DYSCHROMIAS

Melanocytes are specialized cells that originate from the neural crest, an embryonic structure that arises from the neuroectoderm (the germ layer that also gives rise to the nervous system). During development, neural crest cells migrate to various parts of the body, differentiating into different types of cells, including melanocytes.

The primary role of melanocytes is the production of melanin, a pigment that gives color to the skin, hair, and eyes. This process, known as melanogenesis, occurs in structures within the melanocytes called melanosomes. Melanin plays a vital role in protecting the skin against ultraviolet (UV) radiation from the sun by absorbing and dissipating the energy of these radiation, helping prevent DNA damage in skin cells.

Melanocytes reside in the basal layer of the epidermis, the deepest layer of the skin. Here, they establish a relationship with keratinocytes, the main cells of the epidermis, forming the melanocyte–keratinocyte unit. One melanocyte typically associates with 30–40 keratinocytes. The melanin produced is transferred to keratinocytes, where it forms a "shield" over their nucleus to protect their DNA from UV damage.

Molecular Identification of Melanocytes

Melanocytes can be identified at a molecular level by the presence of specific proteins:

- Tyrosinase (TYR): A key enzyme in melanin synthesis. It initiates the oxidation of tyrosine, an amino acid, in the first stage of melanogenesis.
- Tyrosinase-Related Proteins (TYRP1, TYRP2): These proteins act as cofactors in melanin production, regulating the type and quantity of melanin synthesized.
- Melanosomal Matrix Proteins (Pmel17, MART-1): These proteins are essential for the formation and structure of melanosomes, the organelles where melanin is stored and transported within melanocytes and toward keratinocytes.

Melanocyte Density & Pigmentation Diversity

The number of melanocytes in the skin is relatively constant—about 1200 melanocytes per mm^2 of skin—regardless of ethnic background. However, skin tone differences are due to variations in the size, number, and type of melanosomes, as well as the amount of melanin produced and distributed in keratinocytes.

Differences in skin color are not due to melanocyte count, but rather to factors such as:

- Melanosome Size and Number: In individuals with darker skin, melanosomes are larger, more numerous, and more elongated. This allows for greater accumulation and persistence of melanin in the skin.
- Type of Melanin: There are two main types—eumelanin (more common in darker skin) and pheomelanin (more common in lighter skin). The proportion of each influences skin color.
- Melanin Distribution: How melanosomes are distributed and transferred to keratinocytes also affects overall pigmentation.

Melasma and Melanocyte Activity Regulation

This condition involves hyperactive melanocytes producing excessive melanin, resulting in dark patches on the skin, typically in sun-exposed areas. Although the melanocytes are confined to the epidermis, treatments targeting this layer can worsen the condition. Sun-damaged fibroblasts may contribute to melasma by influencing melanocyte activity.

Melanocyte activity is regulated by complex interactions with other skin cells, such as keratinocytes and fibroblasts. These cells send signals that modulate melanin production in response to various stimuli like sunlight

Melanosomes

Melanosomes are specialized organelles within melanocytes where melanin is synthesized and stored. Their development includes four stages:

Stage I: Premelanosomes

In this early stage, melanosomes appear as small round vesicles with an amorphous matrix—meaning no defined internal structure. These vesicles lack melanin and the proteins required for its synthesis.

Stage II: Fibrillar Matrix Formation

Here, melanosomes develop an organized internal structure called a fibrillar matrix, primarily made of gp100 family proteins like glycoprotein Pmel17. Although tyrosinase, a key enzyme for melanin synthesis, is present, melanin production has not yet begun.

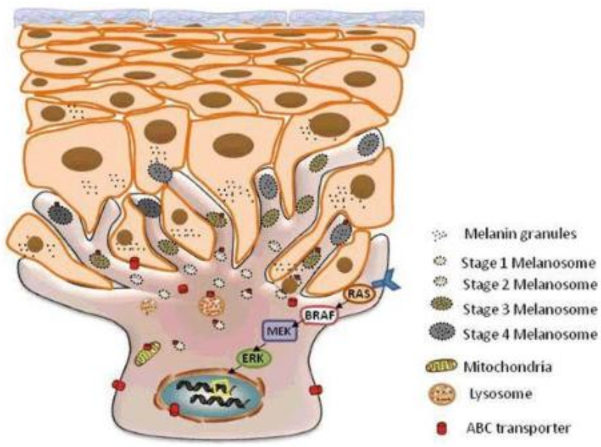
For melanosomes to mature fully, their internal pH must rise from around 5 to 6.8. This shift is facilitated by a protein called protein p, which acts as a proton pump in the melanosome membrane. The pH change is essential for activating melanogenesis enzymes.

Stage III: Melanin Synthesis Begins

At this point, melanin synthesis starts actively. Pigment is deposited on the fibrillar proteins inside the melanosome. Tyrosinase and other related enzymes like TYRP1 and TYRP2 catalyze the chemical reactions necessary for melanin formation.

Stage IV: Mature Melanosomes

In the final stage, melanosomes are fully pigmented. By now, tyrosinase activity has ceased, as melanin synthesis is complete. These pigment-filled melanosomes are then transported to surrounding keratinocytes via the melanocyte's cytoskeletal elements. This transfer process is vital for pigment distribution across the skin, contributing to both coloration and UV protection.



Key Components of Melanosomes

Within melanosomes, there are essential proteins and enzymes for the synthesis and anchoring of melanin:

- Glycoprotein Pmel17: This protein is essential for the formation of the fibrillar matrix where melanin is deposited.
- Tyrosinase and Other Enzymes: Tyrosinase, along with tyrosinase-related proteins TYRP1 and TYRP2, are key enzymes in melanogenesis, the process of melanin production. These enzymes are regulated by a membrane-associated transporter protein (MATP), which controls their entry into melanosomes.

Types of Melanin

There are two main types of melanin, which differ in structure and function:

- Eumelanin: An insoluble dark brown or black polymer. It is the most common type of melanin in people with dark skin and hair, and it is particularly effective at protecting against UV radiation damage, offering superior photoprotection.
- Pheomelanin: A soluble red-yellow polymer formed by the conjugation of cysteine or glutathione. Pheomelanin predominates in individuals with fair skin and red hair (phototypes I and II). People with high levels of pheomelanin are more susceptible to UV damage and have a higher risk of developing skin tumors.

Enzymes Involved in Melanin Synthesis

	Function:	Regulation:
Tyrosinase (TYR)	Tyrosinase is the most important enzyme in melanogenesis. It catalyzes the first two critical reactions in melanin synthesis. The first is the hydroxylation of tyrosine (an amino acid) to DOPA (3,4-dihydroxyphenylalanine). The second is the oxidation of DOPA to DOPAquinone. These initial steps are essential for the formation of both eumelanin and pheomelanin.	Tyrosinase activity is regulated by various factors, including melanosomal pH, copper availability (an essential cofactor), and the expression of the p protein, which helps maintain proper pH inside the melanosome. Additionally, tyrosinase can be influenced by hormonal and environmental factors such as UV exposure.
Tyrosinase-Related Protein 1 (TYRP1)	TYRP1 (also known as DHICA oxidase) plays a role in eumelanin synthesis. It participates in the oxidation of DHICA (5,6-dihydroxyindole-2-carboxylic acid), an intermediate in the eumelanin pathway. Although not fully	Like tyrosinase, TYRP1 expression and activity can be influenced by genetic and environmental factors. It may also affect the type of melanin produced, contributing to variations in skin and hair color.

	understood, TYRP1 is also believed to stabilize tyrosinase and regulate melanosomal pH.	
Tyrosinase-Related Protein 2 (TYRP2/DCT)	TYRP2, also known as dopachrome tautomerase (DCT), converts dopachrome into DHICA. This step is important in eumelanin synthesis, as it prevents the formation of reactive intermediates that could damage cells. Like other enzymes, TYRP2 is crucial for melanin production and affects both the amount and type of pigment formed.	TYRP2 activity is regulated similarly to other melanogenesis enzymes, with expression varying based on genetic and environmental factors.
Tyrosine	Tyrosine is the main precursor in melanin production, the pigment responsible for the color of skin, hair, and eyes. Tyrosinase catalyzes the conversion of tyrosine into DOPA and then into DOPAquinone, the first steps in the melanin biosynthesis pathway.	

What Are Melanotropins?

Melanotropins are hormones that stimulate melanin production, the pigment that gives color to the skin. The most well-known of these is melanocyte-stimulating hormone (MSH). These hormones are produced in the brain, in a region called the pituitary gland, and act on melanocytes, the skin cells that produce melanin.

Relationship with Skin Injuries

1. Protection and Repair:
   When the skin suffers an injury, such as a burn, cut, or excessive sun exposure, melanotropins may be released. These hormones increase melanin production in the affected area. Melanin has protective properties, as it absorbs and neutralizes harmful UV rays, shielding skin cells from further damage.
2. Post-Inflammatory Pigmentation:
   After skin inflammation or injury (e.g., acne, eczema, burns), dark spots often develop. This occurs because melanotropins stimulate melanocytes to produce

more melanin in response to damage. This post-inflammatory hyperpigmentation is a natural protective response.

3. Wound Healing and Skin Remodeling:
   In addition to boosting melanin production, melanotropins influence other skin healing and repair processes. By regulating melanocyte and other skin cell activity, they contribute to recovery and regeneration after injury.

Relationship Between Melasma and Female Hormones

Melasma is a skin condition characterized by dark spots, usually in sun-exposed areas such as the face. It is closely linked to female hormones, particularly estrogen and progesterone. It commonly appears in pregnant women (called chloasma) and those taking oral contraceptives.

Estrogen: What Is It and What Does It Do?

Estrogen is a key female sex hormone. The most active type, estradiol, is produced from the conversion of testosterone via the enzyme aromatase (about 60%). Estrogens play a crucial role in several biological processes, including:

1. Skin Aging: Estrogens affect skin elasticity, thickness, and hydration, helping maintain firmness and a youthful appearance.
2. Skin Pigmentation: Estrogens influence melanogenesis regulation. Melanocytes have estrogen receptors, and when estrogen levels rise (e.g., during pregnancy or contraceptive use), tyrosinase activity increases, boosting melanin production and leading to more pigmentation.
3. Hair Growth and Sebum Production: Estrogens also impact hair growth and sebum production, a substance that protects and softens the skin.

Progesterone: What Is It and What Does It Do?

Progesterone is another female sex hormone produced by the ovaries and placenta, with several important roles:

- Menstrual Cycle: During the menstrual cycle, progesterone prepares the endometrium (uterine lining) for embryo implantation, supporting pregnancy initiation.
- Pregnancy: During pregnancy, progesterone helps maintain a healthy uterine environment, preventing early contractions and supporting fetal development.
- Lactation: Progesterone also prepares the mammary glands for milk production, enlarging the breasts and aiding lactation.

Melasma and Emotions

There is growing evidence that emotional stress plays a significant role in the recurrence and persistence of melasma. This connection can be explained through the neuroendocrine system, particularly the hypothalamic-pituitary axis.

The pituitary gland produces several hormones, including the melanocyte-stimulating hormone (MSH), which, as its name suggests, directly stimulates melanocytes — the cells responsible for pigment production in the skin. The activity of the pituitary is tightly regulated by the hypothalamus, a brain region that integrates signals from the nervous system and the internal environment.

Under conditions of emotional stress, the hypothalamus can trigger a chain reaction:

- It stimulates the pituitary gland,
- Which then increases secretion of MSH,
- Leading to increased melanogenesis (pigment production),
- And potentially, the reappearance or worsening of melisma.

This is why melasma often reappears or darkens during stressful periods, even if the patient is following proper cosmetic treatment and sun protection. Emotional stress also activates cortisol release (via the hypothalamic-pituitary-adrenal axis), which can disrupt skin homeostasis and further contribute to pigmentation irregularities.

In summary, emotional well-being is a fundamental part of managing melasma. Skincare treatments must go hand-in-hand with stress management techniques, such as relaxation, mindfulness, and healthy lifestyle habits, to support both skin health and emotional balance.