Why do we know so much about wound healing— and yet so little about Keloids?

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Wound healing after an injury or a bruise is something our skin deals with everyday by wound closure and subsequent scar formation. After some time a scar may even disappear or flatten out. What appears to be a simple reaction of the body to a dermal assault is a complex series of orchestrated events that involves changes in the extracellular matrix environment of the skin, skin cell migration and immune response [1,2]. The quality of wound healing depends on many factors such as health status, age, environmental factors (e.g., medications, nutrition and life style) and differences in gene regulation to control the succession of wound healing events. There are a number of inherited connective tissue disorders that affect wound healing such as Marfan syndrome [3], Ehlers-Danlos syndrome [4], epidermolysis bullosa [5] or acute or chronic diseases such as diabetes [6]. Patients with reduced immune response or chronic inflammatory disorders can also have delayed wound healing.

Wound healing researchers have accumulated a large encyclopedia of wound healing facts (more than 100,000 PubMed articles) and have made significant progress in assembling individual experimental findings into a coordinated and overlapping action network [1,7]. However, when it comes to managing and explaining pathologic wound healing on a molecular level the field still has some catch up to do.

A prime example of a wound healing disorder with broad clinical interest is keloid formation (Figure 1).

Keloids are defined as scars that grow beyond the margin of the original wound. Keloids are a pathological response to injury of the dermis where scar tissue expands in a tumor-like manner over months or years and predominantly affects individuals of African origin, Asians or Hispanics and is rarely found in Caucasians.

The Public Health Service (PHS) proclaimed in their program “Healthy People 2010” the elimination of ethnic health disparities as a major goal. The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) included in their Strategic Plan for Reducing Health Disparities a mission statement to advance the understanding and treatment of diseases that disproportionally affect minorities with a particular focus on 5 disorders, one of those being keloids. NIAMS recognizes, as do several review articles on keloids over the past few decades that “The current research portfolio in keloids is quite small”. This leads us to the question why is there so little progress and not enough high quality research done in spite of the vivid interest of clinicians, policy makers and funding agencies?

One reason for the limited progress in keloid research and treatment may be the complexity of abnormal wound healing responses in these scars. Several hypotheses for the cause of keloids have been proposed.

The observation that microvessels in keloids are cuffed by myofibroblasts or endothelial cells led to the hypothesis that hypoxia could be the basis for proliferation and matrix expression of keloid fibroblasts [8]. Hypoxia may increase VEGF expression [9] and in turn increase endothelial cell proliferation, thus increasing microvessel cuffing without increasing the number of microvessels in keloid scars [10]. Hypoxia-mediated pathways may also be responsible for the up-regulation of plasminogen activator inhibitor-1 (PAI-1) [11], which hamper protein degradation during matrix remodeling. However, protein degradation is likely impacted by several mechanisms as the level of plasminogen activator is decreased at the same time [12]. In addition, certain matrix metalloproteases (MMPs) and tissue inhibitors of MMPs (TIMPs) are upregulated [13,14]. Another reason for a reduced remodeling rate may be excessive collagen expression by keloid fibroblasts [15,16]. The deposited collagen is heavily cross-linked [17].

There are controversial data on an increased proliferation rate in keloid fibroblasts (probably due to heterogeneity) and some undisputable data on protection of fibroblasts from cell death by altered expression of anti-apoptotic factors. Somatic point and frameshift mutations have been found in the p53 gene which results in reduced expression of the protein [18,19]. Several proto-oncogenic factors are expressed at higher levels in keloids than in normal skin tissue [20] and there is some evidence of downregulated apoptosis-related genes [21,22].

Fibrosis is often associated with continued inflammation and immune response and therefore abnormal immune response has

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Figure 1: Keloids often form on head and neck, ear lobes, shoulder and chest. Keloid scars grow over the margin of the original injury and persist for many years before some keloids flatten and become asymptomatic.
been discussed as a cause for keloids [23]. Increased immune cell infiltrates are indeed found in keloid tissue [24]. Keloid fibroblast cell cultures were associated with expression of specific HLA alleles [25, 26] and with an increase in Toll-like receptors [27].

The hypothesis that keloids are caused by an immune reaction to sebum has been discussed [28,29] but no clear evidence has been provided. Similarly under-investigated is the role of fatty acids in keloids and cultured keloid fibroblasts. It appears that the fatty acid composition of keloids differs from normal scars [30-32]. Fibroblasts cell growth is inhibited by omega-3 fatty acids [33] but the reaction of keloid fibroblasts is more recalcitrant than that of control fibroblasts. As if keloid regulation is not complex enough, we know that most keloids develop in young adults and not in small children or aging individuals. The effect of hormones and growth factors is undeniable although no specific hormone has been directly linked to the age-dependent expression of keloids. Transforming growth factor beta (TGF-β) is the best studied cytokine [7,34] and may also be one of the best targets to treat keloids. Stem cells play an important role in wound healing but the real impact on keloid formation is still to be investigated [35,36].

It is obvious that most of these observable facts are secondary to the initial cause and that the causal or contributory factors for keloids have consequences that affect many aspects of scar formation. Several gene expression studies have been undertaken in the hope to elucidate “the” keloid gene. Large numbers of differentially regulated genes were identified in these studies but unfortunately most of the results were not replicated by other studies [37-40]. Efforts to identify keloid genes by linkage analysis resulted in 2 susceptibility loci on chromosomes 7p11 and 2q23 [41]. However, gene mutations have not been identified as of yet. A genome wide association study (GWAS) in a Japanese keloid population identified potential keloid gene loci on chromosomes 1q41, 3q22 and 15q21 [42]. No gene mutation has been identified [43]. We have expected for long that there is considerable genetic heterogeneity for keloid formation [44]. It is also likely that we will only find a small number of mutations in coding regions of genes and that many gene variants responsible for keloids are located in regulatory regions. A major mode of keloid regulation may actually be epigenetic [45,46].

Interestingly, there is very little work on keloids performed in US laboratories despite the interest of funding agencies - an observation that was re-enforced in the recent Symposium of Advanced Wound Care / Wound Healing Society and a Symposium of the Hampton University Skin of Color Research Institute. Why is industry not becoming involved at the current stage of keloid research? Is it too risky to apply for keloid funding from federal agencies or is the problem too daunting? It is apparent that all major wound healing pathways are affected by the pathogenetic processes that keloids undergo. May be that is why the past clinical and basic keloid research (more than 3,000 publications) did not produce the cause for keloids. I believe that the most important goal for keloid research today should be to identify the gene variants that cause or contribute to keloids. This is also one of the most difficult issues to work on.

Gene expression analyses failed to produce a list of the most likely candidate genes because of the expected genetic variability and because either fibroblast cultures or whole tissue samples were compared to “normal” cells or tissue of the same patient or to scar tissue of matched controls. It is by no means clear that the cause for keloids is within fibroblasts – just because they are the most obvious cell type and easiest to culture. More rigorous comparisons using defined cells within scar tissue are needed. Other genetic approaches either lacked the necessary number of samples (e.g., GWAS) or the technology (e.g., exome sequencing).

A different issue hampering research is the difficulty to obtain tissue, blood or saliva samples for genetic analysis or other investigations. We found that some keloid patients and their families were extremely helpful to participate in a genetic study while others were not willing for a variety of reasons. Obtaining keloid biopsies is also difficult since keloid surgery is only performed when medically necessary or demanded by the patient. As the recurrence rate is high [47,48] obtaining a biopsy solely for research would be unethical. It is important to realize that collaboration from surgeons who perform the surgeries is extremely important to basic researchers.

Since keloid tissue is relatively rarely available we need to develop animal [49] and cell culture models [50] for keloids where single parameters can easily be altered. Alternatively we need sophisticated organ culture methods to keep keloid scar tissue in a viable state [27,51].

In the past, many studies did not distinguish between the outer proliferating zone and the inner regressing zone of a keloid. This omission contributed to the conflicting or inconclusive results and some low standard research publications. Similarly, diagnostic inconsistencies and clinical studies that were undertaken without the necessary level of evidence outnumbered the “good” publications in the past [52].

What the field needs to advance keloid research with the speed and efficiency that patients deserve are concerted efforts between clinicians and basic researchers to identify genes and sequence variants that cause or contribute to keloids. Interpreting genetic mutations and variations will still be a challenge but will eventually help to understand some of the possible causes for keloids. Genetic heterogeneity has been one major obstacle in finding “the keloid gene” but may be beneficial for comprehending the overall keloid pathogenesis because eventually we will learn which pathways are important in keloid scar regulation and which processes are secondary.

I strongly believe that genetic research combined with interdisciplinary cellular, biochemical and molecular collaborations will identify key molecules that can be targets for preventive or personalized treatment of keloids. The benefits from keloid research will most likely influence research on fibrosis and research on “normal” or impaired wound healing. Since keloids are easily accessible for treatment and new highly efficient classes of pharmaceuticals are being developed (e.g., transition-state analogs) it is only a matter of time and dedication until better treatment can be developed. I just hope that this treatment will be affordable for those who need the treatment most, minority patients in this country and patients in Africa and Asia.

References


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