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REVIEW ARTICLE

Novel Insights on Understanding of Keloid Scar: Article Review

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Abstract Keloid scar, dermal benign fibro-proliferative growth that extends outside the original wound and invades adjacent dermal tissue due to extensive production of extracellular matrix, especially collagen, which caused by over expression of cytokines and growth factors. Although many attempts were made to understand the exact pathophysiology and the molecular abnormalities, the pathogenesis of keloid scar is yet to be determined. Even though there are several treatment options for keloid scars include combination of medical and surgical therapies like combination of surgical removal followed by cryotherapy or intralesional steroid therapy, the reoccurrence rate is still high despite the present treatment. In this review, PubMed, clinical key and Wright State Library web site have been used to investigate any update regarding Keloid disease. We used Keloid, scar formation, hypertrophic scar and collagen as key words. More than 40 articles have been reviewed. This paper reviews literature about keloid scar formation mechanism, the most recent therapeutic options including the ones under research.

Introduction

Wound healing is a sophisticated dynamic process that leads to tissue repair or regeneration and has three main time dependent phases: inflammatory phase, proliferative phase and remodeling phase.[1] The healing process starts immediately after skin injury and takes months to complete. During the inflammatory phase, many cytokine mediators are activated by platelet degradation, a process that ultimately leads to recruitment of inflammatory cells, epithelial cells, and fibroblasts. Platelet degranulation leads to activation of clotting cascade to form a hemostatic fibrin clot.[1,2] In the second stage of the wound healing, proliferation begins around day 4 or 5 with the relocation of fibroblasts into the wound matrix and inward migration or epithelialization of keratinocytes from the wound margin or hair follicles.[2,3] The third and last stage in wound healing is the remodeling phase, which usually begins three weeks after tissue injury; this phase is responsible for intra- and interpersonal differences in scar qualities. Microscopic findings of the remodeling stage include decreases in fibroblast count, occlusion of blood vessels, and hardening of collagen fibers. Continuous collagen production and degradation have an effect on remodeling of the mature wound matrix for approximately six months post-closure. In the mature wound, the initial elastic fiber network is no longer observed, thus explaining the rigidity and absence of scar elasticity.[2] Up to this point, collagen production and

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degradation balance each other with no significant change in the amount is observed. A healing of an incisional wound could become an ugly scar if the balance between production and degradation of collagen was lost during the remodeling phase.[3] Ultimately, abnormal scars such as keloid scars and hypertrophic scars can develop as a result of this imbalance. Historically, the earliest-known appearance of keloid scarring was reported around 1700 CE Egypt in the Smith Papyrus. Later, modern terms were used to describe these scars like "cancroïde" and "chéloïde", which belong to dermatologist Baron Jean-Louis Alibert. In the 19th-century, he used the term "to refer to their crab claw-like appearance".[4,5] In fact, the term keloid means crab claws in Greek. Keloid scarring is a fibro-proliferative disease that affects human-beings after escaping the normal process of wound healing.[6] This abnormal activity, is found mainly in people of African descent. Furthermore, around 10% of the keloid incidence occurs in the African-American population. In fact, apart from the hairless tissue of palms and soles, the distribution of keloid is equal in both sexes and the highest incidence of the scar occurs in the second and third decades of life.[2,6] Until now, we understand that wound healing might be complicated by keloid scar formation; however, its pathophysiological mechanisms are not fully understood.[7] Moreover, keloids form after a disruption of skin integrity that follows superficial and deep injuries and, most commonly occur after physical injuries such as incisions, scratches, and insect bites. They also occur after piercing (Fig. 1), iatrogenic trauma like vaccinations, needle sticks, surgical procedures, thermal or chemical burns, and skin eruptions such as chicken pox. In many cases it happens spontaneously after allergic reactions and other insults.[2,8] Keloid disease is labeled as a failure to suppress the wound healing process that results in an excess of scar tissue.[2] In 1962 and 1970 respectively, both Mancini and Peacock classified excessive scarring into hypertrophic and keloid scars. Based on their classification both scars grow above skin level. Additionally, hypertrophic scar does not extend beyond the site of injury; however, keloid scar typically extend beyond the wound site.[2] A keloid scar is a dermal benign fibro-proliferative growth that extends beyond the original wound edges and invades the adjacent normal dermis. Furthermore, once this scar happens the regression is very rare.[9] Actually, keloid scarring appears as fixed, irregular, mildly tender, and pink to purple in color with well-circumscribed margins and a shiny surface with occasional telangiectasia. In contrast, hypertrophic scar has the similar look, and is commonly linear following the shape of wound. Although both lesions are usually itchy, keloids can cause significant pain and hyperesthesia.[10] Despite the fact that keloid is classified as a dermal benign growth, it behaves like malignant cells in terms of invasion and demonstrates biological features similar to malignant tumor cells, including hyper-proliferation.[2] From a histological point of view, hypertrophic scar contains mainly type III collagen

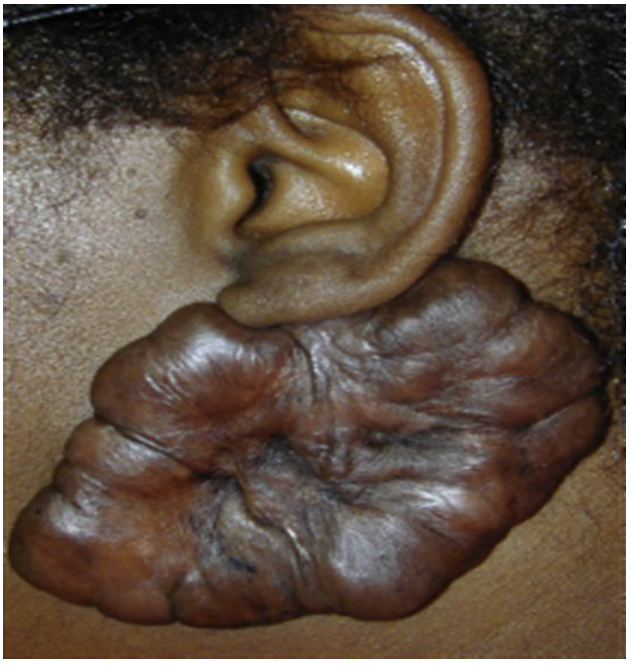

Figure 1

arranged parallel to the epidermal surface and with plentiful nodules and giant extracellular collagen filaments.[2,11] Keloid scar progressively grows over time without inert or regressive phase and invades the adjacent tissue. Furthermore, the main composition of keloids is abnormally thick, haphazardly branched and septal disorganized type I and III collagen bundles with no lumps, extra myofibroblasts[2,11] and numerous overactive fibroblasts. Although there are useful clinical signs used to differentiate both keloid and hypertrophic scars, the clinical behavior and treatments of both scars are different. Some physicians still have difficulty distinguishing between both scars and thus confuse keloid with hypertrophic scars. Hence, it is important to create criteria to differentiate between both scars.[11] From a clinical standpoint, keloid scar appears as a firm, slightly tender, bosselated lumps with a glossy surface with or without telangiectasia. Its epithelium is thinned and occasionally there are focal areas of ulceration. Further, keloid scar is pink to purple in color and usually accompanied by hyperpigmentation.[10,11] Initially, the lesion is erythematous, then the color changes into brownish red, then it becomes paler as it ages. Moreover, the most common locations are the earlobes, shoulders and pre-sternal skin, all areas that have no hair follicles and other glands. Keloid scar is usually projecting above the level of the adjacent skin,[11] whereas hypertrophic scar is usually elevated, but not more than 4 mm above the skin. Moreover, hypertrophic scar is red or pink in color, firm, pruritic, does not extend beyond the margins of the wound, and tend to regress over time.[11,12] Until now, the pathology of keloid scars is not well understood and the precise mechanism of its pathogenesis is still unknown.[6] Scientists consider