The Significance of Renin-Angiotensin System in Keloid Disarray

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Abstract

The fibro proliferative disease Keloid Disorder (KD) is characterized by excessive dermal collagen deposition in response to skin injury and/or inflammation. Treatment for KD remains empirical and unsatisfactory despite much study. Through its direct influence and the resulting hypertension, activation of the Renin-Angiotensin System (RAS) causes fibrosis in many organs as well as immune system activation. The greater frequency of KD among dark-skinned people who are prone to vitamin D deficiency (VDD) and hypertension, as well as the link between KD and hypertension and VDD, both of which are linked to increased RAS activity, shed light on the etiology of KD. Embryonic-like Stem (ESC) cells that exhibit ESC markers inside Keloid-Associated Lymphoid Tissues (KALTs) are increasingly being linked to keloid lesions. The RAS, catharsis B, D, and G, which form RAS bypass loops, and the Vitamin D Receptor (VDR) are all expressed in these primitive cells. This shows that the RAS, both directly and through signalling pathways that converge on it, such as VDR-mediated processes and the immune system, may be important in controlling the primitive population within the KALTs. The importance of the RAS in controlling the ESC-like cells inside the KALTs, as well as its interaction with hypertension, vitamin D, VDR, VDD, and the immune system. By manipulating the RAS and its bypass loops and convergent signalling pathways, these ESC-like cells may be a unique therapeutic target for the treatment of this puzzling and demanding disorder.

Keywords: Keloid lesions • Renin-angiotensin system • Trauma • Keloid disorder

Introduction

Excessive dermal collagen deposition in response to trauma, such as ear piercing, surgery, and burns, or inflammation, such as acne and herpes zoster infection, is characterized by keloid disorder. Keloid Lesions (KLs) frequently spread beyond the initial wound's limits and infiltrate surrounding dermis without the spontaneous scar remodelling seen in normal wound healing. Hypertrophic scars, on the other hand, are contained to the original wound boundaries and spontaneously retreat over time [1]. Keloid lesions are stiff, rubbery, and glossy plaque-like lesions that can produce pruritis discomfort, and functional issues such joint contractures. Acne keloidalis nuchae is a chronic inflammatory disorder marked by scarring around hair follicles. Keloid-like papules are common complications. KLs, particularly bigger lesions, can result in physical and psychological disabilities, as well as a worse quality of life for those who are affected.

The shoulders, anterior chest, upper back, and earlobes are the most prevalent sites for keloid lesions. Surface tension and higher sebaceous gland density have been hypothesized as contributory causes to keloid development that typically impact these locations, although these explanations do not fully explain why earlobes are a predilection site. KD usually strikes during the first and third decades of life, affects both sexes equally, and is more frequent in dark-skinned people, with a family trend [2].

Intraregional corticosteroid injections, topical 5-fluorouracil, surgical excision with intra-operative steroid injection or post-operative radiotherapy, laser therapy, cryotherapy, and silicon occlusive dressing are now used as first-line treatments for KD. With significant recurrence rates of 45%-100% following surgical excision without adjuvant therapy, these empirical therapies for KD remain unsatisfactory, underlining the need to better understand the pathophysiology of this puzzling illness.

KD is an autosomal dominant trait with partial penetrance and varied expressivity, according to its inheritance patterns. In family case studies with numerous syndromes, autosomal recessive inheritance and X-linked patterns have been reported, indicating that several genes contribute to KD susceptibility [3]. Polymorphisms in the human leukocyte antigen gene have also been linked to KD, with four single-nucleotide polymorphisms being linked to keloid development. Although mounting evidence implicates stem cells, the Renin-Angiotensin System (RAS), the Vitamin D Receptor (VDR), and the immune system in endothelial-to-mesenchymal transition (endo-MT), a process in which endothelial cells lose their specific markers and develop a mesenchymal phenotype, the pathogenesis of KD remains unknown.

Renin-angiotensin system and keloid disorder

Blood pressure, tissue perfusion, extracellular volume homeostasis, and electrolyte balance are all affected by the RAS. Renin is a rate-limiting enzyme that is released into the bloodstream in response to a variety of physiological stimuli. Angiotensinogen is transformed to angiotensin I (ATI) by renin cleavage, which is then hydrolysed by Angiotensin-Converting Enzyme (ACE) to create Angiotensin II (ATII), the RAS principal active product. The majority of ATII's physiological and pathophysiological functions are mediated by its binding to the Angiotensin II Receptor 1 (ATIIR1), which results in vasoconstriction, increased blood pressure and cardiac contractility, cardiac hypertrophy, sympathetic nervous system amplification, sodium retention, and angiogenesis [4]. ATII-ATIIR1 binding regulates cellular development and proliferation, inflammation, oxidative stress, and immunological responses that contribute to inflammatory cell recruitment and ECM deposition. Angiotensin II Receptor 2 (ATIIR2) counteracts the activities of ATIIR1 by reducing cardiac hypertrophy and remodelling through its anti-proliferative and apoptotic properties in vascular smooth muscle.

The link between the RAS and tissue fibrosis has been widely established. Through ATIIR1 signalling, ATII is known to cause fibrous remodelling in various organ systems, resulting in renal, cardiac, and idiopathic pulmonary fibrosis, as well as silicosis and asbestosis. Increased production of TGF-β1 produced by ATII, which plays a key role in fibrogenesis, is thought to be the mechanism underlying the link between RAS activity and fibrosis. Overexpression of TGF-β1, which stimulates myofibroblast development and ECM protein production, has also been identified as a critical contributor to fibrosis in practically all tissue types. Connective tissue growth factor, a profibrotic mediator that influences fibroblast proliferation, cellular adhesion, and ECM deposition, is also highly induced.

The expression of pro-renin receptor, ACE, ATIIR1, and ATIIR2 on the endothelium of micro vessels and perivascular cells within the KALTs was recently reported. Researchers discovered that damaged skin and pathological scar tissue have considerably greater ACE activity than normal skin, meaning that both circumstances have higher amounts of ATII [5]. The pliability and vascularity of KLs and hypertrophic scars are greatly reduced when they are treated with ATIIR1 blockers. This finding, together with improvements in KLs after therapy with low-dose enalapril, an ACE inhibitor, adds to the evidence that the RAS plays a role in KD.

Chymase, a serine protease found in mast cells, is involved in wound healing, pathologic scarring, and tissue ATII production. It is a RAS bypass loop that leads to KL development by stimulating TGF-β1/Smad signalling and has six times more expression in KLs than in normal skin. In keloid

fibroblasts, it catalyses the synthesis of ATII and elevates collagen I, TGF-β1, and interleukin (IL)-1β. TGF-β1 mRNA expression is dramatically reduced in keloid fibroblasts treated with either the ACE inhibitor captopril or the ATIIR1 blocker valsartan. The RAS is involved in the control of stem cell proliferation and differentiation, which might explain why KD patients have fibroblasts and myofibroblasts [6]. Modulation of the RAS has been recommended as a possible therapeutic target for the ESC-like population inside the KALTs. This primitive population inside the KALTs also expresses cathepsins B, D, and G, which may operate as RAS bypass loops. This shows that, in addition to traditional RAS blockers, bypass loop inhibitors may be required for more effective RAS control.

The pro-fibrotic character of the RAS, which is mediated by TGF-β1 expression, promotes pathological scarring like KD and may govern ESC-like population proliferation and differentiation inside the KALTs of KLs.

Conclusion

Treatment for KD remains empirical and unsatisfactory despite much study. A growing body of data implies that an ESC-like population plays a critical role in KALTs. The proliferation and accumulation of keloid fibroblasts and myofibroblasts can be regulated by a micro environmental niche centred on the RAS, including its bypass loops made up of enzymes like cathepsins B, D, and G, as well as converging signalling pathways like VDR-mediated mechanisms and the immune system. The complicated interplay between the RAS, VDR, other chemicals, and the immune system, which together comprise the micro environmental niche, may lead to innovative targeted therapeutics for this puzzling and difficult condition.

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