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Keloids: what do we know and what do we do next?

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It is believed that the knowledge of excessive scarring and keloids as a pathologic consequence of cutaneous injury was first described in approximately 1700 BCE as outlined in the Edwin Smith Papyrus.¹ Keloids represent a pathologic response to dermal injuries resulting in firm, rubbery tumors with a shiny surface appearance that grow beyond initial wound boundaries. Keloid scarring is unique to human beings, and it occurs predominantly on the chest, back, shoulders, and earlobes, whereas it rarely occurs on the soles or palms. One plausible explanation stems from the fact that humans have different sebaceous glands than other mammals and that these higher risk areas of the human body may have higher concentrations of sebaceous glands. The so-called “sebum hypothesis” proposes that the sebum released by the sebaceous glands onto the skin surface may come into contact with T-cells after cutaneous injury and cause an inflammatory reaction that leads to keloid progression,² but more in-depth studies to prove this hypothesis are warranted.

Fibroblasts derived from keloids are marked by an overproduction of fibronectin and type I procollagen, a high expression of transforming growth factor (TGF)- β 1, TGF- β 2, vascular endothelial growth factor (VEGF), and plasminogen activator inhibitor-1, and an upregulation of platelet derived growth factor receptors.³ The genetic basis for these alterations in fibroblast response remain unanswered, but several studies examining differential gene expression in keloid fibroblasts have observed an upregulation of antiapoptotic genes such as p53,⁴ bcl-2,⁴ and PEA-15.⁵ Other studies have demonstrated differential apoptotic gene expression according to the area of the keloid with antiapoptotic AVEN upregulation at the keloid leading edge and proapoptotic ADAM-12 gene upregulation in the central core of the keloid.⁶ These findings suggest an important role for apoptosis in the progression of the disease and a genetic variability depending on the location of the sample acquisition. Moreover, certain ethnic groups such as Blacks, Hispanics, and Asians have been shown to be more predisposed to keloids,⁷ and a family history of keloids has also been associated with a higher probability of keloid formation after cutaneous injury.⁸ These observations suggest a genetic predisposition that may give us further insight into the pathophysiology of the disease. Interestingly, studies involving entire genome scans of families whom are susceptible to keloid formation have pointed to specific genes,⁸ but unequivocal proof of a gene responsible for keloid propensity has yet to be determined.

As stated, this fibroproliferative disorder can occur as a consequence of cutaneous injuries such as surgery, burns, and other trauma, but there is also evidence of spontaneous keloid formation in the absence of injury. It has also been reported that keloids can develop several years after a minor injury, which undermines evidence of their potential for spontaneous formation. Further-more, the delayed keloid response also make the investigation of its early stage pathologic mechanism, as well as diagnosis, that much more difficult to assess.⁹

We need to face the fact that we do not know much about keloids, their pathologic mechanisms, their genetic footprint, or even effective therapies to treat them; only then can we begin to ask ourselves the right questions. One important hurdle is the lack of a well-characterized diagnosis of keloids and its clear distinction from hypertrophic scarring, a problem that still remains widespread in the medical community.¹⁰ Research into effective therapies for the treatment of keloids has been confounded by this lack of a proper characterization of keloids and their differentiation from hypertrophic events. This point is well highlighted by Durani and Bayat¹¹ in a meta-analysis review of 112 different clinical studies, where they reported a lack of confidence in current research on keloid therapeutic outcomes. How, then, can we begin to solve a problem when the problem itself is not well defined? Researchers need to go back to the basics and try to understand the pathologic mechanisms of keloids before any therapeutic treatments can be investigated. In this issue of *Translational Research*, Mogili et al¹² report on the balance of angiogenic and antiangiogenic factors in the systemic and local environment in patients with keloids. The authors report an upregulation of VEGF and a downregulation of endostatin in the serum and the affected tissue of patients who suffer from keloids. Although the upregulation of VEGF in keloids is not an original finding, the discovery of a downregulation of endostatin is a more interesting finding considering some controversy on this subject in the literature. However, this preliminary study does have its limitations. The low sample size makes it difficult to make accurate claims regarding tissue expression levels of VEGF and endostatin. In addition, the authors fail to demonstrate any evidence for therapeutic potential from the observed findings by not delving deeper into the underlying pathobiologic mechanisms of the VEGF/endostatin changes. Regardless, the findings from this study add one more piece to solving the complex puzzle of keloid characterization, and more studies are warranted to provide additional insight into keloid pathology.

Once keloids have been better characterized and better differentiated from other fibroproliferative skin pathologies, a more in-depth analysis of well-designed, randomized control studies of keloid therapeutic strategies will be required. However, research into novel experimental therapies is also warranted. One such approach stems from the similarities between keloids and cancerous tumors. Currently, treatments such as surgical excision, radiotherapy, and laser therapy have been applied commonly for the treatment of both cancer and keloids. In 1999, Fitzpatrick¹³ was the first to demonstrate the use of 5-Fluorouracil, a common chemotherapy agent, to effectively reduce keloid size. This work opens the door for a whole gamut of potential therapies, and it may be worthwhile to look closely at the vast knowledge of cancer therapeutics and borrow certain techniques for the management of keloids. Another promising avenue of research toward effective keloid therapy lies in the use of stem cells. In light of their role in the innate wound healing process, mesenchymal stem cells (MSCs) have been proposed as potential therapeutics to promote scarless wound

healing. Mansilla et al¹⁴ demonstrated that treatment of mouse skin defects with human MSCs resulted in scarless healing after 14 days. Moreover, Klinger et al¹⁵ demonstrated the potential use of lipofilling to improve scar quality, presumably mediated by adipose tissue-derived stem cells. However, Akino et al¹⁶ reported that human mesenchymal stem cells may actually play a role in promoting keloid formation. Nevertheless, more studies investigating the use of stem cell technology for the treatment of keloids are warranted.

In conclusion, we do not know a lot about keloids, yet we are making strides to closer understanding the problem, and promising therapies have begun to be generated and will continue to evolve over the years to come.

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