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About strawberry, crab claws, and the Sir James Black's invention. Hypothesis: Can we battle keloids with propranolol?

Charles Jean G. de Mesquita *

Federal University of Ceará, Fortaleza, Ceará, Brazil

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ABSTRACT

The cutaneous hemangiomas of infancy or infantile hemangiomas are the most common benign tumor of childhood. They were formerly known as strawberry hemangiomas in reason of its typical appearance although uncommon morphologic variations can be found. Usually hemangiomas are harmless growths that are the result of proliferation of endothelial cells during early childhood. Involution of the lesion occurs at 12–18 months and can last up to 7 years. Occasionally, infantile hemangiomas suffer dramatic overgrowth causing esthetical damages, as well compromises to vital structures that requires prompt intervention. Propranolol, a beta-adrenergic receptor antagonist that was invented by Sir James Black in 1960s, appears to be an effective treatment for infantile hemangiomas and should now be used as a first-line treatment in hemangiomas when intervention is required. Keloids (that resembles crab claws) and hypertrophic scars are fibrous tissue outgrowths that result from a derailment in the normal wound-healing process. Systemic or intralesional propranolol may play a role in the amelioration of keloids and hypertrophic scars due to their potential to induce vasoconstriction of over proliferating tissues, triggering apoptosis of endothelial cells and also to their effect as modulator of inflammatory process during wound healing. In adding the propranolol to the melting pot of abnormal (or supra-normal) wound healing, we hypothesized that we can battle keloids with propranolol.

About strawberry

The cutaneous hemangiomas of infancy or infantile hemangiomas (IHs) are the most common benign tumor of childhood [1]. They were formerly known as strawberry hemangiomas in reason of its typical appearance although uncommon morphologic variations can be found [2]. In the past, the Greek suffix *-oma* was related to any swelling or tumor. Nowadays, the suffix *oma* refers to tumor characterized by increased cellular turnover and hyperplasia [2,3]. IH has a characteristic clinical course marked by early proliferation for the first 3–8 months of life, a plateau is reached between 9 and 12 months that is followed by slow and spontaneous involution from 3 to 7 years [1–4]. Usually hemangiomas are harmless growths that are the result of proliferation of endothelial cells during early childhood. Occasionally, IH suffer dramatic overgrowth causing esthetical damages, as well compromises to vital structures that requires prompt intervention, e.g., periocular hemangiomas [5], subglottic hemangiomas [6]. Rarely, a cutaneous hemangioma is associated with one or more underlying congenital anomalies as like PHACES [7] (posterior fossa malformation, hemangioma, arterial anomalies, coarctation of the aorta, eye abnormalities, and *sterna* defects) and PELVIS [8] (perineal hemangioma, external genitalia malformations, lipomyelomeningocele, vesicorenal abnormalities, imperforate anus, and skin tag) syndromes.

Data about regulators of hemangioma growth and involution are scarce and much remains to be learned about their interrelations. Experimental data suggest that proangiogenic, pro-apoptosis and inflammatory factors are involved. According to Frieden and collaborators [7], two major proangiogenic factors are involved: basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) during the growth phase. They have demonstrated that both endothelial and interstitial cells are actively dividing in this phase and that apoptosis occurs during the involution phase [7]. Infantile hemangiomas are a mixture of cell types, including endothelial cells (expressed by CD31 – a vascular marker – positive, glucose transporter (GLUT)-1 protein that is specific to IH endothelial cells), pericytes positive for smooth muscle actin (SMA+), dendritic cells (factor XIIIa+), and mast cells (MCs) [9,10]. MCs probably play a complex and dual role involving stimulation of new blood vessels from pre-existing endothelium in the proliferative phase and inhibition of angiogenesis in the involution phase [11,12]. The pathophysiological mechanisms leading to endothelial cell proliferation and involution are poorly understood, and the variety of articles on the subject reflects many competing

* Address: Rua Professor Costa Mendes 1608, 3° andar, Rodolfo Teófilo, CEP 60430-140, Fortaleza, Ceará, Brazil. Tel.: +55 85 3366 8063; fax: +55 85 3366 8064.
E-mail address: cjeanbr@yahoo.com.br
URL: http://www.cirurgia.ufc.br/default.htm

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theories There are excellent reviews that provide comprehensive overviews about hemangioma of infancy including discussions of hemangioma classification and pathogenesis, natural history, management options and highlighting potential future research directions [4,9–12].

Until recently, preferred treatment options for uncommon, alarming or life-threatening presentations forms included the use of glucocorticoids (corticotherapy), vincristine or interferon with variable, but largely transient success [10]. Unfortunately, these therapeutic regimens have frequent side effects, toxicity and exhibits rebound effects. Steroids exert, possibly, an antiangiogenic effect that decreases endothelial cell proliferation and causes endothelial cell apoptosis [13]. High-dose systemic steroids are, de facto, the standard of care for dangerous IHs, though these drugs are not approved by USA Food and Drug Administration (FDA) for this indication. Currently there is no prospective study in hemangioma patients answering critical questions such as: which type of steroid should be used, how much should we use and for how long time [14]. Short-term side effects of systemic steroids include personality changes, gastric irritation, diminished gain of height and weight, non-systemic fungal infections, and cushingoid appearance. Potential long-term side effects of steroid use include immunosuppression and suppression of the hypothalamic pituitary adrenal function, besides hypertension, hyperglycemia, ophthalmologic changes, myositis, osteoporosis, cardiomyopathy, and neurologic changes [10,14]. For children who steroids have failed or was not well tolerated, vincristine (VCR) is the preferred second systemic therapeutic agent. In vitro studies shown that VCR interferes with mitotic spindle microtubules and induces tumor cell apoptosis. Well known VCR side effect includes peripheral neuropathy, irritability, electrolyte disturbances and constipation [10]. The VCR usage for IHs is described in some retrospective studies with limited number of patients [10,15,16]. The third line of action is interferon (IFN)-α2b [10,17]. IFN act as an antiangiogenic agent, decreasing endothelial cell proliferation and down-regulating bFGF [18,19]. Frequent complications of IFN injection include flulike symptoms (e.g., headache, fever, and myalgia) that may be lessened with the prophylactic administration of acetaminophen [10,20]. The reported efficacy of IFN-α2a and IFN-α2b for treating infantile hemangiomas with a complete response rates of 40–50% using high daily doses [17]. Interferon usage in infants has fallen out of favor mainly because of its neurologic side effects, consisting of spastic diplegia and other developmental motor disturbances [21].

Imiquimod, an immune response modifier, is another therapeutic approach for battling infantile hemangiomas [22–24]. Imiquimod is a low-molecular weight compound, a toll-like receptor (TLR)-7-agonist that is topically applied and induces local production of IFNs at the site of application [25]. The TLR7 ligand activates dendritic cells and macrophages (and possibly other cells) and is expressed in human skin [25,26]. Sauder [25] proposed that imiquimod acts through TLR7, promoting a cellular recognition of microbial and viral patterns beside "dangerous" and anomalous proteins. The recognition is followed by signaling and promoting cellular secretion of proinflammatory cytokines that includes IFNs and pro-apoptotic signaling. Thus, the targeted cells, i.e., virus-infected keratinocytes, mutated or preneoplastic epidermal cells are eliminated [25–27]. By this purportedly mechanism of action, imiquimod exerts antangiogenic, antiproliferative and pro-apoptotic effects. The major side effect is mild-to-marked irritation at the site of application. Hyperpigmentation develops in 50% of treated wounds. Sidbury and colleagues [27] investigated the efficacy and mechanism of action of imiquimod over vascular neoplasm using a mouse hemangioendothelioma model. These authors demonstrated that topically applied imiquimod significantly decreased tumor cell proliferation, increased tumor apoptosis, and increased expression of tissue inhibitor of matrix metalloproteinase (MMP)-1, with decreased activity of MMP-9, both of which are observed in the natural involution of infantile hemangiomas. Based in these findings, authors suggest imiquimod as a novel, less toxic means of treating infantile hemangioendotheliomas and perhaps other cutaneous vascular tumors [27]. Although imiquimod off-label usage for cutaneous infantile hemangiomas are promising, this immunomodulator is not FDA approved for use in children, and only a few case reports and one small open-label uncontrolled trial suggest efficacy of imiquimod for the treatment of infantile hemangiomas [22–24].

Propranolol have recently emerged as a promising treatment for cutaneous proliferative disorders after the serendipitous discovery of French researchers that non-selective β-adrenergic receptor (AR) blockade is highly effective in treating severe infantile hemangiomas [28,29]. Good science and good luck met in the form of Leauté-Labreze et al. article, published June 12, 2008 [28]. The authors observed that propranolol, a non-selective β-blocker usually used for cardiac illness, could lead to a decreased in volume of serious hemangiomas of the face. The exact mechanism by which propranolol promotes this slowing or stopping growth is unknown. Several in vitro and in vivo studies suggests that β-blockers can act in mitotically active (proliferating or involuting) endothelial cells through complexes interactions between fibroblasts, keratinocytes and MCs, interfering with angiogenesis, apoptosis and inflammatory process [30]. Some authors postulates that the therapeutic effect of propranolol on infantile capillary hemangiomas include vasoconstriction, decreased expression of VEGF and bFGF genes through the down-regulation of the RAF-mitogen-activated protein kinase pathway, and the triggering of apoptosis of capillary endothelial cells [31,32]. Denoyele et al. reported two infants with subglottic hemangiomas, which were resistant to other established medical treatments [33]. Both were subsequently treated with systemic propranolol and patients' subglottic hemangiomas responded dramatically to systemic propranolol with no side effects. They concluded that propranolol appears to be an effective treatment for subglottic hemangiomas and should now be used as a first-line treatment for this illness when intervention is required [33].

At one institution (Albert Sabin Pediatric Hospital), we have successfully treated few children affected by infantile hemangiomas using systemic propranolol (2 mg/kg/day per oris). After informed and written consent from parents and approval from our local ethics committee, two white-girls (aged 7 and 13 months, respectively), and a black boy (aged 6-year old) were propranolol-treated. The infants were admitted to pediatric unity and submitted to clinical, laboratory and image exams to rule-out contraindications and concomitant diseases that can precludes propranolol usage (e.g., asthma, diabetes, and cancer). Propranolol was started at a dose of 0.66 mg/kg each 8 h (1 mg/kg/per day) which was doubled the next day. During hospitalization (72 h) children were monitored for vital signs, glucose levels and non-invasive mean arterial pressure. After verification of no side effects, children were discharged and propranolol dosing-regimen maintained during 4–10 weeks. The maximum follow-up time to present day is 6 months. The first girl had an intermittently bleeding upper-lip hemangioma (15 × 10 mm) that prevented normal nutrition and that was unsuccessful treated with steroids during 2 months. She was propranolol-treated for 4 weeks with an uneventful clinical course and the lip hemangioma stopped growing during the first week and improved rapidly. The second girl exhibited a voluminous inferior-lid/periorbital hemangioma (20 × 20 mm) with marked ectropion. Propranolol was immediately initiated (without steroid pretreatment) and we noticed spectacular hemangioma involution and almost complete ectropion vanishing. Propranolol was stopped after 8 weeks and, until the

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present moment, no further procedure was necessary. The third child had a cervical, irregular shaped infantile hemangioma (20 × 20 mm) and a lumbosacral hemangioma located at right buttock (8 × 17 cm). After 6 weeks of treatment, cervical hemangioma becomes flatten and the lumbosacral hemangioma volume was reduced in about 50% with no further improvement until 10 weeks. So, we performed surgical resection of the entirely involved buttock area, closing wound directly. No recurrences were observed.

About crab claws

The healing of skin wound is a natural restorative response that has many unique aspects. It is a complex and dynamics process requiring the collaborative efforts of many different tissues and cell lineages [34,35] with scarring no longer being an inevitable consequence of non-fetal skin healing [36]. Scar management continues to be a challenging clinical problem. Some wounds heal to excess scar due to abnormal responses to healing [37]. People with abnormal skin scarring may face physical, aesthetic, psychological and social consequences that may be associated with substantial emotional and financial costs [38]. Hypertrophic scar (HSc) and keloid are common forms of abnormal skin scars. The distinction between them may be difficult. Both are raised scars. The HSc are often red, itchy, and even painful, and remain within the boundaries of the original lesion, generally regressing spontaneously 12–18 months after the initial injury [37,38]. HSc are common after burn injury on the trunk and extremities and correlate with the length of time required to close the wound [38]. The incidence of hypertrophic scarring in human rises from 33% if healing is delayed for 3 weeks to 78% if healing is delayed for 6 weeks [39]. Keloid scars are benign fibrous cutaneous tumor that appears 3–6 months after trauma. Unlike HSc, keloids extend beyond the borders of the original wound invading the surrounding normal skin in a way that is site specific [40]. A keloid appears firm, painful and continues to grow over time, does not regress spontaneously, and almost invariably recurs after simple excision [38]. Keloids are unique to humans, and there seems to be some genetic predisposition, with dark skinned races being more prone to them, though there are few large epidemiological studies [41]. The incidence of keloids in blacks and Hispanics varies from 4.5% to 16%, with higher incidences during puberty and pregnancy, suggesting a hormonal influence [42,43]. Keloids represent the most extreme example of cutaneous scarring and are the most difficult to treat [40–44]. The term *cheloids* (that resembles crab claws) was coined by Jean Louis Alibert in 1806 to describe the lateral extensions of keloid scar growing into surrounding normal tissue [45].

The pathogenesis of HSc and keloid formation is poorly understood. These disorders represent aberrations in the fundamental processes of wound healing, which include hemostasis, inflammation, increased synthesis and secretion of cytokines and extracellular matrix (ECM) proteins, cell migration and proliferation, and maturation or remodeling of the newly synthesized matrix [34–36,44,46]. Unlike the maturation or remodeling phase of normal wound healing where the scar tissue soften and flatten due to ongoing simultaneous collagen synthesis and degradation and the connective tissue elements regress after the third week, in keloid scar, the collagen synthesis is approximately 20 times as great as that in normal skin and three times as great as in hypertrophic scars [47]. Nakaoka et al. postulates that, in keloids, occurs collagen overproduction that can be attributed to the stronger proliferating activity of keloid fibroblasts [48]. Fibroblasts derived from keloids overproduce type I procollagen, express higher levels of VEGF, transforming growth factor-(TGF-) β1/β2, platelet derived growth factor-(PDGF-)α receptors, and have reduced growth factor requirements in vitro [48,49]. Researchers have demonstrated that keloidal fibroblasts have lower rates of apoptosis and exhibit a down-regulation of apoptosis-related genes [50]. Robles and Berg hypothesized that aberrant healing of wounds in HSc and keloids is secondary to an inability to activate or respond to the negative feedback mechanism in place to suppress fibroblast activity [51]. Recently, Alonso and co-workers hypothesized that healthy individuals carrying a virus, whether known or unknown, associated to some adjuvant, and having some genetic susceptibility, may develop keloids during the scar maturation process [52]. They argue that the virus would make the bone marrow or lymphatic system its reservoir, resting there in a silent state until reach the wound via internal and external circuits. Using internal circuit the viral genome would be transported to the wound via bone marrows or chemotactically attracted circulating fibroblasts. By the external circuit, infecting virus would be shed in damaged skin directly and/or indirectly via contaminated saliva or fomites. Into wounded site, the virus would switch from silent to latent state due some chemical stimulus from repairing tissues, deranging the normal process of wound healing of predisposed individuals [52].

Simple surgical excision of keloid scars has a 50–80% risk of recurrence in despite of sophisticated techniques [40]. Although there are a plethora of therapies for treating keloids, a combination of surgery with either intralesional corticosteroid injection or radiotherapy has been the mainstay of treatment [42,44,46,53]. Briefly, surgical approaches combined with postoperative radiation therapy or intralesional corticosteroid injection – particularly the longer acting ones, such as triamcinolone, that has shown results ranging from spectacular to non-existent [42,44,52–54] – are considered as well established therapeutic regimen for keloid scars, based on extensive clinical experiences. Another therapeutic options for keloids (as like infantile hemangiomas) its interferon (IFN)-α2b and IFN-γ. Both of them interfere with the fibroblast's ability to synthesize collagen [16–18]. Specifically in keloid, IFN-α2b normalizes the collagen and glycosaminoglican (GAG) [55]. Also, interferon is an antiangiogenic agent that decreases endothelial cell proliferation by down-regulating bFGF [53]. A novel therapeutic option is imiquimod. For keloid treatment, imiquimod is started immediately after surgery and continued daily for 8 weeks [56]. Hyperpigmentation develops in 50% of treated wounds and the major side effect is mild-to-marked irritation at the site of application [55,56]. Recently, we conducted an in vivo study about the effect of imiquimod in partial-thickness burns (PTB) [57]. We demonstrated that short-term topical imiquimod treatment on PTB in rats did not improve clinical appearance and scarring (using a clinical assessment scale and a visual analog scale) but rather decreased fibrosis (as shown in samples stained with Sirius Red that were analyzed under polarized light for collagen morphometry) when compared to saline-treated burns. Significant differences in collagen deposition were observed between the treatments. Types-I and III collagen deposition increased in the saline group and decreased in the imiquimod group. Conversely, the proportion between types-I and III collagen differed significantly between treatments in 4 and 21 days postburn ($p < 0.05$ in both cases). Digital planimetry analysis shown that imiquimod-treated scars exhibited lower wound edge migration-rate ($p < 0.05$). Also, we confirmed the immunomodulatory imiquimod effect. Samples stained with hematoxylin-eosin submitted to conventional histology showed accentuated inflammation and delayed reepithelialization in the imiquimod group [57].

In summary, keloid and HSc (K&HSc) differ histologically from healthy skin by a rich vasculature, high mesenchymal cell density, and thickened epidermal cell layer. As afore mentioned, some keloids and HSc have a pink or red appearance with notable telangiectasias that mimics the gross appearance of infantile capillary hemangiomas.

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The Sir James Black's invention and the hypothesis

Systemic or intralesional propranolol may play a role in the amelioration of keloids and hypertrophic scars due to their potential to induce vasoconstriction of over proliferating tissues, triggering apoptosis of endothelial cells and also to their effect as modulator of inflammatory process during wound healing [28–33]. Sir James Black, an academic and an industrial pharmacologist invented propranolol in the 1960's [58]. Propranolol is the β-adrenergic receptor antagonist that revolutionized the medical management of angina pectoris in last 50 years. Sir James's method of research, and experiments about adrenergic pharmacology, and his clarification of the mechanisms of cardiac action, conducted him to receive a MB degree from St. Andrews University in Scotland, and finally to be awarded with the Nobel Prize in Medicine in 1988 [58,59]. Sir James wrote that he began his work to find a way of reducing myocardial demand for oxygen in hearts whose supply was restricted by arterial disease based in Ahlquist's discovery of adrenergic receptors [60]. Raymond Ahlquist proposed in 1948 that different receptors, instead of different molecular modifiers, caused different tissue responses. These specific receptors for epinephrine and norepinephrine, which he localized to different tissues, were generically named α- and β-receptors [60,61]. As quoted by Stapleton: "Sir James defines a discovery as the elucidation of something that exists with or without human understanding of it (e.g., the structure of DNA). An invention, on the other hand, does not exist until the researcher has created it (e.g., a drug such as propranolol)" [58].

In fact, the initial studies about the use of propranolol in hemangiomas come from countries bordering the Mediterranean [28,29,33]. Furthermore, the scarce wound-healing studies involving adrenergic receptors (adrenoceptors-ARs) and β-ARs blockers have been conducted in developing countries [30,44]. Propranolol studies trajectory in this field parallels the Mediterranean diet pathway, from initial incredulity in the so-called French paradox to subsequent empirical experimentation and finally, to scientific facto [62]. In adding propranolol to the melting pot of abnormal (or supra-normal) wound healing, we hypothesized that we can battle keloids with propranolol.

Discussion

There are many similarities and differences between keloids and infantile hemangiomas. Juvenile hemangiomas affect more females than males (the ratio is 3:1) [63]. Although we have seen more and more keloids in pre-pubertal children, they frequently start at puberty (e.g., acnes keloidalis), can grow in size during pregnancy and extend into menopausal years [64]. These facts strongly suggest the potential involvement of hormonal influence. Sasaki et al. hypothesized that hemangiomas contain steroid hormones receptors that mediate cellular proliferation [65]. They found four times higher levels of serum estradiol levels in infants with proliferating hemangiomas than in control samples or serum with vascular malformation. Furthermore, the serum estradiol levels diminished in corticoid-treated IHs. For both, keloids and infantile hemangiomas, researchers have failed in developing a suitable model in lower animals for studies into their pathogenesis. Thus, investigation on this field must rely on analysis of available tissue specimens in different manners and studies of the molecular biology of these benign neoplastic conditions.

Keloid scar can be largely differentiated from IH by their clinical appearance, histopathology features and biologic behavior. However, some clues and evidences suggest a possible link between IH and keloid: cellular hyper proliferation and cell hyperplasia. At optical microscopy, keloid exhibits a hapharzadous deposition of collagen fibers within the dermis, encircled by a mucinous ECM with scarce macrophages and lymphocytes and a plethora of eosinophils, mast cells and plasma cells [66]. Abnormally large collagen bundle complexes were identified in keloids but were absent from hypertrophic scars [41]. On keloid, collagen appears as thick hyalinized bands of eosinophilic nodules, surrounded by numerous small vessels, frequently occluded [39]. Kischer et al. have compared the microvasculature of HSc and keloids with that of normal dermis and normal scars [66]. These authors observed increased occlusion of the microvessels by endothelial cell proliferation in abnormal scars when compared to normal dermis. They suggested that perivascular myofibroblasts contraction may contribute significantly to increased occlusion of microvasculature that leads to hypoxia producing detrimental modulating effects on collagen production [67].

MCs are resident connective tissue cells able to secrete numerous inflammatory mediators in response to chemical and immunological insults and might be implicated in the fibrotic processes of various tissues [67]. MCs play an essential role in the production of keloid and hypertrophic scarring and have been demonstrated in vitro that MCs are pro-fibrogenic [68–70]. In fact, the presence of MCs in early fibrosis and their participation in fibrotic diseases with different pathologies is well known, although the exact contribution of MCs to these conditions is largely unknown [69]. A direct role of human MCs on skin fibrosis was shown by Garbuzenko et al. by investigating the in vitro effect of MCs on skin fibroblasts [67]. In their study, mast cells were found to stimulate skin fibroblast proliferation, collagen synthesis and three-dimensional collagen lattice contraction [71].

Histologically, hemangioma appearance varies according to its developmental stage [68]. Immature hemangiomas, i.e., in early proliferation phase during the first year of life, are characterized by unencapsulated masses and dense cords of mitotically active, plump endothelial cells in close association with pericytes, forming syncytial aggregates, the hallmark of this stage [63]. Few and compressed small caliber lumina are present. Special stains – reticulin and periodic acid-Schiff (PAS) – reveal well-developed basement lamina around primitive vessels [63,66–68]. MCs are known to play a role in neoangiogenesis, they increase during the proliferating phase and are present in varying numbers in all stages [72]. Later in the proliferative phase, the vascular lumina enlarge and are blood filled. The more mature hemangioma is usually lobulated. An increase of apoptotic endothelial cells and a decrease in plump, mitotically active endothelial cells herald the involution phase. After the first year, proliferation and involution occur concurrently. As involution progresses, the endothelial cells continue to mature and assume a flatter appearance. The vascular channels continue to enlarge until few, mature ectatic vessels remain [35,56,67]. Ultrastructural studies of involuting phase hemangiomas reveals signs of endothelial discontinuity and vessel degradation [73]. The MCs fall to normal levels as involution is concluded [11,12]. Much of the proliferating endothelial cell mass is replaced with inter- and intralobular fat tissue and dense collagen deposited in the perivascular areas fibro-fatty tissue. Varying degrees of epidermal atrophy, scar tissue, and loss of elastic tissue can be seen in late involuting lesions [11,12,67,72]. Qu et al. studied MCs from tissue samples characterized by fibrosis, hyperplasia and neovascularization (idiopathic pulmonary fibrosis, rheumatoid arthritis and cutaneous hemangioma), and normal lung tissue and normal skin [74]. Using specific antibodies to mast cell tryptase, tissue macrophage, and to bFGF – a potent angiogenic and mitogenic polypeptide that has been implicated in the wound-healing process – they found bFGF is localized to the majority of MCs. Qu and co-workers suggests that bFGF may contribute to cell proliferation and angiogenesis associated with MCs, also contributing to that pathological conditions by releasing this polypeptide [74].

Several studies have shown that eosinophils and their products are present in a number of fibrotic conditions [75–77]. Eosinophils

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are pleiotropic multifunctional leukocytes involved in initiation and propagation of diverse inflammatory responses, as well as modulators of innate and adaptive immunity by producing Th1 and Th2 cytokines as well as regulatory cytokines and chemokines [76]. In vitro studies proven that the effects of eosinophils on fibroblasts parallel MCs activities. Solomon et al. produced an extensive and well written review focused on the cross-talk that occurs among MCs, eosinophils and fibroblasts in terms of their importance in the perpetuation of allergic inflammation and in contributing to the fibrosis and/or remodeling processes that occurs in vernal keratoconjunctivitis (VKC) [77]. These authors summarized data from many studies and the enrollment of some of the eosinophil-associated mediators such as eosinophil cationic protein (ECP), major basic protein (MBP), IL-4, IL-6, IL-9, IL-13, TGF-β, GM-CSF and nerve growth factor (NGF) in pro-fibrogenic and/or anti-fibrolytic activities in different stages of inflammation and wound repair [77]. Piliponski et al. investigated the in vitro effects of eosinophils on MCs co-cultured with fibroblasts. They have demonstrated that the membrane form of stem cell factor (SCF), the main human mast cell survival and differentiation factor, is involved in the increased responsiveness of mast cells to IgE-independent activation when in presence of fibroblasts [78]. Solomon and his group also demonstrated that fibroblasts also enhanced the viability and functional activity of peripheral blood eosinophils in vitro, possibly via by fibroblast-derived granulocyte-macrophage colony-stimulating factor (GM-CSF) [79]. In addition, Leonardi and co-workers confirmed that fibroblasts produce survival factor for eosinophils which prolongs their persistence in tissues [80]. Studying fibroblasts cultured from conjunctival biopsies from VKC patients they found that Th2 cytokines significantly decreased the production of MMP-1 and increased that of the tissue inhibitor of metalloproteinase (TIMP)-1, thereby enhancing the eosinophils survival and build-up of collagen in the tissue [80].

According to previously cited studies, despite some differences at histological level, therapeutic strategies for keloids and hemangiomas are quite similar. They are equally difficult to treat, requiring multifarious modalities of treatment and enrollment of several medical specialties; no single treatment is always successful and also, they frequently recur. Keloids have no gender preference. There is little evidence for efficacy based on controlled studies and the current options for the treatment and prevention of both conditions are not satisfying. To discuss all of them would be beyond the scope of this article. The β-adrenoceptors blocker (i.e., propranolol) appears on the horizon as a promising therapeutic strategy.

Sixty plus years of research have led to our current understanding of adrenergic receptors since they were first discovered and classified into α and β-adrenoceptors by Ahlquist in 1948 [60,61,81,82]. The β-ARs were further identified in various tissues by both pharmacological and molecular approaches [81–84]. Currently there are four subgroups of β-ARs identified. Although these receptors may be found in more than one location in the human body, β1-ARs are primarily found on cardiac myocytes, β2-ARs are located chiefly in vascular and bronchial smooth muscle, β3-ARs are concentrated in adipocytes, and β4 ARs reside in the myocardium [82–86].

The β-ARs are competitive pharmacologic inhibitors of catecholamine actions that influence a wide number of physiologic and metabolic activities in human beings [30,85–86]. Propranolol is the representative drug of the β-adrenergic blockade agents and is considered non-selective with respect to its β-1 and β-2 receptor antagonism. Moreover, it has been described that propranolol has a low antagonist potency against β3-ARs [30]. The efficacy of propranolol in both intravenous and oral forms was largely proven and it quickly became an accepted drug for rhythm disturbances, hypertension and hypertrophic cardiomyopathy [58,59]. Notwithstanding their narrow therapeutic index [84–86] and the fact that β-blockers have been more extensively studied due its cardiac effects, novel insights derived from clinical and experimental studies about non-cardiac β-blockers effects have highlighted the role of β-ARs in wound-healing process. Souza and associates [30] have shown that non-selective β-AR blockade impairs wound healing of excisional cutaneous lesions in rats. In propranolol-treated animals, wound contraction and the formation of the neo-epidermis and granulation tissue were delayed. These authors speculated that delayed wound contraction caused by β1- and β2-adrenoceptor blockade may be related to alterations in the composition of the ECM that disturb the interaction between myofibroblasts and the ECM. Souza et al. [30] also observed that non-selective blockade increased polymorphonuclear (PMN) cells migration in its experimental model leading to delayed wound healing, possibly via inhibition of adenil-cyclase and a subsequent reduction in cAMP levels produced by keratinocytes. They speculated that propranolol delayed formation of the neo-epidermis possibly by inhibiting keratinocyte migration and via the same mechanism of action. In propranolol-treated animals, these authors observed a significant reduction of the reepithelialized wound area, with an increase in the amount of proliferating keratinocytes (proliferating cell nuclear antigen (PCNA) – positive) and in the thickness of the neo-epidermis. They assumed that although propranolol may have increased myofibroblast density, the β1- and β2-AR blockade have enhanced the biodisponibilty of β3-ARs resulting in reduced density of collagen fibers and hydroxyproline levels [30].

Keloid and HSc represent aberrations in the fundamental processes of wound healing [44]. Some K&HSc mimics the gross appearance of infantile capillary hemangioma. Although K&HSc seems have no gender preference, as like IH they suffer hormonal influences [64,65]. We have seen patients submitted to open heart surgery (the great majority aged more than 60-year old) in search for sternotomy-scar treatment. After June 2008 (when the work from French investigators was published) we have sought asking patients about propranolol or other β-AR blocker usage. We observed more pronounced scars in non-β-ARs blocker user (in view of publication). Now, at our institution, we are starting an interdisciplinary retrospective study involving cardiac surgeons, pediatric cardiologists and other plastic surgeons to investigate if hypertrophic and keloid scars can be improved by propranolol usage. Also, we are developing a protocol to culture keloid tissue in the guinea pig cheek pouch with the intention of studying integration of this xenograft and the effects of various β-ARs blocker in graft versus host disease.

Conclusion

We agree with the words of Albert Szentgyorgyi (Nobel's Prize awarded for isolating Vitamin C) that "Scientific inquiry is seeing what everyone else is seeing, but thinking of what no one else has thought" [87]. Notwithstanding, all of us have to follow the fundamental medical precept of Hippocrates (ca. 460-ca, 377 B.C.): *Primum non nocere* (First do no harm). Propranolol usage can be the missing ingredient in the wound-healing bouillon that can lead us to better fighting keloid and, perhaps, hypertrophic scars. Meanwhile, its widespread use can lead to significant poisoning from overdose. A better knowledge of beta-adrenergic system pathophysiology and the pharmacokinetics of β-blockers, besides understanding their role in immunomodulation are, undoubtedly, urgent and necessary.

Conflict of interest statement

None declared.

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