Can Antimicrobial Peptides Be Repurposed as a Novel Therapy for Keloids?

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Dear Editor,

Keloids are traditionally viewed as benign fibroproliferative scars with aggressive dermal growth that extend outside the borders of the original wound or injury owing to excessive production of extracellular matrix, in particular collagen, which is caused by overexpression of growth factors and inflammatory cytokines. Although many treatment modalities have hitherto been exploited, the management of keloids still remains challenging for clinicians [1]. Current therapies of keloid comprise corticosteroids, cryotherapy, laser therapy, surgery, radiotherapy, and various pharmaceutical drugs. Over the past years, researchers have propounded promising antikeloid therapeutic approaches including antihypertensive pharmaceuticals, calcineurin inhibitors, electrical stimulation, microneedle physical contact, and RNA-based therapies [2].

Antimicrobial peptides (AMPs) or host-defense peptides are prominent constituents of the intrinsic defense system of virtually all organisms, serving as endogenous antibiotics to ward off invading pathogens. They

usually display common physicochemical characteristics: (I) short chain length (typically <50 amino acids), (II) a net positive charge, (III) a balance between polar and hydrophobic regions, and (IV) a potential to adopt different secondary structures in membranous environments [3, 4]. AMPs have spurred new interest among researchers for developing novel anti-infective agents owing to their broad-spectrum and fast-acting microbicidal effects along with their low tendency to elicit target-based resistance. Remarkably, several therapeutic functions beyond anti-infective properties have been described for some AMPs such as immunomodulatory, anticancer, antidiabetic, and analgesic effects [4]. It should be borne in mind that some AMPs play a vital role in both skin barrier and function. From a dermatological viewpoint, some AMPs have the potential to treat multiple skin maladies, which are exemplified by melanoma, acne, diabetic foot ulcer, and psoriasis [5].

Experimental studies revealed that human cathelicidin LL-37 is capable of suppressing excessive collagen synthesis. For instance, a lower expression of peptide LL-37 has been detected in the overlying epidermis of keloids compared to normal skin samples, as evidenced by immunostaining technique. In human dermal fibroblast cell

line culture, the expressions of COL1A1, COL1A2, and COL3A1 mRNAs were also substantially decreased in exposure to 40 nM of LL-37. Furthermore, LL-37 was shown to hamper transforming growth factor- β (TGF- β) induction of Smad2 and Smad3 phosphorylation. It is noteworthy to mention that LL-37 has the capacity to inhibit human dermal fibroblast collagen production through G-protein-coupled receptor-, extracellular signal-regulated kinase-, and Ets-1-dependent pathways [6]. Consistent with these findings, another study demonstrated that intracolonic administration of LL-37 or intravenous delivery of LL-37 gene (*Camp*)-expressing lentivirus considerably lessened colonic COL1A2 mRNA expression in trinitrobenzene sulfonic acid-exposed mice. When administered intravenously, *Camp*-expressing lentivirus reduced cecal fibrosis in mice during *Salmonella* infection. Furthermore, both 3- and 5-mM concentrations of LL-37 were able to decrease TGF- β 1- and/or insulin-like growth factor 1-mediated collagen protein synthesis in human intestinal fibroblasts isolated from 3 normal subjects and 2 patients with Crohn's disease as well as in human colonic CCD-18Co fibroblasts [7]. Based on these findings, LL-37 mitigates collagen production through different signaling pathways, thus attesting to its antifibrogenic properties.

In keloid tissues, expression of two keratinocyte-produced S100 peptides including psoriasin and koebnerisin has been shown to be markedly diminished, as assessed by quantitative PCR, immunoblotting, and immunofluorescent staining. These peptides seem to have a prominent role during the physiological wound healing process. S100 peptides also influence collagen production in cultured fibroblasts [1]. In this context, data showed that psoriasin (0.01, 0.1, and 1 μ g/mL) significantly reduced levels of COL3A1 mRNA compared to controls ($p < 0.05$). Likewise, a considerable decrement in mRNA expression levels of COL1A1 and COL3A1 was noticed following exposure to koebnerisin at most of the mentioned concentrations. Both S100 peptides act synergistically to attenuate the expression of collagens, fibronectin-1, α -smooth-muscle actin, and TGF- β by fibroblasts as well as inhibiting fibroblast proliferation [1].

In an attempt to compare peptidomic profiles of human hypertrophic scar tissue with matched normal skin, Li et al. [8] divulged that out of 1,697 peptides, 179 peptides were differentially expressed in human hypertrophic scar tissue using liquid chromatography-tandem mass spectrometry (fold change >1.5 , $p < 0.05$). Accordingly, in comparison to normal skin tissue, 95 and 85 peptides were upregulated and downregulated in hypertro-

phic scar tissues, respectively. Intriguingly, bioinformatics analysis indicated that 78 differentially expressed peptides shared homology with AMPs. In line with these findings, one study showed different expression profiles of human beta defensins (HBD) in 10 patients with keloid compared to normal skin samples. At either mRNA or protein level, no expression of HDB-2 was noticed in keloid samples, whilst expression levels of both HDB-1 and HBD-3 in keloids were 3- and 5-fold as high as normal skin samples, respectively [9]. Collectively, both upregulation and downregulation of some AMPs are involved in keloid pathogenesis.

In recent years, admirable efforts have been devoted to potentiating current antikeloid therapies. It seems that AMPs can be repurposed for the treatment of fibrotic diseases such as keloids and hypertrophic scars, though the exact antifibrotic mechanisms of AMPs are not completely comprehended. In spite of encouraging properties of some AMPs in the treatment of keloids, the results should be extrapolated by further clinical experiments prior to their therapeutic utility. Some challenges such as medical safety and route of administration still lie ahead in the path toward clinical application of AMPs against keloids. All in all, AMPs can open up new avenues in different fields of medicine, in particular dermatology.

Key Message

Antimicrobial peptides can serve as a promising candidate for the treatment of keloids.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

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Author Contributions

All authors contributed equally to this work.

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