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**WOUND REPAIR
AND
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Keloid scarring or disease: unresolved quasi-neoplastic tendencies in the human skin

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Abstract

Keloids are benign fibroproliferative dermal scars of unknown aetiopathogenesis resulting in an exophytic protuberant growth with persistent and progressive perilesional expansile behaviour. Keloids are likened to benign neoplastic lesions due to their aggressive clinical behavior, genotypic-phenotypic tissue-characteristics and resistance to treatment. Keloids are traditionally viewed as scars on the healing spectrum, however keloids are a distinct pathology provoked by cutaneous injury rather than a continuum. In order to elucidate the aetiopathogenesis of keloids, the distinction between scar and disease must be made. Therefore, we hypothesize that the link between keloids and their quasi-neoplastic tendencies distinguish it as a disease rather than a scar alone. The biomarker expression profile in these diseases highlights the striking parallels between keloids and both benign and malignant mesenchymal tumors. Signaling pathways common to these diseases have been found to guide the matrix composition of keloids. This hypothesis underscores the need to identify keloids as a disease in order to develop targeted therapy, which can lead to enhanced diagnosis and theranosis.

Biomedical Hypothesis

Keloids present as benign fibroproliferative reticular dermal tumors of unknown aetiopathogenesis that can occur following any dermal trauma leading to an exophytic protuberant growth that invades into the adjacent normal skin beyond the site of the original injury (Figure 1a).¹ Keloids display unique features of aggressive, persistent and progressive peri-lesional expansile behavior. Other scar types do not behave in this manner and respond well to monotherapy alone unlike keloids, which can recur after any treatment modality. Phenotypically, keloids are consistent with non-malignant dermal tumors due to the excessive overproduction of collagen and they never metastasize. However, the morphology and clinically aggressive behaviour of keloids is thought to bear a resemblance to neoplastic dermal tumors. Keloids are traditionally viewed as scars on the healing spectrum, however keloids are a distinct pathology provoked by cutaneous injury rather than a continuum. In order to elucidate the aetiopathogenesis of keloids, however, the distinction between scar and disease must be made. Therefore, we hypothesize that the link between keloids and their quasi-neoplastic tendencies distinguish it as a disease rather than a scar alone (Figure 1b).

Although keloids are not routinely classified as true neoplasms due to their lack of spontaneous occurrence and absence of metastasis, they can display various cancer-like characteristics such as uncontrolled proliferation, vascularization, lack of spontaneous regression and invasiveness into surrounding tissue.² Their locally aggressive clinical phenotype suggests possible links with skin or mesenchymal tumors that need to be explored in further detail. There is potentially a key regulator or group of pre-requisite factors, which when activated after skin injury, triggers a

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3 cascade of events that culminate in KD formation. The various relationships between
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5 tumour-related factors expressed in keloids are complex and their roles in sustaining
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7 keloid growth are still unclear.³
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12 Neoplasia is known as new growth and the terms benign and malignant correlate to
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14 the course of the neoplasm. Benign neoplasms remain localised in one area, whilst
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16 malignant neoplasms invade the surrounding tissue and, in most cases, can
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18 metastasize to other organs. In order to become neoplastic, a normal cell develops
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20 mutations enabling it to no longer be confined to the boundaries of adjacent cells,
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22 therefore, leading to uncontrolled growth and the ability to produce its own blood
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24 supply.⁴ This is also evident in the clinical behaviour of KD as it invades healthy
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26 surrounding skin and is characterised by excessive fibroproliferation associated with
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28 significant increases in collagen synthesis and deposition, gradual expansion beyond
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30 the boundaries of the original wound and lacking in spontaneous regression.
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39 Gene expression patterns of biopsy tissue and cultured fibroblasts from different
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41 anatomical sites within KD (margin versus centre) have been investigated, and shown
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43 to display a signature of candidate genes which appear unique to those lesional sites,
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45 furthermore confirming the oncologic behaviour displayed by KD.⁵ Extralesional
46
47 excision of the margins has been advocated for skin cancers, which correlates with
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49 emerging role of active cells found at the margin of KD.
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54 It has long been known that KD often tend to develop in body regions constantly
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56 subject to skin mechanical tension. The effects of stretching and tension on KD have
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58 shown an overexpression of tension-related proteins. Cellular tension influences tissue
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3 rheology, epidermal homeostasis and tumor growth and progression in squamous cell
4 carcinoma.⁶ Furthermore, increased tissue rigidity from extracellular matrix (ECM)
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6 accumulation in the stroma causes enhanced tumour cell growth and the organisation
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8 of collagen fibers at the edge of stromal tumours promote tumor cell invasion and
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10 metastasis. Fibroblasts exert an opposing contractile force on the ECM through
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12 tensional homeostasis. Alterations in this mechanism can lead to the promotion of
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14 fibroblasts to differentiate into cancer associated fibroblasts which results in enhanced
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16 contraction.
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24 Tissue hypoxia is a hallmark of tumors and has been shown to increase macrophage
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26 migration inhibitory factor expression in tumor cells.^{7,8} The similarity in the hypoxic
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28 microenvironment in solid tumors and KD led to the study of the response of KD
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30 fibroblasts to hypoxia and hypoxia-mimetic agents.⁷ Keloid fibroblasts showed
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32 bioenergetics of cancer cells by generating ATP mainly from glycolysis as
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34 demonstrated by increased lactate production.
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40 Both keloids and neoplastic lesions have over-active signaling pathways, therefore,
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42 we consider examples of the implications of genetic alterations in critical components
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44 in these pathways or upstream activators. There has been a reported association
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46 between fibrosis and poor prognosis in several cancers.⁹ Fibrosis in cancer is induced
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48 by cancer-associated fibroblasts or myofibroblasts, which can induce epithelial-
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50 mesenchymal transition (EMT) and cancer cell migration.¹⁰ There is a growing body
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52 of evidence recognizing the importance of EMT in keloid pathophysiology. Whilst
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54 EMT is known to promote the migratory behavior of metastatic cells, the benign
55
56 nature of keloids makes it unclear whether they are the result of type II fibrotic EMT
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or suspended type III metastatic EMT.¹⁰ There is no evidence of significant epidermal-dermal basement membrane breakdown or disrupted collagen IV expression in keloids which may explain why they do not metastasize. Investigating other cell motility factors in keloids may reveal unique key agents in metastatic prevention. Inhibition of the mTOR pathway has recently become of major interest in the control of tumor growth as it regulates cell mobility, survival, proliferation, transcription, and protein synthesis.¹¹ It has been reported that KD tissue contains elevated levels of activated mTOR and may be a plausible target pathway in management of KD. This has also been shown in a study on the anti-tumor effects of the mTOR inhibitor everolimus against melanoma. Growing evidence implicates Notch signaling in the regulation of tissue homeostasis such as regulation of endothelial cell proliferation and migration during angiogenesis in normal tissue and tumors.¹² Aberrant Notch signaling may contribute directly to skin pathogenesis and altered expression of Notch receptors identified in KD.¹³ Several microarray studies have shown overexpression of JAG-1 in KD compared to normal skin fibroblasts. Abnormal Notch signaling is seen in many skin cancers and thus, research has focused on how the inhibition of Notch signaling can lead to growth arrest and differentiation in those cells and how this can represent a target for cancer therapy. Retinoic acid (RA) is a signaling pathway that plays an important role in tissue regeneration and has been shown to induce squamous cell carcinoma tumour regression.¹⁴ In addition, a study identified up-regulation of the aldo-keto reductase AKR1B10, a key enzyme in RA metabolism in KD epidermis.¹⁵

In conclusion, keloid presents with quasi-neoplastic genotypic and phenotypic characteristics with morbid cancer-like behaviour due to its aggressive progressive

nature as it invades into unscarred surrounding skin beyond the site of the original lesion. KD shows a persistent recurrent phenotype following even the most severe oncologic treatments. The notion that keloids behave like non-malignant locally aggressive cutaneous cancers is not new and this is evident in both its phenotypical and genetic properties (Figure 2a). However, the biomarker expression profile in these diseases highlights the parallels between keloids and both benign and malignant mesenchymal tumors (Figure 2b). Signaling pathways common to these diseases have been found to guide the matrix composition of keloids. This leads to many questions in relation to keloid pathobiology which need to be answered, in order to understand how these quasi-neoplastic processes result in keloid formation. Adoption of this hypothesis could enable better understanding of the mechanistic basis for development of keloid and in turn could lead to development of targeted therapy, which can lead to enhanced diagnosis and theranosis.

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Figure Legends

Figure 1a) The diagram demonstrates the circle of cutaneous repair. A) Non-keloid tendency; (i) a sutured incised surgical wound can become (ii) a normal fine line (linear) scar which can either lead to (iii) a stretched scar or (iv) an atrophic scar. B) Keloid tendency; the incised wound can also become (v) a hypertrophic scar which can either lead to (vi) a contracted scar or (vii) a keloid scar. C) Severe keloid tendency; a keloid scar can be excised surgically: (viii) excised keloid scar (surgery alone) which can also recur: (ix) recurred keloid scar and this can (x) continue to grow and develop into a larger keloid scar.

Figure 1b) A diagram showing the key processes and characteristic features of keloid in relation to quasi-neoplastic tendencies.

Figure 2a) A diagram to demonstrate the quasi-neoplastic tendencies features of keloid disease including; Clinical features (high recurrence, multiple sites, responsive to oncologic therapy), genetic susceptibility (familial, skin type, CNVs, SNPs), tissue characteristics (invasive margins, progressively migratory, hypoxia, mechanosensitive) and molecular targets (NEDD4, TGF β 1, mTOR pathway, NF-K β , retinoic acid pathway).

Figure 2b) Key processes contributing to the quasi-neoplastic expression of keloid pathobiology including; proliferative signalling, growth, angiogenesis, invasion, resistance to cell death and response to cancer therapies.

Figure 1a

291x204mm (300 x 300 DPI)

Figure 1b

278x202mm (150 x 150 DPI)

Figure 2a

398x366mm (150 x 150 DPI)

Figure 2b

204x181mm (150 x 150 DPI)

Supplementary References (Figure 2b)

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