explain why drugs such as halothane and APAP seem to be more hepatotoxic in the context of obesity and NAFLD since CYP2E1 transforms these drugs into the highly reactive metabolites trichloroacetyl chloride and N-acetyl-*p*-benzoquinone imine (NAPQI), respectively.

When generated in excess, these reactive metabolites can induce hepatic oxidative stress, severe mitochondrial dysfunction and cytolysis.

It is noteworthy that higher risk of APAP-induced acute liver injury in obese individuals with NAFLD is mostly suspected in the context of APAP overdose, although therapeutic doses of this pain killer could also be involved.

Another mechanism that could explain higher risk of drug-induced acute hepatitis in obesity is reduced levels of GSH, in particular at the mitochondrial level, which could impair the removal of CYP-generated reactive metabolites.

Because obesity is associated with reduced activity of some CYPs such as CYP3A4, higher risk of acute hepatitis is not expected with all drugs able to generate toxic metabolites.

Moreover, enhanced glucuronosyltransferase activity seems to be common in obesity, which may favor the detoxication of some compounds.

Finally, it is also noteworthy that under-dosing is expected with drugs whose dosage is not adapted to higher body mass index.

Clearly, more investigations are needed in order to decipher the mechanisms whereby some drugs are more toxic on the obese liver.

From a clinical viewpoint, a better identification of the drugs presenting such harmful effects is urgently warranted. This should prompt physicians to carry out a regular monitoring of liver function in obese patients treated with these drugs in order to detect any deterioration of the pre-existing NAFLD, or the occurrence of acute hepatitis.

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BLACK SEA
SCIENTIFIC JOURNAL OF ACADEMIC RESEARCH
ISSN: 1987 - 6521, E – ISSN: 2346 – 7541
JANUARY-MARCH 2020 VOLUME 53 ISSUE 02

SKIN PROTECTANT CELLULAR AND INTRACELLULAR EFFECTS OF MELATONIN

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ABSTRACT

The environmental factors as radiation, physical injuries, chemicals, pollution, and microorganisms, the skin requires protective chemical molecules and pathways. Melatonin, a highly conserved ancient molecule, plays a crucial role in the maintenance of skin. As human skin has functional melatonin receptors and also acts as a complete system that is capable of producing and regulating melatonin synthesis, melatonin is a promising candidate for its maintenance and protection. Below, we review the studies of new metabolic pathways involved in the protective functions of melatonin in dermal cells. We also discuss the advantages of the topical use of melatonin for therapeutic purposes and skin protection. In our view, endogenous intracutaneous melatonin production, together with topically-applied exogenous melatonin and its metabolites, represent two of the most potent defense systems against external damage to the skin.
Keywords: protective chemical molecules and pathways, functional melatonin receptors.

The pineal gland secretes melatonin into the blood circulation to exert a range of well-documented physiological functions. Classical chronobiology considers melatonin exclusively a hormone that regulates the circadian day–night rhythm and seasonal biorhythms. At least in part, these effects of melatonin are indirectly mediated by coupling to other endocrine systems, whose output/signalling activity is modulated by the photoperiod-dependent pineal secretion of melatonin. Additionally, currently recognized physiological melatonin activities in the mammalian system include the modulation of immune defense responses, body weight and reproduction, tumor growth inhibitory and anti-jet-lag effects [1].

Independent of these effects, melatonin exerts many direct, receptor-independent activities, acting for example as a potent direct antioxidant, as a chemotoxicity reducing agent and a putative anti-aging substance Melatonin is a highly lipophilic substance that easily penetrates organic membranes and therefore is able to protect important intracellular structures including mitochondria and DNA from oxidative damage directly at the sites where such damage occurs.

Intriguingly, melatonin also up-regulates gene expression and activity of several antioxidative enzymes such as Cu/Zn-superoxide dismutase (CuZn-SOD), Mn-superoxide dismutase (Mn-SOD), catalase and glutathione peroxidase (GPx)[2]. Thus, melatonin not only acts as a potent antioxidant itself, but also is capable of activating an entire endogenous enzymatic protective system against oxidative stress t is now evident that the physiological level of melatonin has to be defined individually for each tissue, since the body liquids, tissues or organs mentioned above reveal melatonin levels which are 10- to 1000-fold higher than plasma melatonin concentrations which formerly might have been considered as ‘pharmacological’. However, this observation throughout several completely different body compartments is highly suggestive for local tissue-specific melatonin synthesis since plasma levels would be too low to build this high tissue levels[3]. Therefore, the presence of tissue-specific, local melatoninergic systems have been suggested that would have the biological role of counteracting specific, tissue-related regional stressors exactly at the place where they occur.

In fact, such a melatoninergic antioxidative system (MAS) has been discovered recently in a highly differentiated manner in the skin Since changes in skin and coat phenotype/function represent a major form of mammalian adaptation to changing environmental challenges, it is not surprising that melatonin – the major neuroendocrine regulator that couples photoperiod changes to complex endocrine responses – impacts on mammalian skin physiology. In fact, indications that melatonin is involved in the regulation of seasonal hair growth and pigmentation can already be traced back several decades[4]. For example, in several mammalian species, melatonin can alter wool and cashmere production, the development and frequency of pelage cycling and seasonal moulting as well as coat colour.

While the effects of melatonin on hair follicle biology have long been most obvious, yet are still insufficiently understood. This should not detract from the accumulating body of evidence that melatonin’s functions in skin biology and skin pathology extend far beyond the modulation of hair growth and/or pigmentation. A few examples may suffice to illustrate this wide range of – at times, seemingly contradictory – functions.

Melatonin suppresses apoptosis and stimulates growth in both serum-starving HaCaT keratinocytes and serum-free-cultured fibroblasts. In contrast, the growth of serum-supplemented HaCaT keratinocytes is inhibited by melatonin at low concentrations, whereas very high concentrations of melatonin (4–20 × 10^{-6} MOL) were found to stimulate cell growth under the same serum-supplemented culture condition.

Strikingly, pinealectomized (i.e. melatonin-deficient) rats have been reported to show markedly reduced back, abdominal and thoracic skin thickness, along with an increase of lipid peroxidation and a decrease in the number of dermal papillae

and hair follicles as well as of antioxidative enzymes (CAT, GPx). Melatonin substitution to these rats reportedly restored skin thickness, reduced lipid peroxidation and enhanced antioxidative enzyme activity These results were later supplemented by the same group by ultrastructural evidence: compared to unsubstituted animals, melatonin-treated, pinealectomized rats showed reduced cytological atypia, decrease of nuclear irregularity, normalization of tonofilament distribution and mitochondrial integrity as well as of dermal collagen fibre structure[4].

Collagen synthesis is controlled by proline hydroxylase which uses superoxide anion radical as the specific substrate together with L-proline yielding hydroxyproline on the precollagens. The removal of the ROS superoxide anion radical by melatonin would therefore prevent collagen synthesis. This corresponds well to the finding that melatonin also protects against pressure-induced ulcer formation in rat skin, as reflected by reduced lipid peroxidation, tissue neutrophil infiltration, along with increased glutathione (GSH) levels and reduced degenerative skin changes. One of many arguments that advocate the administration of melatonin as a therapeutic adjuvant in burns patients is that skin damage induced by thermal injury is reduced by melatonin, likely by limiting oxidative damage[5]. Oxidative damage is also a key pathogeneic element in skin flap necrosis after plastic surgery: in pinealectomized rats, skin flaps of melatonin-treated animals exhibited reduced lipid peroxidation, nitric oxide formation and ratio of skin flap necrosis, along with increasing levels of GSH, GPx and superoxide dismutase (SOD) compared to non-melatonin-treated rats.

Clinically, topically applied 0.5% melatonin reduces UV-erythema when administered before, but not when applied after UV-irradiation. This was confirmed by another group showing that not only melatonin but also other antioxidants (vitamin E and vitamin C) have no effect on UV-erythema when administered after UV-irradiation, irrespective of the time course of application.

Associated immunological skin responses, as exemplified by UV-induced suppression of the Mantoux response, are also not inhibited by melatonin when applied after UV-exposure. This indicates that the UV-induced free radical formation in skin is an immediate event which can only be antagonized by antioxidants that are already present at the target sites and at the time point of UV-exposure.

The antioxidant and DNA repair properties of melatonin raise the theoretical possibility that it may also prevent or reduce cutaneous photo-aging. In healthy skin, melatonin reduces the collagen accumulation, an indicator of skin aging. Melatonin also inhibits chemically induced carcinogenesis in rat skin, represented by reduction of the number of benzo(a)pyrene-induced papillomas; this is paralleled by attenuated lipid peroxidation and prevention of the binding of benzo(a)pyrene or its metabolites to DNA [6].Indeed, melatonin treatment reportedly reduced benzo(a)pyrene-induced tumor frequency by 30% in mice. Melatonin may also play a role in the thermoregulatory control of human skin blood flow, at least in healthy males.

A few selected aspects of melatonin's proposed role as a major skin protectant deserve to be discussed in more detail, since they are of particular clinical and/or pharmaceutical interest. The photo-induced melatonin metabolism leading to the generation of antioxidant melatonin metabolites in human keratinocytes represents an antioxidative cascade which has been described earlier for chemical or other tissue homogenate systems and has now been identified in the skin to protect this important barrier organ against UVR-induced oxidative stress-mediated damaging events on DNA subcellular, protein and cell morphology level. This newly identified MAS of the skin likely extends to skin compartments beyond the epidermis, namely to the dermis and the hair follicle, and may have evolved as a defense mechanism against the multi-facetted threats of environmental stress, especially UVR, to which the skin is life-long exposed.

The UV-induced melatonin metabolites, especially AFMK, are themselves potent antioxidants . ROS – mainly the hydroxyl radical – occurring under UV-irradiation in the skin react directly with melatonin. The latter is either autonomously produced in epidermal and/or hair follicle keratinocytes where it engages in intracrine signalling/interactions or released into the extracellular space to regulate auto-, para- or endocrine signalling. The reaction of melatonin with hydroxyl radicals induces the formation of 2-OH-melatonin and 4-OH-melatonin which are then further metabolized to AFMK and by arylamine formamidase or catalase to AMK[7]. During this process, hydroxyl radicals are scavenged, and resulting damaging events are either indirectly or directly reduced via decrease of lipid peroxidation, protein oxidation, mitochondrial damage and DNA damage.

For application in clinical dermatology, exogenous melatonin should rather be used topically than orally, since orally administered melatonin appears in rather low levels in the blood due to prominent first-pass degradation in the liver, thus limiting skin access.

Topical administration circumvents this problem. In addition, as we could show in our own investigations, melatonin can penetrate into the stratum corneum and build there a depot due to its distinct lipophilic chemical structure.

Therefore, endogenous intracutaneous melatonin production, together with topically applied exogenous melatonin, can be expected to provide the most potent defense system against cutaneous photodamage and multiple other pathologic conditions that produce oxidative stress (e.g. in chronic skin inflammation, such as atopic dermatitis)

In chemotherapy-induced damage, melatonin significantly reduces cisplatin-induced testicular toxicity in rats. Also, amicacin- or cisplatin-induced nephrotoxicity in rats is prevented by melatonin through enhancement of the GSH (reduced glutathione)/GSSG (oxidized glutathione) ratio, reduction of lipid peroxidation and restoration of the enzymatic antioxidant

ISSN: 1987 - 6521, E – ISSN: 2346 – 7541
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GPx. In primary rat renal tubular cisplatin-treated epithelial cells, melatonin exerts its protective effects via scavenging ROS and reducing DNA fragmentation, much stronger than its precursors or metabolites such as tryptophan, serotonin or 6-hydroxymelatonin[8]. Melatonin also protects against doxorubicin-induced cardiotoxicity in rats by stimulating the activity of antioxidative enzymes (CAT, GSH), reducing lipid peroxidation and protecting against mitochondrial damage.
This suggests that melatonin can potently protect against chemotherapy-induced damage through different biological mechanisms in a number of organs. Unfortunately, this has not yet been investigated in a dermatological context.
Melatonin may even protect the skin against the highly destructive effects of IR. The skin ranks among the chief target tissues for the well-recognized undesired effects of IR (years, while SCC development is strongly correlated with IR in combination with cumulative UV-irradiation exposure[9], with basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) representing the most common IR-induced skin malignancies. BCC specially develops when IR occurs before the age of 20). The molecular precondition for IR-induced skin cancer development is severe and widespread DNA damage, predominantly due to IR-mediated hydroxyl radical generation.
Hydroxyl radicals are a result of IR-induced radiolysis of water, leading to formation of oxidized bases, DNA–DNA intrastrand adducts, DNA single- and double-strand breaks and DNA–protein cross-linking which all lead to genomic instability, a prerequisite for tumor promotion and development .
Since melatonin is a highly efficient hydroxyl radical scavenger, it is not unexpected that it acts highly protective against IR-induced damage at a single time point or from lymphocytes which were preincubated).
Melatonin markedly inhibited formation of chromosome aberrations and micronuclei in IR-exposed lymphocytes separated before IR from healthy volunteers who orally took melatonin (300 *in vitro* m with melatonin at the concentration of 2MOL (Gy of IR, the cell survival rate was reduced to 37%, whereas preincubation with melatonin.
When cultured human fibroblasts were exposed to 8μMOL) led to an increased survival rate of 68%. These survival enhancing effects of melatonin correlated with reduced lipid peroxidation of the cell membranes (represented by lowered malondialdehyde levels) and decreased apoptotic pre-G1 peak. Of note, the pathways influenced by melatonin were not p53- nor p21-dependent. Interestingly, the use of different antioxidants (including trolox, the water-soluble analogue of α-tocopherol) has shown that the antioxidant must be applied before IR-exposure in order to effectively scavenge ROS formed during IR, just as it is true for the antioxidant effects of melatonin in connection with UVR.
Since the discovery of the strong antioxidant properties of melatonin, which until then had exclusively been appreciated as a circadian and seasonal biorhythm regulator, a tremendously wide spectrum of targets and effects of melatonin has evolved in a great variety of tissues and organisms.
The predominant feature of melatonin that has surfaced in consequence is that of a potent cytoprotective substance on multiple different levels of cell damage, both in physiological and pharmacological concentrations.
The presence of specific and functionally active membrane, cytosolic and nuclear melatonin receptors in mammalian (including human) skin and its appendages suggests the skin to be a major melatonin target. Parallely the demonstration of AANAT activity in hamster skin of transcripts for melatonin-synthesizing enzymes in human skin and hair follicle cells as well as in cutaneous tissues and of inducible melatonin synthesis and metabolism in keratinocytes and hair follicles identifies mammalian skin and its appendages as major extrapineal sites of melatonin synthesis and metabolism[10]. A steadily growing body of evidence now supports that the functional role of melatonin and its metabolites fully extends to skin and hair biology/pathology including the effects of melatonin on heat- and pressure-induced skin injury, ulcer formation, apoptosis, necrosis, melanogenesis, hair shaft growth and hair follicle receptor modulation as well as tumor growth suppression. Finally, the main environmental skin stressors (UVR, IR) are effectively counteracted by melatonin in the context of a complex intracutaneous MAS.In fact, in human biology, the skin may be unrivalled as a model organ for elucidating the full range of melatonin functions, targets, metabolism, receptors and regulation in health and disease. Moreover, growing evidence suggests that ligands of membrane, nuclear and cytosolic melatonin receptors (including antioxidant melatonin photoproducts) may be recruited as adjuvant therapy in a wide range of problems in clinical dermatology, ranging from wound healing via vitiligo, atopic eczema, sarcoidosis, diabetic foot syndrome and pruritus to carcinoma and melanoma.

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BLACK SEA
SCIENTIFIC JOURNAL OF ACADEMIC RESEARCH
ISSN: 1987 - 6521, E – ISSN: 2346 – 7541
JANUARY-MARCH 2020 VOLUME 53 ISSUE 02

ГНОТОБИОНТЫ – ЭКСПЕРИМЕНТАЛЬНАЯ МОДЕЛЬ

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ABSTRACT

This paper presents the results of the studies of biological behavior and morphology of the lymphoid system in gnotobionts–animals with controlled microflora, namely: 1) age-related changes are determined in the thymus – the central organ of the lymphoid system in gnotobionts, in which maturation of the T-dependent lymphocytes is delayed, causing inhibition of the cellular immunity reactions; 2) comparative cytological profile and morphology of the peripheral lymphoid organs (spleen, visceral and somatic lymph nodes) are analyzed with regard to age; 3) the leading morphofunctional mechanisms responsible for development of non-coronary damages of the myocardium and the microcirculatory bed are indicated; 4) test morphological studies of the mucous membrane of the ileum are performed with a detailed cytological profile of the lymphoid tissue followed by determination of presence or absence of the structures of both “acceptor” and “protective” immunity.
Keywords: gnotobiotic animal’s, microflora, acceptive and protective immunity

РЕЗЮМЕ

В данной работе представлены результаты исследований биологического поведения и морфологии лимфоидной системы у гнотобионтов-животных с контролируемой микрофлорой, а именно: 1) определяются возрастные изменения в тимусе - центральном органе лимфоидной системы у гнотобионтов, в какое созревание Т-зависимых лимфоцитов задерживается, вызывая ингибирование реакций клеточного иммунитета; 2) сравнительный цитологический профиль и морфология периферических лимфоидных органов (селезенки, висцеральных и соматических лимфатических узлов) анализируются с учетом возраста; 3) указаны ведущие морфофункциональные механизмы, ответственные за развитие некоронарных повреждений миокарда и микроциркуляторного русла; 4) проводят тест морфологических исследований слизистой оболочки подвздошной кишки с подробным цитологическим профилем лимфоидной ткани с последующим определением наличия или отсутствия структур как «акцепторного», так и «защитного» иммунитета.
Ключевые слова: гнотобиотики животных, микрофлора, акцептивный и защитный иммунитет.

В настоящее время широко используются различные медико-биологические экспериментальные модели, с целью установления общебиологических морфофункциональных особенностей организма в норме и патологии. Следует отметить, что эти модели создаются с учетом современных технологий и основных параметров объекта моделирования на различных (генетических, микробиологических, экологических и др.) уровнях исследования; они легко контролируемы, а результаты, полученные с их помощью, достоверны и вполне адекватны.

В последнее время в качестве экспериментальной модели все чаще используются лабораторные животные с контролируемой микрофлорой – так называемые гнотобионты, которые по своему микробиологическому статусу полностью соответствуют требованиям экологической медицины. Существуют различного типа гнотобионты – от полностью безмикробных до полиассоциированных (имеющих известную непатогенную форму). Гнотобионты содержатся в специальных пластиковых изоляторах, дышат воздухом, поступающим через микробонепроницаемые мембраны, пьют пропущенную через миллипоровый фильтр дистиллированную воду, питаются термически (в автоклавах) и химически (надуксусной кислотой и др.) обработанной пищей [1, 2].

Несмотря на то, что в литературе имеется немало сведений об экспериментах, проведенных на гнотобионтах, они все еще требуют подкрепления фундаментальными экспериментальными и научно обоснованными фактами.

В течение последних двадцати лет в экспериментах, проводимых ТГМУ в Департаменте клинической и экспериментальной патологии Института морфологии им. А.Н.Натишвили Тбилисского Государственного Университета им. И.Джавахишвили используются крысы гнотобионты, так называемые «Germ free» животные.

Гнотобионты получены из лаборатории экспериментально-биологических моделей “Iffa-Credo” (Лион, Франция). Животные, рождались с помощью кесарева сечения, содержались в специальных пластиковых изоляторах типа “Trexler”, в определенных, строго соблюдаемых условиях вивария. Питание, уход и микробиологический контроль гнотобионтов осуществлялся по специально подобранной методике, в полном соответствии со всеми технологическими требованиями гнотобиологии, исключающей возможность их случайной контаминации (загрязнения непатогенной микрофлорой).

Данные каждого эксперимента сравнивались с результатами, полученными при использовании обычных, так называемых конвенциональных животных, полученных тем же путем, то есть в результате кесарева сечения, однако, в отличие от гнотобионтов, проживающих в стандартных условиях микробного окружения вивария той же экспериментально-биологической клиники (контрольная группа).

В настоящей работе нами представлен неполный перечень исследований, проведеных на крысах-гнотобионтах.

1. Исследование возрастных изменений центрального органа лимфоидной системы – тимуса привлекает особое внимание, так как на фоне минимализации антигенной нагрузки, в отличие от конвенциональных животных, у гнотобионтов происходит задержка созревания Т-зависимых лимфоцитов, что вызывает ингибицию реакций клеточного иммунитета [2].

Проведенные исследования показали, что лимфоидная ткань тимуса гнотобионтов, пропорционально уменьшению антигенной нагрузки, является менее созревшей и развитой, о чем свидетельствует инволюция Т-лимфоцитов, а также интенсивная соединительнотканная субституция тимуса. Анализ проведенных исследований дает основание предположить, что несмотря на отставании в развитии и созревании, возрастные измениения лимфоидной ткани как конвенциональных (контрольная группа), так и животных – гнотобионтов, имеют однонаправленный характер [3].

I. Сравнительное исследование цитологического профиля и морфологии периферических лимфоидных органов (селезенка, висцеральные и соматические лимфатические узлы) у животных с различной антигенной нагрузкой с учетом возраста дало возможность заключить, что для периферических лимфоидных органов как гнотобионтов, так и конвенциональных животных в зрелом возрасте характерно превалирование малых лимфоцитов I типа по сравнению со II типом; в тоже время как у старых животных обеих групп выявляется совершенно противоположное соотношение отмеченных клеток. В первом периоде старости возрастные изменения в селезенке и брыжеечных лимфатических узлах гнотобионтов выражены сравнительно в меньшей степени, чем у конвенциональных животных, что проявляется в лучшей сохранности, цитоархитектоники и морфологических особенностей этих органов. Содержание и степень зрелости клеток-эффекторов гуморального звена иммунитета в селезенке и брыжеечных узлах, в основном, не зависит от возрастного фактора и уровня антигенного окружения, клеточное же звено иммунитета в паховых лимфатических узлах подавлено в соответствие с уменьшением микробного статуса. Иммунный статус висцеральных (брыжеечных) лимфатических узлов, по сравнению с соматическими (паховыми), в меньшей степени подвержен возрастным изменениям и воздействию факторов внешней среды. Зависимость морфологических особенностей и клеточного состава лимфоидной ткани от антигенной нагрузки и возраста, по нашим данным не имеет однозначрый характер [4].

II. Представляет интерес использование в качестве экспериментальной модели безмикробных организмов – гнотобионтов для выяснения ведущих морфофункциональных механизмов, ответственных за патогенез некоронарогенных повреждений миокарда и его микроциркуляционного русла, а также дифференциации так называемых «чистых» морфологических изменениий от первычных аутоиммунных при моделировании аутоиммунного поражения сердца как в нативном состоянии, так и при введении гетеро- и гомологичных субстратов [5].

III. Наиболее интересный и наглядный результат использования в качастве экспериментальной модели гнотобионтов был получен при сравнительном морфологическом исследовании слизистой подвздошной кишки гнотобионтов и конвенциональных животных с прицельной детализацией цитологического профиля. Известно, что механизмы формирования микробиоценоза и его взаимоотношения с иммунной системой у человека и других млекопитающих до сегодняшнего дня недостаточно изучены, так как все исследования должны касаться не одного, а сотен видов микроорганизмов, что довольно затруднительно. Именно поэтому в качестве экспериментальной модели многими исследователями используются безмикробные животные – гнотобионты. Гнотобионты, развивающиеся в стерильных условиях, имеют незрелую лимфоидную ткань кишечника, (MALT) [6, 7].

Нами было высказано предположение, что у гнотобионтов должны быть в наличи и сравнительно хорошо развитые морфологические структуры, обеспечивающие «акцептивный» иммунитет (взаимодействие иммунной системы с нормальным микроокружением), аналогичный с конвенциальными животными, однако должны отсутствовать структуры, ответственные за «протективный» иммунитет, имеющийся у лишь у конвенциальных

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животных. Термин «акцепсивный» иммунитет был предложен в 2002 году В.Б.Климовичем [8] для обозначения взаимодействия иммуной системы с нормальным микроокружением организма.

Таким образом, гомеостатический механизм, обеспечивающий симбионтные взаимоотношения на уровне реакции врожденного и адаптивного иммунитета отличается сложностью структурного обеспечения. Выявилось, что иммунная система кишечника созревает после взаимодействия с кишечной микрофлорой. Данная экспериментальная модель отражает также нормальный процесс параллельного становления биоценоза иммунной системы у новорожденных.
Проведенные исследования также выявили существенные различия «акцептивного» звена иммунитета от «протективного» по структуре: весь сложный комплекс иммунных реакций протекает в пределах нормального физиологического процесса, важно подчеркнуть, что отсутствуют признаки воспаления. Данный феномен объясняется тем, что взаимодействие с комменсалами представляет собой физиологическую норму. В слизистой кишечника симбионтные взаимоотношения обеспечиваются гомеостатическим механизмом, происходящем на уровне клеток эпителиального покрова. Следовательно, в задачи «акцептивного» звена иммунитета входят сложные процессы: изоляция бактерий и создание условий для их проживания, ограничение трансэпителиального проникновения бактерий во внутреннюю среду организма, учет и контроль проживающих микроорганизмов, создание и постоянное поддержание иммунологической толерантности к антигенам нормальной микробиоты, а также сохранение и передача полезных бактерий своему потомству. В частности, имеется в виду активная роль симбионтов в формировании иммунорезистентности организма, обмена веществ, синтеза витаминов и основных аминокислот, в целом ряде биологически активных соединений [8].
Наши исследования фвляются ещн одним подтверждением в пользу существования «акцепторного» иммунитета.
Все вышеотмеченное усиливает интерес к гнотобионтам («наивных» организмах, не имеющих контакта с антигенами), которые отличаются от обычных конвенциональных животных рядом основных механизмов морфогенеза. Результаты таких исследований могут быть приняты за «эталон» контроля особенностей, характерных для той или иной патологии. Гнотобиология дает стимул новым идеям и интересным перспективам, которые, конечно, в объязательном порядке должы быть подкреплены фундаментальными экспериментами и научно обоснованными фактами.

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SCIENTIFIC JOURNAL OF ACADEMIC RESEARCH

GNOTOBIONTS – EXPERIMENTAL MODEL

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ABSTRACT

This paper presents the results of the studies of biological behavior and morphology of the lymphoid system in gnotobionts–animals with controlled microflora, namely: 1) age-related changes are determined in the thymus – the central organ of the lymphoid system in gnotobionts, in which maturation of the T-dependent lymphocytes is delayed, causing inhibition of the cellular immunity reactions; 2) comparative cytological profile and morphology of the peripheral lymphoid organs (spleen, visceral and somatic lymph nodes) are analyzed with regard to age; 3) the leading morphofunctional mechanisms responsible for development of non-coronary damages of the myocardium and the microcirculatory bed are indicated; 4) test morphological studies of the mucous membrane of the ileum are performed with a detailed cytological profile of the lymphoid tissue followed by determination of presence or absence of the structures of both “acceptor” and “protective” immunity.
Key words: gnotobiotic animal’s, microflora, acceptive and protective immunity

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SCIENTIFIC JOURNAL OF ACADEMIC RESEARCH
ISSN: 1987 - 6521, E – ISSN: 2346 – 7541
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SENSITIVITY OF SERUM PROTEINS OF GI CANCER PATIENTS TO CHEMOTHERAPY COURSES

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ABSTRACT

Gastrointestinal cancers (GI) are one of the most abundant types of cancers among the world population, though statistical data indicate that in eastern Asia these types of cancer occur 4 times more often than in Western Europe. Absence of treatment of bacterial infections, obesity, and lack of vegetable food in a diet can be the case of GI cancer. All pathologies are inevitably connected to the changes in cell cycle, abnormal protein amount and their dysfunction. Serum proteins are widely used as an additional source of information about body condition, also changes in protein composition can point out the mechanism of disease development and effectiveness of treatment. In the presented work we studied protein composition of GI cancer patients in different stages of cancer development, after and before chemotherapy and compared these data to protein composition of healthy control group of voluntaries. Treatment of patients was performed according the guidelines appropriate for the GI cancer. Association of the effectiveness of treatment at the different stages of chemotherapeutic courses and changes of protein composition of blood serum has been assessed. Proteins composition was studies by SDS-PAGE electrophoresis and densitometry analysis. Experimentally gained molecular and statistical information exposed the most vulnerable groups of proteins affected by chemotherapeutic agents indicating targets for searching new biomarkers for treatment effectiveness.
Research involving human patients performed in accordance with the requirements of the Council of Europe Convention on Human Rights and Biomedicine, Biomedical Research, as well as the UNESCO Declaration of Bioethics and Human Rights.
Key wards: Gastrointestinal cancer, chemotherapy, proteins, biomarkers

Acknowledgement: Project granted from Shota Rustaveli National Science Foundation 2016-2019, N217342

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JANUARY-MARCH 2020 VOLUME 52 ISSUE 01
THE BALTIC SCIENTIFIC JOURNALS
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CHANGES IN OPEN FIELD BEHAVIOR AND DECLARATIVE MEMORY IN "DEPRESSIVE" RATS WITH HIGH IMMOBILITY AND DECREASED LEVEL OF BRAIN MONOAMINES

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INTRODUCTION

Changes in some forms of motivational-emotional behavior, learning and memory are thought to be characteristic for major depressive disease. However, results existing until today about the character of changes in motivational-emotional and exploratory behavior as well as character of disorders in declarative memory, accompanying major depressive disease, are not unambiguous. Therefore, studying them in animal models of depression is very topical and important.

METHODS

Experiments were conducted on adult white wild rats (with 250-300 g weight). "Depressive" and "non- depressive" rats were selected according to the level of immobility in forced swim test. Rats with low level of immobility, "non-depressive" rats, constituted control group and rats with high level of immobility, "depressive" rats, constituted the experimental group (10 rats in each).
Changes of motivational-emotional and exploratory behavior were studied in open field test.
The changes of learning and memory were studied in the fear motivated one trial passive avoidance test considered as the declarative memory test. Experiments were carried out on "non-depressive", control and "depressive", experimental groups (10 rats in each).
Obtained results were processed statistically by Student's t-test.

RESULTS

Sharp decrease in locomotion was found in rats with high level of immobility. It was manifested in a significant decrease of the number of crossed squares. The quantitative indices of vertical activity, vertical standings, head risings, were also sharply decreased. Fear reaction was considerably increased in "depressive" rats, manifested in the significant decrease of the number of entering in the center of open field and grooming and sharp increase in defecation rate.
Investigation of the changes of learning and memory in the passive avoidance test has shown that the latency of entering from the light into dark section of passive avoidance camera, in the learning session, was sharply increased in "depressive" rats. They revealed an impaired ability to evaluate the level of danger coming from the brightly illuminated open area and therefore they do not hurry to escape from the dangerous section. The difference between "depressive" and "non-depressive" rats was maintained even after 24 hours from receiving a painful stimulation. In particular, the animals of control group remember that they have received a painful stimulation in dark section during learning session and do not enter there during testing session, whereas the experimental animals with considerable delay but still enter in the dark section during testing session, therefore, they show significant impairment of declarative memory in passive avoidance task.

CONCLUSIONS

Locomotor and exploratory behavior are impaired and fear motivation is increased in the open field in "depressive" rats with high immobility and low level of monoamines content in the brain. Learning and memory in one of the tests of declarative memory, so called passive avoidance task, is disturbed.
Keywords: "Depressive" rats, Open field Behavior, Declarative Memory and Monoamines Deficiency.

ISSN: 1987 - 6521, E – ISSN: 2346 – 7541
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ISSN: 1987 - 6521, E – ISSN: 2346 – 7541
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THE BALTIC SCIENTIFIC JOURNALS
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PRELIMINARY RESULTS ON THE USING TANDEM MASS SPECTROMETRY IN DIAGNOSIS OF INHERITED METABOLIC DISEASES

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BACKGROUND

According to the results of the researches common indexes of the prevalence of inherited metabolic diseases (IMD) varies from 1 to 800 on 1 to 2500 alive newborns. IMD are taking one of the first places among children pathology, early children death (40%) and disability[1]. According to systematic review of the 43 forms of the inborn errors of metabolism are related to unexpected death of newborns. For IMD it is common to have a wide spectrum of the unusual clinical manifestation, often they are not diagnosed, while well timed diagnoses and proper treatment are able to prevent severe systematic lesions, which lead to death and disability[2]. For that reason one of the most significant problems of the modern pediatrics is to early diagnosis of IMD. The only way to diagnosis of orphan metabolic diseases is the tandem mass spectrometry (TMS) [3].

AIM

Scientifically substantiate the need for implementation of selective screening IMD of children using TMS method in Republic of Kazakhstan (RK) for early diagnosis, therapy of the inherited metabolic diseases, to reduce disability and death rate.

MATERIALS AND METHODS

Material of the research – dry blood spots, taken using standard methodology on filtered DBS papers, which are used in RK in the program of neonatal screening (for retrospective research – archived samples of the dry blood spots of the children dead during first year of life). Method of the research is tandem mass spectometry (QSight Perkin Elmer).

RESULTS

Analysis of the archived dry blood spot samples showed metabolic deviations in 20.4% of the cases. The detected changes are related to amino acids metabolic disorders, defects of β-oxidation of the fat acids, decrease activity of the glucocerebrosidase (Gaucher's disease) and sphingomyelinase (Nimman – Pick disease). Results of the selective screening have shown metabolic disorders in 5% of the cases (defects of β-oxidation of the fat acids, aminoacidopathy, organic aciduria).

CONCLUSIONS

The preliminary results of the using TMS for the diagnosis of IMD have shown the need for implementation of selective screening IMD using TMS, which is able to conduct diagnosis of 75 metabolites of 49 IMD in single blood spot, which were not detected in RK previously. Taking into the consideration economic expenses of the government, related to the

ISSN: 1987 - 6521, E – ISSN: 2346 – 7541
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costs of the systematic treatment, medical service, life expectancy and lifelong support of the disabled children with IMD, early detection of orphan metabolic diseases is the vital condition of the decrease of newborn and children death rate, sickness rate and disability.

This research study was carried out as a part of a scientific project funded by West Kazakhstan Marat Ospanov Medical University.

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ISSN: 1987 - 6521, E – ISSN: 2346 – 7541
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THE BALTIC SCIENTIFIC JOURNALS
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ВОПРОСЫ ПРЕПОДАВАНИЯ МЕДИЦИНСКОЙ БИОХИМИИ В РАМКАХ ИНТЕГРИРОВАННОЙ ОБРАЗОВАТЕЛЬНОЙ ПРОГРАММЫ В МЕДИЦИНСКОМ ВУЗЕ

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РЕЗЮМЕ

Современные мировые тенденции развития медицинского образования определяют необходимость разработки интегрированных образовательных программ, ориентированных на потребности системы здравоохранения и на достижение конечных результатов обучения. Интегрированный подход к обучению и преподаванию медицинской биохимии обеспечивает целостность и системность изучения биохимических процессов организма. В данной статье авторы делятся опытом преподавания медицинской биохимии в рамках интегрированной образовательной программы, где знания по определенной системе объединены в один модуль и изучаются в интеграции с несколькими дисциплинами. Приводятся примеры разработки конечных результатов обучения на основе таксономии Блума и в зависимости от уровня сложностей. Рассматривается использование ситуационных задач в виде мини-кейсов для конечных результатов высокого уровня для применение знаний в решении определенных задач. Для совершенствования методов достижения конечных результатов обучения, описывается использование инновационных методов обучения. Это обеспечивает формирование теоретической основы для дальнейшего усвоения клинических дисциплин.
Ключевые слова: медицинская биохимия, интегрированная образовательная программа, конечные результаты обучения, таксономия Блума, инновационные методы обучения

ABSTRACT

Current global trends in the development of medical education determine the need to develop integrated educational programs that focus on the needs of the healthcare system and to achieve the final results of training. An integrated approach to the teaching and teaching of medical biochemistry ensures the integrity and systematic study of the biochemical processes of the body. In this article, the authors share their experience in teaching medical biochemistry as part of an integrated educational program developed in conjunction with a strategic partner - Bashkent University. A new educational program in medical biochemistry according to a certain system is combined into modules and studied in integration with several basic disciplines. Examples of the development of learning outcomes based on Bloom's taxonomy and depending on the level of complexity are given. The use of situational tasks in the form of mini-cases to achieve high-level end results and apply knowledge in solving certain problems is considered. The experience of using innovative teaching methods to improve teaching methods is described. This ensures the formation of a theoretical basis for the further assimilation of clinical disciplines and thereby ensures a close relationship between basic and clinical disciplines; a basis is formed for applying the obtained theoretical knowledge to the solution of a specific clinical problem.
Keywords: medical biochemistry, integrated educational program, learning outcomes, Bloom's taxonomy, innovative teaching methods

Основная цель высшего медицинского образования – достижение качества подготовки кадров здравоохранения. Как отметил Елбасы Н.А.Назарбаев в Стратегии «Казахстан-2050: новый политический курс состоявшегося государства», знания и профессиональные навыки- ключевые ориентиры современной системы образования, подготовки и переподготовки кадров [1,2].

На сегодняшний день перед высшими медицинскими учебными заведениями стоит задача не только дать хорошие знания студентам, но и подготовить специалистов нового формата, обладающих умением использовать полученные теоретические знания для решения профессиональных задач. Данная задача определяет необходимость ориентации образовательных программ вузов на потребности практического здравоохранения и на достижение конечных результатов обучения, определения наиболее эффективных образовательных методик для подготовки конкурентоспособных специалистов на рынке труда. Анализ мировых тенденций развития медицинского образования показывает, что во всем мире идет постепенный переход от традиционного

ISSN: 1987 - 6521, E – ISSN: 2346 – 7541
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дисциплинарно-ориентированного образования к интегрированному, так как дисциплинарно-ориентированное обучение характеризуется разрывом между теоретическими знаниями и возможностью использовать эти знания в практической деятельности врача, что приводит к необходимости усовершенствования образовательного процесса [3, 4].

Новый Государственный общеобязательный стандарт высшего образования определяет, что программы дисциплин и модулей должны иметь междисциплинарный и мультидисциплинарный характер, обеспечивающий подготовку кадров на стыке ряда областей знаний [5].

В связи с переходом на новую модель интегрированного образования, преподавание дисциплины «Медицинская биохимия» на кафедре биохимии и химических дисциплина НАО «Медицинский университет Семей» претерпел ряд новых преобразований. Прежде всего изменилось содержание дисциплины, которое направлено на обеспечение взаимосвязи между фундаментальными и клиническими науками. При этом учитывалось, что медицинская биохимия является базовой дисциплиной и способствует формированию базовых знаний основных закономерностей живого организма и содержит элементы патохимии, необходимой для изучения клинических дисциплин [6,7].

В соответствии новой образовательной программой, в первую очередь были определены интегрированые модули с другими базовыми дисциплинами, конечные результаты обучения. Известный европейский ученый С. Адам определяет, что результаты обучения – это письменная формулировка того, что успешный студент, как ожидается, будет в состоянии делать по итогам обучения» [8]. И здесь надо заметить, что акцент делается на понятие «делать», а не «знать» или «уметь». Для дифференцировки конечных результатов обучения по трем уровням сложности мы руководствовались таксономией Блума. С точки зрения Блума, цели обучения напрямую зависят от иерархии мыслительных процессов, таких как запоминание (remembering), понимание (understanding), применение (applying), анализ (analizing), синтез (evaluating) и оценка (creating) [9].

Соответственно данному подходу конечные результаты обучения по каждой теме модулей были разделены по уровням сложности: высокий, средний, низкий. К каждому уровню с помощью соответствующих глаголов определены задачи. Темы занятий были разработаны на основании анализа образовательной программы стратегического партнера – Башкент университета совместно с преподавателями других дисциплин в интеграции и с учетом потребностей клинических кафедр.

На первом курсе дисциплина «Медицинская биохимия» изучается по нескольким модулям. Например, модуль «Клеточный метаболизм» изучается в интеграции с такими базовыми дисциплинами, как физиология, микробиология. По теме «Введение в метаболизм. Биологическое окисление. Общие пути катаболизма» для низкого уровня конечных результатов поставлены задачи, соответствующие уровню запоминание: называет определение метаболизма и его основные этапы, экзергонические и эндергонические реакции, записывает схему катаболизма основных пищевых веществ, называет конечные продукты обмена веществ и макроэргические соединения и т.д. Конечные результаты обучения среднего уровня достигаются путем объяснения, описания, определения, обсуждения, формулирования, иллюстрирования, демонстрации определенных задач, например, объясняет значение обмена веществ для жизнедеятельности организма, механизм дегидрирования субстратов и окисление водорода как источника энергии в клетке и т.д. Высокий уровень конечных результатов нацелен на применение знаний: обосновывает механизмы трансформации энергии в живом организме для обеспечения метаболических процессов, тем самым на первом курсе закладываются базовые знания для понимания биохимических механизмов развития патологического состояния.

Для этого модули 2 курса были определены по основным системам, которые изучаются в интеграции с другими дисциплинами, как нормальная физиология, анатомия, гистология, медицинская биология с овновами генетики, и здесь по высокому уровню сложности на первый план выходит применение знаний для решения определенных задач, например, по теме «Механизмы переваривания липидов и всасывание в отделах желудочно-кишечного тракта» задачей высокого уровня определено обоснование биохимических механизмов переваривания и всасывания липидов для объяснения причин нарушений в клинических случаях, особенности данных механизмов у взрослых и детей. Для этого на кафедре используются ситуационные задачи, моделирующие биохимические процессы, протекающие в живом организме. Высокий уровень конечных результатов достигается после освоения задач среднего и низкого уровней.

На занятиях используются мини-кейсы, то есть мини-ситуационные задачи, которые являются небольшие по объему (от 0,5 до 1 страницы). Данные задачи представляют собой клиническую ситуацию с полным описанием клинико-биохимических показателей, которые в достаточном объеме представляют проблему и её решение [10,11]. Ситуационные задачи предназначены преимущественно для проблематизации и иллюстрации конечных результатов высокого уровня, рассматриваемых в ходе аудиторных занятий. Они не требуют предварительной подготовки, а их обсуждение, как правило, занимает менее половины практического занятия. В конце изучения каждого модуля или раздела для углубления интеграции базовых и клинических дисциплин проводится занятие по решению интегрированного кейса, разработанного клиническими кафедрами на примере конкретных клинических

проблем. Содержание кейса разработано непосредственно с клиническим контекстом, чтобы продемонстрировать студентам актуальность изучения фундаментальных наук для их будущей практической деятельности. Кроме этого на кафедре активно используются такие инновационные методы обучения, как работа в малых группах, «мозговой штурм», биохимический диктант, занятия по методике TBL (командно-ориентированное обучение) и другие.

Таким образом, для изучения дисциплины «Медицинская биохимия» в рамках интегрированной программы мы определили ожидаемые конечные результаты обучения, разработали учебный план, определили методы преподавания, обучения и оценивания таким образом, чтобы сделать возможным достижение результатов. Интегрированное обучение дисциплин способствует формированию целостной системы знаний, собирать различные факты по определенной системе или модулю в единую цепь, с тем, чтобы получить полную картину о клинической ситуации и формировать основу для последующего освоения клинических дисциплин. Данная стратегия образовательной деятельности обеспечивает тесную взаимосвязь медицинской биохимии с будущей профессиональной деятельностью врача. Разработанные новые программы по медицинской биохимии позволяют установить междисциплинарные связи как по вертикали с кафедрами клинического профилей, так и по горизонтали, проведя интеграцию преподавания всех базовых дисциплин.

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QUESTIONS OF TEACHING MEDICAL BIOCHEMISTRY AS PART OF AN INTEGRATED EDUCATIONAL PROGRAM IN A MEDICAL UNIVERSITY

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ISSN: 1987 - 6521, E – ISSN: 2346 – 7541
JANUARY-MARCH 2020 VOLUME 53 ISSUE 02

ABSTRACT

Current global trends in the development of medical education determine the need to develop integrated educational programs that focus on the needs of the healthcare system and to achieve the final results of training. An integrated approach to the teaching and teaching of medical biochemistry ensures the integrity and systematic study of the biochemical processes of the body. In this article, the authors share their experience in teaching medical biochemistry as part of an integrated educational program developed in conjunction with a strategic partner - Bashkent University. A new educational program in medical biochemistry according to a certain system is combined into modules and studied in integration with several basic disciplines. Examples of the development of learning outcomes based on Bloom's taxonomy and depending on the level of complexity are given. The use of situational tasks in the form of mini-cases to achieve high-level end results and apply knowledge in solving certain problems is considered. The experience of using innovative teaching methods to improve teaching methods is described. This ensures the formation of a theoretical basis for the further assimilation of clinical disciplines and thereby ensures a close relationship between basic and clinical disciplines; a basis is formed for applying the obtained theoretical knowledge to the solution of a specific clinical problem.
Keywords: medical biochemistry, integrated educational program, learning outcomes, Bloom's taxonomy, innovative teaching methods

ISSN: 1987 - 6521, E – ISSN: 2346 – 7541
JANUARY-MARCH 2020 VOLUME 52 ISSUE 01
THE BALTIC SCIENTIFIC JOURNALS
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MODERN METHODS TO DIFFERENTIATE BETWEEN CHEST PAIN AND CARDIAC ISCHEMIA

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Acute coronary syndrome (ACS) is a group of conditions which often present with similar signs and symptoms while having different outcomes and complications. Therefore it is essential to differentiate between them as soon as possible and provide appropriate management.
Acute coronary syndromes are classified into two categories: STE-ACS (ST segment Elevation Acute Coronary Syndrome) and NSTE-ACS (Non ST segment Elevation Acute Coronary Syndrome). STE-ACS stands for ST Elevation Acute Coronary Syndrome all of which demonstrate significant ST elevations on ECG due to complete blockage of artery by thrombus, while NSTE-ACS is due to partial occlusion of artery which exhibit ST segment depression and/or T wave inversions. Patients with NSTE-ACS who do not develop infarction are diagnosed with unstable angina, which itself is a precursor of myocardial infarction.
Acute coronary syndromes are considered multifactorial and risk factors most commonly associated with development of acute coronary syndromes include: hypertension, smoking, diabetes, obesity, sedentary life-style, hereditary conditions etc. Chronic stress to the coronary endothelium eventually leads to inflammation and atherosclerotic plaque formation. Plaque at some point with additional stress will rupture and trigger thrombus formation. Probability of plaque rupture depends on its composition: stable plaques contain small fatty core and thick fibrous cap, unstable plaque have larger fatty cores and thin fibrous cap.
Patients with acute coronary syndromes present with chest pain and/or discomfort and may experience tightness and pressure sensation; pain may radiate to left or both arms, jaw, back or stomach, sweating, dyspnea and dizziness are also common complaints.
Whenever we suspect ACS first diagnostic tests is always ECG (Electrocardiography). If ST segment is persistently elevated STEMI (ST Elevation Myocardial Infarction) can be diagnosed and reperfusion therapy is indicated; but if ST segment is depressed and/or T wave inversion is present laboratory tests are necessary for diagnosis. Cardiac biomarkers mainly used in the clinic are Troponins and CK-MB (Creatine Kinase MB), yet LDH (lactate dehydrogenase), B-type natriuretic peptide and C-reactive protein can be used additionally.
Several studies have been conducted in hopes to find other myocardial markers useful for diagnosis of ACS, one of which tested candidate biomarkers such as hFABP (Heart-type fatty acid binding protein), GPBB (Glycogen Phosphorylase Isoenzyme BB), S100, PAPP-A (Pregnancy-associated plasma protein A), TNF (Tumor Necrosis Factor), IL6 (Interleukin 6), IL18 (Interleukin 18), CD40 (Cluster of differentiation 40) ligand, MPO (Myeloperoxidase), MMP9 (Matrix metallopeptidase 9), cell-adhesion molecules, oxidized LDL (Low Density Lipoprotein), glutathione, homocysteine, fibrinogen, and D-dimer, procalcitonin. The idea of this study was to estimate usefulness of combining enzymatic markers with nonenzymatic ones in the clinical settings.
Keywords: cardiac ischemia, enzymatic biomarkers, STEMI

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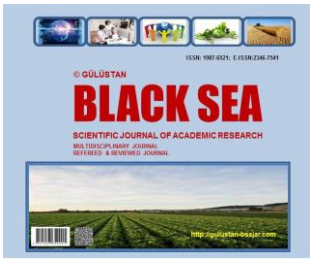

The Caucasus Economic and Social Analysis Journal has ISSN, E-ISSN and UDC numbering:
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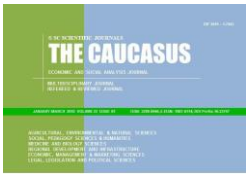

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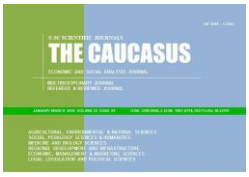

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ISSN: 1987-6521; E-ISSN:2346-7541; DOI prefix: 10.36962

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Director and shareholder: Alexandra Cuco. Lawyer. Portugal.
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Direkotrun müavini və Payçı: Namig Isazade. PhD in Business Administration.
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ISSN: 1987-6521; E-ISSN:2346-7541, DOI:10.36962/GBSSJAR
JANUARY-MARCH 2020 VOLUME 52 ISSUE 01

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