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Pathological niche environment transforms dermal stem cells to keloid stem cells: A hypothesis of keloid formation and development

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ABSTRACT

Keloid is a disease that is difficult to cure because of its high recurrence rate after chemotherapy or radiotherapy, therefore it is considered as a benign skin tumor. Tumor stem cells are proposed as the source for tumor development and post-therapy recurrence. Interestingly, keloid stem cells have also been discovered, which share some characters with those of skin progenitor cells. Keloid patients possess specific diathesis including genetic predisposition and gene mutation, abnormal levels of hormones, growth factors and cytokines, and strong inflammatory response. This article reviews related literatures and hypothesizes that keloid stem cells might be transformed from normal dermal progenitor cells in the pathological niche of keloid tissues. These keloid stem cells are highly self-renewal and drug resistant, and can sustain themselves by asymmetric division, and continually generate new keloid cells to replenish the cells killed by drugs or radiation, thus leading to over growth of keloid and high post-therapy recurrence rate.

Introduction

Keloid is defined as an exuberant scar unique to human being, which is usually triggered by skin trauma. Keloid is similar to benign tumor in their biological behaviors such as aggressive growth beyond the original boundary of skin injury and invasion into normal tissue. Unlike hypertrophic scars, keloid rarely regresses [1], recurs at a high rate after therapies such as surgical excision, chemotherapy and radiotherapy [2] and can resist drug treatments. Because of these features, a hypothesis that keloid originates as a tumor has been proposed according to literatures [3,4]. Studies have also shown that keloid fibroblasts (KFs) behave similarly to tumor cells but differently from normal dermal fibroblasts (NFs). For example, keloid fibroblasts express some tumor-related genes [5]. Keloids also exhibit the trend of genetic predisposition and familial aggregation [6]. In addition, over expression of oncogenes, gene mutation and inactivation of anti-oncogenes as well as abnormal expression of growth factors and abnormal signaling pathways have also been observed in keloids [5,6], providing the evidences in favor of tumor origin hypothesis.

One of the major achievements of cancer research is the finding of tumor stem cells which serve as the source of tumor growth and recurrence after therapies [7]. Furthermore, these tumor stem cells are likely to be transformed from normal stem cells when they are exposed to a pathological niche environment [8]. As a matter of fact, adult stem cells have been found in almost all normal tissues [9], which may provide the sources for the development of various kinds of tumors.

Similarly, stem cells have also been found in human dermis as reported by Bartsch et al. [10] and Toma et al. [11,12]. Importantly, it is well recognized that a pathological environment exists in those patients prone to keloid development, so called "specific diathesis" including the abnormalities in immune responses, growth factor expression and hormone levels, etc. which are likely to lead to gene mutations, cell phenotype changes and abnormal biological behaviors [1]. We thus believe that the pathogenic factors presented in keloid patients may constitute a pathological niche environment that is able to transform normal dermal stem cells (NDSCs) into special "keloid stem cells or keloid progenitor cells (KPCs)", which are responsible for keloid behaviors. We provide literature evidences to support this proposed potential mechanism.

There exists a pathologic niche in keloid patients

Keloid only occurs in human beings

Many studies have tried to reproduce keloid disease in animal models but failed. Waki et al. [13], Kischer et al. [14] and Supp

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et al. [15] attempted to apply human keloid grafts or fibroblasts to nude mice to establish a keloid model. Although implanted keloids resembled the parent keloids histologically in peripheral vascularized area and collagen bundles, the presence of the implant did not appear to prompt a continuing vascular growth into or throughout the implant and could not bulge over the top of adjacent mouse skin. Differently, Zhang et al.[16] transplanted keloid precursor cells (KPCs) to immuno-compromised mice and found these cells could proliferate and differentiate into scar-like connective tissues that expressed collagen I, but still failed to reproduce keloid tissue in animals, suggesting that keloid cells, even KPCs, are not able to form keloid without a favorable pathological niche environment.

Keloid patients possess specific diathesis

Keloids are found mainly in young people. Colored people are particularly liable to develop keloid. Generally, skin injury can serve as an external factor to trigger keloid formation and development, such as infection, surgery, injection and mosquito's bite, etc. Nevertheless, only the patients with specific diathesis will respond to trigger factors or even form keloid spontaneously. It remains unclear what constitutes this diathesis. Literatures of clinical studies provide some clues as listed in the followings.

First, keloid patients usually exhibited genetic predisposition and familial aggregation. Monozygotic twins have similar incidence of developing keloid. The disease seems to run in families with an autosomal dominant transmission, incomplete penetrance, variable expressivity and delayed dominance [6]. Recent studies also showed that gene mutation was observed in keloid tissue such as p53 [5] and Fas [17].

Secondly, a hormonal influence was suggested as well, because keloids often appear in puberty [18], resolve after menopause, and enlarge during pregnancy [19].Patients with acne keloidalis, for example, were proved to have a significantly higher level of serum testosterone compared to the level of normal persons [20]. Interestingly, active keloid fibroblasts usually express a higher level of testosterone-binding receptors [21]. Additionally, keloids preferentially occur on anatomical sites with high concentrations of sebaceous glands, such as the chest wall, shoulder and pubic area, but rarely occur on anatomical sites lacking sebaceous glands, such as the palm and sole. This may explain why young people are prone to keloid formation during their puberty [22].

Thirdly, abnormal expression of growth factors and cytokines are believed to play important roles in keloid formation. Some growth factors of high expression level are proved to promote cell proliferation and extracellular matrix (ECM) production and inhibit ECM degradation, such as transforming growth factor-β (TGF-β) and platelet derived growth factor (PDGF) [23,24]. Meanwhile with a relatively higher level, basic fibroblast growth factor (bFGF) induces neovascularization [25] and insulin-like growth factor-1 (IGF-1) decreases the production of collagenase [26].

Likewise, inflammatory factors and cytokines are also important for keloid formation. Studies have shown that the concentrations of interferon-α (IFN-α), interferon-γ (IFN-γ) and tumor necrosis factor-β (TNF-β) were markedly decreased in the peripheral blood of keloid patients, whereas the productions of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and interferon-β (IFN-β) increased compared to those of non-keloid individuals [27,28], and TNF-α can promote inflammatory response, cell migration and proliferation [29]. IL-6 and TNF-α can recruit T cells to wound sites [30,31]. Additionally, IFN-α can decrease keloidal collagen synthesis [28,32]. Furthermore, IFN-α, IFN-β and IFN-γ all inhibit the proliferation of rapidly dividing fibroblasts [33,34]. Actually, IFN-γ has already been successfully used in scar treatment by its inhibition on collagen gene expression and protein production [35].

Immunoglobulin (Ig) is also an important part of inflammatory factors. Keloid patients exhibited the presence of antinuclear antibodies from different immunoglobulin classes against fibroblasts, epithelial, and endothelial cells in their blood, but these antibodies were not found in the blood of hypertrophic scar patients [36]. The incidence of excessive scar formation for race, sex, and age is directly correlated with the serum levels of IgE [37] and keloid patients revealed a higher frequency of allergic symptoms compared with hypertrophic scar patients [38]. Serum concentrations of IgM [39] and IgG [40] were reported increased, whereas IgA was reported decreased in keloid patients compared with non-keloid-forming patients [39].

There exist stem cells in keloid tissues

Moon et al. [41] reported the finding of stem cells in keloids namely keloid-derived mesenchymal-like stem cells (KMLSCs), because they behaved like mesenchymal stem cells with multi-differentiation potential such as osteogenic, chondrogenic, adipogenic and angiogenic lineages. In addition, KMLSCs are also similar to skin-derived precursors (SKPs) [42] in term of the expression profiles of neural-crest stem cell markers such as Sox2, nestin and CD133, and MSC markers such as CD13, CD29, CD44 and CD90.

With single cell cloning method, Zhang et al.[16] have isolated and characterized a population of tumor-like stem cells from keloid dermis, termed keloid-derived precursor cells (KPCs), which share some properties with those of SKPs [42], including clonogenicity, self-renewal, enhanced telomerase activity, multipotent differentiation potentials and distinct cell surface markers of embryonic stem cells, such as Oct-4, Rex-1, Nanog, and makers of mesenchymal stem cells, such as CD90, Stro-1 and CD105. Therefore, KPCs may represent the benign tumor-like stem cells, a pathological counterpart of SKPs, which might contribute, at least in part, to the high proliferative status of keloid via its asymmetrical division. In our recent preliminary study, a side population was observed in freshly isolated keloid cells (0.5–1%) but not in normal dermal cells when Hoechest33342 stained cells were analyzed with flow cytometry (detailed cell resource was shown in Fig. 1).

Transformation of normal stem cells to tumor stem cells

One of the major advancements in cancer research is the discovery of tumor stem cells (TSCs) [7], which exist in tumor tissues and bear the capacity of infinite self-renewal, multi-differentiation potentials and potent proliferation. These characters lead to the production of different types of tumor cells, and thus result in an enlarging tumor mass *in vivo*. Importantly, TSCs are characterized by their ability of migration, tumorigenesis, invasion, and resistance to chemotherapy and radiotherapy, therefore they are believed to be the origin of tumor growth, invasion, migration, drug resistance and relapse [7].

In regard to the origin of TSCs, there has been a popular hypothesis that TSCs originate from the mutation or transformation of normal stem cells (NSCs). In recent years, substantial evidences suggested that tumors originate from their corresponding tissue stem cells, such as hemopoietic stem cells [43], neural stem cells [44], liver stem cells [45], breast stem cells and other types of stem cells [46–48] which have been discovered in their tissue niche environments. For example, Qian et al. [49] have proposed a hypothesis that, when stimulated by both of hepatitis viruses and chronic inflammation, liver stem cells and mutated hepatocytes may cause intercellular fusion with exchanges of intercellular proteins and micro RNAs, thus leading to the production of liver tumor stem cells. Another study [50] confirmed that, when cell signaling pathways become abnormal, the stem cells in the breast