Opinion

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Psychological stress enhances keloid development via stress hormone-induced abnormal cytokine profiles and inflammatory responses

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Abstract

Keloid is a fibroproliferative disorder resulting from the abnormal wound healing process, and it causes both cosmetic concerns and functional disabilities. Genetic predisposition, wound trauma, foreign body reaction, mechanical stretch, and immune dysfunction are common risk factors, but there remain mechanisms unclarified, leaving challenges in addressing the clinical concerns of recurrence and resistance. However, similar patterns of growth and metabolism between keloids and cancers provide a unique insight into the future exploration of keloid pathogenesis. Psychological stress has been demonstrated to be involved in the development and drug resistance of multiple cancers, but this aspect remains less-explored in keloids. Clinical observations and published investigations have noticed that persistent stress is common among keloid patients and their symptoms tend to deteriorate under stressful conditions. Following a thorough review of the published literature, we have identified three signaling pathways that might imply how stress hormones are likely to influence the keloid pathogenesis via activating adrenergic receptors and dysregulating the immune system. Thus, we hypothesized that psychological stress would be a key risk factor for keloid development via stimulating fibrosis, aggravating local hypoxia, and inflammation.

INTRODUCTION

Keloids give rise to both cosmetic concerns and functional disabilities as a result of fibroproliferative disorder and excessive collagen deposition after abnormal wound healing. Furthermore, subjective symptoms derived from this disease such as pain and pruritus could dramatically affect patients' quality of life by causing significant psychological stress. Previous studies have revealed that the genetic background, wound trauma, foreign body reaction, mechanical stretch, and immune dysfunction are critical risk factors for keloid development, but the exact mechanism of keloid formation could be more complicated than what has been found and other risk factors are also likely to be involved, posing challenges to clinical treatment.

Described as "the non-specific response of the body"[1], psychological stress has a complicated and profound influence on the functional state of affected human bodies by secreting various stress hormones. These primarily include glucocorticoids through the activation of the hypothalamic-pituitary-adrenal axis and catecholamines through the sympathetic nervous system[2]. Glucocorticoids can significantly affect cell metabolism and immune functions in the long term, while the effects of catecholamines [norepinephrine (NE), epinephrine (E)] are mediated via binding to α-adrenergic receptors (α-AR) or β-adrenergic receptors (β-ARs) facilitating the human body to react to all kinds of stressors. However, if the stressful situation becomes overwhelming, the combined action of stress stimulators remains persistent the physiologically maintained balance maybe disrupted leading to enhancement of pathophysiological processes for multiple diseases.

Psychological stress has been indicated for contributing to cancer development for decades. For example, in patients with lung cancers, stress has become an established predictor of mortality[3]. Stress hormones (NE, E) can also promote resistance to tyrosine kinase inhibitors (TKIs) of epidermal growth factor receptor (EGFR) in non-small cell lung cancer (NSCLC)[4] and increase tumor-derived interleukin-6 (IL-6) overexpression in ovarian cancer cells[5]. Featured with uncontrollable proliferation, invasiveness, and glycolysis-dominant metabolic pattern[6], keloids are regarded as benign skin tumors and the accumulating literature evidence suggests that certain pathogenic signaling pathways might be shared between keloids and tumors. As an example, the elevation of IL-6 level, which was determined as a promoting agent in NSCLC resistance and its poor prognosis, has also been identified to contribute to keloid formation[7]. Therefore, it would be reasonable to investigate whether psychological stress influences keloid pathogenesis and explore the potential of stress hormones (NE, E) as therapeutic targets.

The psychological and mental impacts of pathological scars have been studied in clinical settings and been reported in an investigation among a black African population. Of this, 48.9% of keloid patients thought they were stigmatized and 35.8% complained about their limited social interactions[8]. Furtado *et al.*[9] from Brazil have reported psychological stress as a risk factor for postoperative keloid recurrence in a clinical study and proposed a novel psycho-neuro-immune-endocrine etiology where they pictured a macroscope of the "brain-skin connection" in keloid pathogenesis without mentioning detailed pathways[10]. For quite a long time, the potential association between stress hormones and keloid pathogenesis has been neglected according to Pubmed and Embase database searched with key words: keloid AND stress, keloid AND psychological stress, keloid AND mood disorders. By analyzing the published evidence with regards to bio-active molecules in keloid tissues and the effects of stress hormones (NE, E) on skin fibroblasts and immune cells (macrophages) in vitro and immune cytokine profiles both *in vitro* and *in vivo*, we outline in this manuscript three possible signaling pathways that might explain these phenomena.
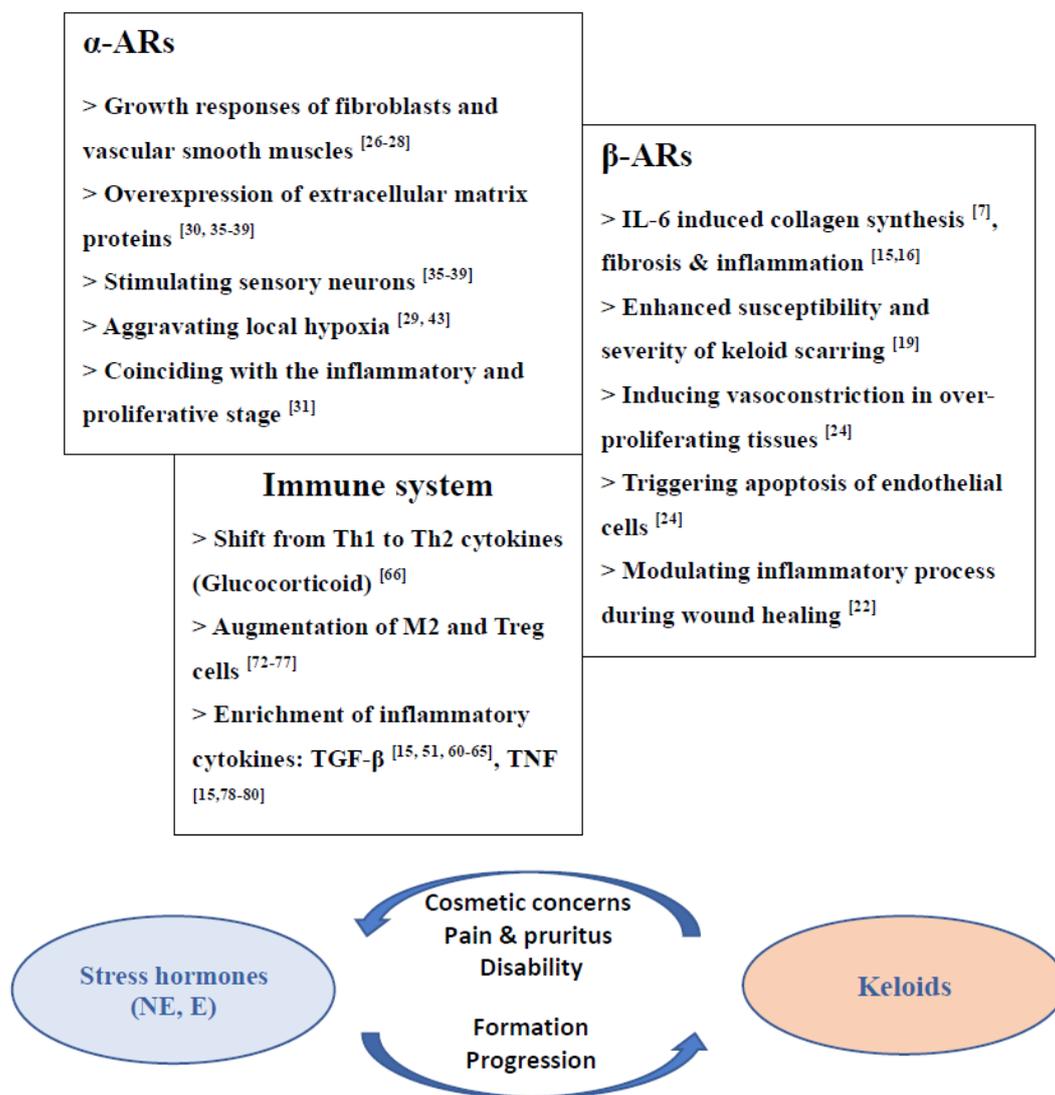
α-ARs

> Growth responses of fibroblasts and vascular smooth muscles [26-28]
> Overexpression of extracellular matrix proteins [30, 35-39]
> Stimulating sensory neurons [35-39]
> Aggravating local hypoxia [29, 43]
> Coinciding with the inflammatory and proliferative stage [31]

β-ARs

> IL-6 induced collagen synthesis [7], fibrosis & inflammation [15,16]
> Enhanced susceptibility and severity of keloid scarring [19]
> Inducing vasoconstriction in over-proliferating tissues [24]
> Triggering apoptosis of endothelial cells [24]
> Modulating inflammatory process during wound healing [22]

Immune system

> Shift from Th1 to Th2 cytokines (Glucocorticoid) [66]
> Augmentation of M2 and Treg cells [72-77]
> Enrichment of inflammatory cytokines: TGF-β [15, 51, 60-65], TNF [15,78-80]

Stress hormones (NE, E)

Cosmetic concerns
Pain & pruritus
Disability

Formation
Progression

Keloids

Figure 1. Three possible pathways that may explain how stress hormones (NE, E) could induce abnormal cytokine profiles and inflammatory responses. TGF: transforming growth factor; TNF: tumor necrosis factor; AR: adrenergic receptors; IL: interleukin; NE: norepinephrine; E: epinephrine

HYPOTHESIS

The psychological and mental state of keloid patients has been investigated and observed in clinical practice, but unfortunately, the association between the psychological stress-induced pathological alterations in keloids has been neglected. Based on the published literature, we propose the hypothesis that psychological stress can be a risk factor of keloid development as stress hormones (NE, E) might contribute to keloid pathogenesis [Figure 1]. Therefore, attenuating the AR-receptor function(s) may enhance the efficacy of traditional keloid treatments and reduce the therapeutic resistance. The following sections provide a detailed description of the hypothesis with related supporting evidence from the literature.

EVALUATIONS OF THE HYPOTHESIS: THE PROMOTING EFFECT OF PSYCHOLOGICAL STRESS ON KELOID PATHOGENESIS

Stress hormones could increase IL-6 expression to enhance fibrosis via activating β-ARs

As a critical mediator of fibrosis[11-14] and inflammation[15], elevated IL-6 level has been identified in both keloid tissues and psychologically stressed population. Other studies revealed that the stress hormones

(NE, E) increased IL-6 expression and increased resistance in NSCLC patients[4]. Therefore, we hypothesize that the psychological stress (NE, E) might stimulate keloid pathogenesis by enhancing IL-6 expression via activating β-ARs, and the use of β-blockers such as propranolol might facilitate the efficacy of current keloid treatments.

IL-6 is one of the Th1 type cytokines related to pro-fibrosis and inflammation[16,17], which has been regarded as a marker of keloid progression. A significant increase of IL-6 and IL-6 signaling elements was observed in keloid fibroblasts (KFs) compared to normal fibroblasts (NFs)[7]. Moreover, the induction of IL-6 by IL-6 peptide in NF cultures or inhibition of IL-6 or IL-6Ra by their corresponding antibodies in KF cultures rendered a dose-dependent increase or decrease in the synthesis of collagen type I[7]. This was possibly the result of the suppression of matrix metalloproteinases (MMPs) at mRNA level and pro-matrix MMPs at the protein level[18]. Besides, a Japanese population-based study involving IL6R genotypic and allelic analyses among 239 normal and 376 keloid patients revealed that the IL-6 572G/C polymorphism is associated with susceptibility to keloid formation and the severity of keloid scarring[19].

Multiple stress models have confirmed that a higher plasma level of IL-6 was also observed in people with depressive symptoms or at a stressed state (for example, angry couples after a domestic conflict or vaccination with an influenza virus vaccine)[20,21], suggesting a stress hormone (NE, E)-mediated IL-6 augmentation.

The importance of psycho-physiological interactions has gained increasing attention recently, and NE-induced IL-6 elevation has been taken as a predictor of treatment resistance and poor outcomes in certain cancers. For example, researchers found that by binding to β2-ARs, stress hormones (NE, E) can subsequently induce IL-6 expression via suppressing liver kinase B1 and activating cAMP-responsive element-binding protein. Therefore, Combinational treatments with propranolol (β-AR inhibitor) could effectively lower the IL-6 concentration and prolong the progression-free survival in EGFR TKIs resistant patients[4]. Apart from lung cancers, it was also observed that the NE/E induced activation of ARs also resulted in a similar increase of IL-6 in ovarian cancer cells[5].

The β-ARs have been suggested as potential pharmacologic targets of catecholamine actions that influence numerous physiological and metabolic activities systemically in human bodies[22,23]. Both *in vitro* and *in vivo* studies of β-ARs carried out over the past decades focused mainly on their effects on cardiac function, whereas reported studies on non-cardiac β-blocker effects focused on their roles in the wound healing process[22]. Propranolol is a representative nonselective β-adrenergic blockade agent with promising efficacy in rhythm disturbances and hypertension. It was found that in propranolol-treated animals, wound contraction and the formation of the neo-epidermis and granulation tissue were delayed[22]. de Mesquita[24] hypothesized that systemic or intralesional injection of propranolol could serve as a novel cure of keloids because of its potential to induce vasoconstriction in over-proliferating tissues, trigger apoptosis of endothelial cells, and modulate inflammatory process during wound healing. Moreover, one single-institution case-control study in 2017 also observed better scar formation in post-surgery patients who were administrated with β blockers[25]. It is noteworthy that patients with abnormal scar histories or family tendency are excluded in this study, and the administration of other hypertension drugs such as calcium channel blockers showed no association with the scar quality, a phenomenon that indirectly supports our hypothesis that adrenergic activation might be an independent risk factor for the pathogenesis of keloid and hypertrophic scars[25]. Noticeably, yearlong administration of oxandrolone and propranolol successfully reduced scar severity and pliability in the -post-burn hypertrophic scar patients and their emotional health state was also improved[26]. Encouraged by the findings of the propranolol-based study showingthe reduction in NE-induced IL-6 elevation with an altered prognosis of NSCLC patients and the studies outlined above, we strongly propose that it might be promising to use propranolol for targeting β-ARs on keloid cells to disrupt IL-6 mediated keloid pathogenesis.

Stress hormones could activate α-ARs to promote keloid formation by enhancing growth-related responses and aggravating local hypoxia environment

The α-ARs are another group of adrenergic receptors that were found to be increased in keloid tissues and peripheral sensory neurons of scarred skin. Stress hormones could activate α-ARs to promote keloid formation by enhancing growth-related responses and aggravating the local hypoxia environment. Furthermore, their enhanced expression was associated with cell proliferation, inflammation, and uncomfortable symptoms of pain and pruritus in hypertrophic scars.

Activated α-ARs can evoke growth-related responses after bonding to stress hormones (NE, E). For example, the α-1B subtype stimulates cell proliferation[27-29] and the activation of the α-1A subtype evokes protein biosynthesis and cell hypertrophy[30]. Tissue biopsy and immunohistochemistry detected an increase of α-ARs in keloid scars compared to burn scars and unscarred skins in the regenerated epidermis, dense bands of cells in the upper dermis and collagen fibers in the deep dermis, coinciding with the inflammatory and proliferative stage[31]. Since it was reported that injury-induced growth-related responses are α1-AR subtype-dependent[32-34], over-expression of α1-ARs might result in both hyperplasia and hypertrophy of fibroblasts and vascular smooth muscles in keloid tissues. Moreover, the adrenergic activation of fibroblasts could increase the production of extracellular matrix proteins (such as collagen and fibronectin) and the expression of α1-ARs in peripheral sensory neurons was in line with enhanced sensitivity to adrenergic agents in injured tissues, suggesting that the up-regulation of α1-ARs might not only be involved in the inflammation and wound healing processes, but also be a significant source of pain, itching, and hyperaesthesia[31].

Apart from α1-AR-induced growth-related responses that have been discussed, the vasoconstriction caused by activated α1-ARs in vascular smooth muscles is another important aspect that could aggravate the local hypoxia of keloid microenvironment and trigger hypoxia-related pathogenesis. Hypoxia is a common environmental stress factor associated with various physiological and pathological conditions, including angiogenesis, cell proliferation, glucose metabolism, pH regulation, and migration[35,36]. Accumulating evidence suggested an anoxic microenvironment is crucial in keloid pathogenesis because of abnormal hypoxia-associated occluded microvessels, which is also partially responsible for keloid resistance to radiation therapy[37]. It was observed that the central area of keloid is severely ischemic, exhibiting higher hypoxia-inducible factor-1a (HIF-1a) expression and lower vascular density than their marginal areas and normal skin borders[38,39]. The HIF-1α is also involved in the inflammatory process by regulating angiogenesis and inflammatory cell functions[40-42]. Blocking HIF-1 signal pathways by either 2ME2 or HIF-1α siRNA has been shown to successfully increase the radiation-induced apoptosis in keloid fibroblasts[37]. Hypoxia can also drive the transition of human dermal fibroblasts to a myofibroblast-like phenotype via the transforming growth factor -β1/SMAD3 pathway[36], and increase the expression of vascular endothelial growth factor (VEGF) in keloids[35,38]. Glycolysis, the major glucose metabolic pattern for keloid tissues, could also interact with hypoxia and promote the lactate accumulation, resulting in excessive collagen production and fibrogenic activities[43].

Stress hormones might influence keloid formation by dysregulating the immune system and inflammation

The classical model of wound healing involves three distinct but overlapping phases that chronologically occur as the inflammatory, the proliferative, and the remodeling phases. Disturbance of these processes, especially the prolonged and excessive inflammatory reactions could lead to an increase of fibroblast activities and excessive extracellular matrix (ECM) production[44]. The available evidence indicates that malfunction of the immune system and inflammation might be involved in keloid formation. Keloid tissues are highly infiltrated with various immune cells, immunoglobulins and complements[45], as well as growth factors, cytokines and proteases, such as IL-6, tumor necrosis factor (TNF), transforming growth

factor-β (TGF-β), platelet-derived growth factor (PDGF) and epidermal growth factor (EGF)[46,47], which are critical for the migration, proliferation and collagen synthesis of fibroblasts. Moreover, previous studies have demonstrated that the expression of several immune-related genes was also dysregulated in keloid tissues[48,49].

The elevated C-reactive protein (CRP, a marker of inflammation) plasma concentration in caregivers of Alzheimer's patients[50,51] also implied that psychological stress was a potent inducer of the chronic inflammation state. Analysis of stress models revealed that stress hormones (NE, E, glucocorticoid) have detrimental effects on immune functions as well as the inflammation process from various aspects[52]. Here are some keloid-associated inflammatory molecules or mechanisms that have been identified dysregulated in stressed conditions.

TGF-β

TGF-β is probably the most fibrogenic factor associated with keloid formation by acting as a strong chemotactic agent for fibroblasts[53] and increasing cell rigidity through TGF-β1 receptor-smooth muscle actin axis[54]. It is also known as a regulatory resolution factor that can induce remodeling within sites of damaged tissues upon mood disorder-associated inflammatory processes[15].

In the inflammatory and proliferative phase, degranulation of platelets releases and activates several fibrogenic growth factors and chemotactic agents including TGF-β1 and TGF-β2[44], to increase the corresponding receptors and responsiveness compared to fibroblasts from normal tissues[55-58]. Although there is no direct evidence that stress hormones can enhance the efficacy of TGF-β in keloids, it is nevertheless clear that TGF-β plays a pivotal role in keloid formation and stress-derived inflammatory conditions.

The cells and cytokines

CD4 T cells express T helper lymphocyte (Th)1 or Th2 responses, while glucocorticoids are thought to cause a shift from Th1 to Th2 cytokines by downregulating Th1 cytokines and upregulating Th2 cytokines[59]. Th1 responses produce interferons and IL-12 and are thought to be related to the attenuation of fibrogenesis, whereas Th2 responses (IL-4, IL-5, IL-10 and IL-13. IL-1, and IL-6) are generally related to fibrogenesis, among which IL-4, IL-5, IL-6, and IL-13 are thought to be essential for promoting fibroblast recruitment and proliferation, ECM deposition, angiogenesis and re-epithelialization[16,17,47] (except for IL-10, which are mainly related to anti-fibrosis[60-62]. In a published report, stress was associated with a decrease in IL-2 receptor (IL-2R) mRNA levels and the protein expression in peripheral blood leukocytes compared to the baseline[63]. In a longitudinal study over 6 years, caregivers and former caregiver's (a kind of stress model) showed elevated plasma IL-6 levels that increased at a rate four times faster than those of age-matched controls[50]. Elevation of serum IL-6 (a marker of inflammation) levels have been previously described in both chronically stressed older adults[64] and keloid patients. Since a clear NE-IL-6 pathway has been identified in NSCLCs and ovarian cancer[4,5], we presumed that a similar NE-induced IL-6 elevation might exist in keloid. Stress hormones and related receptors could thus serve as feasible therapeutic targets.

Macrophages and treg cells

Macrophages are divided into two subsets, the IL-12- and inducible nitric oxide synthase (iNOS)-expressing M1 type and the IL-10- and TGF-β-expressing M2 type[65]. The classically-activated (M1) cells that secrete pro-inflammatory cytokines, whereas alternatively-activated (M2) cells that foster tissue repair and regeneration[66,67]. It was found that M1-associated genes, including iNOS and IL-12, were less elevated in keloid tissues than M2-associated genes, including IL-10 and TGF-β[68], suggesting that macrophages in keloids were shifted toward the M2 polarization.

The Foxp3^{+}CD4^{+} regulatory T (Treg) cells represent a critical T cell subset, the dysfunction of which was implicated in multiple inflammatory diseases[69]. While the normal skin displays a relative lack of CD3^{+} T cells, the levels of Foxp3^{+} Treg were significantly higher in keloid tissues (range of 25.5%-72.5%) in contrast to those in the circulation of keloid patients (4%-10.5%)[68]. Additionally, it was also observed in the same research that incubating circulating CD3^{+} T cells with keloid macrophages could significantly raise the expression of Foxp3, suggesting that these keloid macrophages could promote Treg differentiation by upregulating Foxp3 expression.

Even though no research on the levels of macrophages and depression in patients with skin conditions has been reported thus far, other previous studies did show that the activation and polarization of microglia (central nervous system-resident macrophages) could modulate the production and secretion of pro-inflammatory cytokines, implicating the involvement of macrophages in the etiology of major depressive disorder, which was referred as the "macrophage theory of depression"[70]. In light of this, it could be argued that an abundance of pro-inflammatory cytokines induced by the altered profile of macrophages inside keloids might exist, and further investigations, therefore, need to be performed in keloid patients with diagnosed depression.

The tumor necrosis factor

TNF produced by monocytes and macrophages during the inflammatory phase has been known to induce collagen degranulation and minimize excessive scarring possibly by increasing the MMP1/TIMP3, MMP2/TIMP3 ratios[71].

Various animal and patient-based clinical studies have demonstrated the associations between the concentration of pro-inflammatory cytokines, specifically IL-1β, IL-6, TNF, and depressive symptoms[15]. They also showed a general normalization (decline) of IL-6 and TNF concentration after antidepressant treatment[72,73].

CONCLUSION

As a benign skin tumor outgrowing the original wound boundary or growing spontaneously on the normal skin, keloid can bring great pain and inconvenience to patients. Although risk factors such as genes and infection have been noticed, the pathologic mechanisms remain unclear, leading to challenges for treatment resistance and keloid recurrence, including 9%-50% recurrent rate of the corticosteroid injection, 45%-100% recurrence rate of the surgical removal and 9.59% relapse rate of the radiotherapy[44].

Psychological stress evoked by traumatic events and depressive conditions has huge impacts on the overall health state. Through stress hormones (NE, E, glucocorticoids) and their respective receptors, tissue-specific responses are triggered as well as the general modulation of the immune system and inflammation. Studies have confirmed that stress hormones are critical for the initiation and development of multiple diseases[2,3,52], but the impact of psychological stress on keloid pathogenesis has been neglected.

As for keloid patients, the original trauma, uncomfortable feelings, together with the cosmetic concerns are all potent and constant underlying stressors, which make them very likely to be trapped in a stress-intensive state. Therefore, psychological stress is a pivotal and inevitable element that should be taken into consideration in formulating optimal treatment regimens. In view of the reviewed literature, especially with regards to stress hormone-induced cellular and physiological changes observed during psychological stress, we advance the hypothesis that stress hormones (NE, E) may participate in the keloid formation by: (1) increasing the expression of keloid-associated IL-6 via activating β-ARs; (2) triggering growth responses of fibroblasts and symptoms(pain and pruritus) in scar tissues by directly activating α-ARs; (3) exacerbating

the local hypoxia conditions; and (4) dysregulating immune systems to provide an inflammatory microenvironment that is in favor of keloid formation, thus promoting keloid pathogenesis.

Although the impact of psychological stress on the pathogenesis of diseases, such as cancers, has been known for decades, its relevance and impact concerning keloid pathogenesis and therapy have barely been studied. Although the stressed state in keloid patients has been well-observed during clinical practice and demonstrated by investigations in an African population, more direct evidence are required in the future. For example, current studies have detected elevated adrenergic receptors, but the concentration and distribution of catecholamines in keloid tissues remain uninvestigated, so are specific cytokines and immune cells in the targeted population. Clinically, large-scale evaluations of psychological stress among keloid patients should also be undertaken as a follow up to "as a proof of principle" pilot studies. Moreover, studies combing α, β-receptor antagonists and anti-depressant medicines with conventional keloid therapies could be explored in future clinical trials to realize better treatment outcomes.

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Author's contributions
Made substantial contributions to the conception of the hypothesis: Yang YT, Wu XL, Liu W

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Not applicable.

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