See related article on pg 98

# IL-6 Signaling Pathway in Keloids: A Target for Pharmacologic Intervention?

Jouni Uitto[1]

**Keloids are cosmetically devastating lesions with considerable morbidity. Ghazizadeh *et al*. document enhanced expression of IL-6 and its receptors in keloid fibroblasts, with a concomitant increase in collagen biosynthesis. Anti-IL-6 antibodies or blocking the IL-6 receptors elicits reduced collagen synthesis, suggesting a role for IL-6 in the regulation of collagen gene expression. These observations imply the feasibility of a pharmacologic platform, based on the targeting of the IL-6 signaling pathway, in keloids.**

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Fibrotic skin diseases, a diverse group of phenotypically distinct cutaneous disorders, are clinically characterized by thickening of the skin due to accumulation of extracellular matrix of connective tissue (Uitto and Kouba, 2000). A prototype of fibrotic skin diseases is keloids, localized lesions of considerable cosmetic concern associated with significant morbidity in terms of inflammation, infections, pruritus, and pigmentary alterations. The primary cause of keloids is currently unknown, but their development is clearly associated with trauma to the skin predicated on genetic predisposition of the susceptible individuals. Keloids are frequently encountered in individuals of African ancestry or of Asian origin, but keloid-like lesions are also present in white individuals, often demonstrating autosomal dominant inheritance with incomplete penetrance. The genetic basis of keloid formation has also been explored by genome-wide linkage analyses, which have suggested the presence of susceptibility loci on chromosomal regions 2q23 and 7p11 in a Japanese and an African-American family, respectively (Marneros *et al*., 2004). The observed locus heterogeneity may well reflect the phenotypic heterogeneity and spectrum of severity of this disease. A plethora of treatment modalities has been proposed and tested in keloids, apparently reflecting the fact that no approach is singularly superb, and recurrence rates are substantial after treatment attempts. Thus, keloids represent a major clinical challenge with unmet needs for therapeutic intervention that could be addressed with the use of novel approaches.

A characteristic hallmark of keloids is excessive accumulation of collagen, primarily types I and VI, associated with deposition of other extracellular matrix components, such as fibronectin (Abergel *et al*., 1985; Peltonen *et al*., 1991). As schematically depicted in Figure 1, collagen accumulation could result from either increased biosynthesis or decreased degradation, and currently a number of modulator molecules interfering with both synthetic and degradative pathways of collagen metabolism in fibroblasts have been recognized (Mauviel and Uitto, 1993). The preponderance of evidence suggests that in keloids, increased biosynthesis is responsible for collagen accumulation, although abnormalities in the degradative pathways mediated by matrix metalloproteinases and in their inhibitors, tissue inhibitors of metalloproteinase (TIMPs), have also been invoked (Uitto *et al*., 1985). Consistent with the increased rate of collagen biosynthesis, transforming growth factor-β, a potent profibrotic cytokine, has been shown to be abundantly present in keloid connective tissues, both in perivascular location and in association with activated fibroblasts (Peltonen *et al*., 1991). Thus, cytokines, particularly profibrotic molecules such as transforming growth factor-β, in relation to its antagonists, IFN-γ and tumor necrosis factor-α, have been postulated to play a role in growth and development of keloid lesions.

Ghazizadeh *et al*. (2007) report on their studies exploring the pathomechanisms of keloids with a focus on the IL-6 signaling pathway. Their investigations were initially directed at this particular cytokine by previous demonstrations that IL-6 expression is increased in keloid fibroblast cultures (Xu *et al*., 2000) and that IL-6 induces collagen synthesis in fibroblasts (Duncan and Berman, 1991). As a follow-up, these investigators compared early-passage fibroblast cultures established from keloid lesions (KF) and from non-lesional skin (NF) in regard to the IL-6 pathway. The KF cells demonstrated a number of differences in comparison with NFs, including significantly increased growth rate, and upregulation of IL-6 and its receptors (IL-6Rα and IL-6Rβ). The mean IL-6 secretion

> There is a role for IL-6 and its receptor-mediated signaling pathway in the accumulation of collagen and the phenotypic development of keloids.

[1]*Department of Dermatology and Cutaneous Biology, Jefferson Medical College, and Jefferson Institute of Molecular Medicine, Thomas Jefferson University, Philadelphia, Pennsylvania, USA*

*Correspondence: Dr. Jouni Uitto, Department of Dermatology and Cutaneous Biology, Thomas Jefferson University, 233 South 10th Street, Philadelphia, Pennsylvania 19107, USA. E-mail: Jouni.Uitto@jefferson.edu*

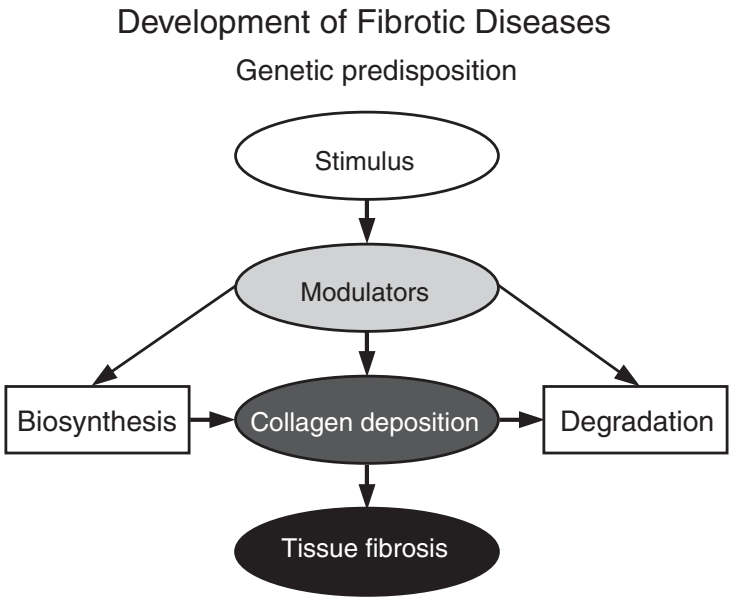


**Figure 1. Schematic representation of pathways potentially resulting in accumulation of collagen in fibrotic skin diseases.** The net deposition of collagen is a balance between the rate of synthesis and the rate of degradation, both of which can be modulated by a number of factors, such as cytokines. These factors can be evoked by stimuli such as trauma to the skin. When superimposed on the individual's genetic background, an imbalance in the flux through these pathways can result in collagen accumulation manifesting as tissue fibrosis. Adapted from Uitto and Kouba, 2000.

levels in KFs were elevated approximately sixfold on average. In addition to IL-6 and its receptors, expression of a number of downstream target molecules, including JAK1, STAT3, RAF1, and ELK1, was markedly elevated in KF cells as determined by semiquantitative reverse transcription–PCR and by Western blot analyses. In accordance with the latter findings, the same downstream target molecules were expressed in most keloid lesions tested by immunohistochemistry, but the activation/phosphorylation status of these molecules in keloid lesions *in vivo* was not determined. Finally, the authors examined the functionality of IL-6 expression by adding recombinant IL-6 protein to cell culture or by antagonizing IL-6 or blocking its receptor with antibodies and using type I collagen biosynthesis as readout. Addition of IL-6 to NF cultures resulted in a significant dose-dependent increase, whereas incubation of KF cultures with anti-IL-6 or anti-IL-6Rα antibodies decreased the synthesis of type I collagen.

Collectively, the observations reported by Ghazizadeh *et al.* (2007) suggest there is a role for IL-6 and its receptor-mediated signaling pathway in the accumulation of collagen and the phenotypic development of keloids. The pathomechanistic implications of their findings are somewhat unclear, however, for several reasons. Specifically, it is unclear, from the present studies, which of the many signaling pathways, including those of JAK/STAT3 and ERK/MAP kinase, is mechanistically responsible for enhanced collagen production in response to IL-6/receptor activation. Thus, it may well be that activation of these signal transaction pathways, noted in KF but not in NF cells, results in phenotypic manifestations other than changes in collagen production, such as the enhanced cell proliferation noted in lesional fibroblast cultures. In fact, precise dissection of the signal transduction pathways could potentially provide novel insights into the regulation of collagen gene expression in dermal fibroblasts, with pharmacologic implications.

So, what are the implications of the results of this study for treatment and patient care? In other words, are there approaches, based on the current findings, that can be offered to the patients suffering from this devastating, often life-altering condition? The answer is: apparently not yet. However, identification of IL-6 signaling as a critical pathway contributing to collagen accumulation and keloid formation potentially offers novel possibilities for pharmacologic intervention. For example, development of specific antibodies that antagonize IL-6 or block its receptor could result in reduced collagen accumulation, predicated on the results of this study. Similarly, development of peptide antagonists or receptor decoy molecules based on molecular modeling of the receptor–ligand binding characteristics could potentially be used for the same purpose. Another approach would be to screen for small molecules, potentially identifying compounds that antagonize the IL-6 receptor and its downstream signaling. The potential problems with these approaches are somewhat generic to these classes of molecules and relate to delivery, efficacy, and specificity. For example, how effectively would topically applied antibodies diffuse to keloids consisting of compact collagen fibers, so as to reach the cell-surface molecules in the center of these fibrotic lesions? What effective concentrations are required to elicit biologically and clinically meaningful inhibition of collagen biosynthesis? What is the specificity of these contemplated approaches with respect to cell biology in general and collagen biosynthesis in particular? In this context, it should be noted that IL-6 has been implicated in a number of biological processes, as attested by reduced reepithelialization, angiogenesis, and impaired wound healing in transgenic IL-6-deficient mice (Gallucci *et al.*, 2000; Lin *et al.*, 2003). Thus, inhibition of the IL-6 signaling pathway may have a number of effects, unrelated to collagen biosynthesis. These potential obstacles notwithstanding, the findings articulated by Ghazizadeh *et al.* (2007) warrant further exploration of the IL-6 signaling pathway as a potential pharmacologic target toward development of novel management strategies for this devastating, currently intractable disease.

CONFLICT OF INTEREST
The author states no conflict of interest.

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*See related article on pg 129*

# Breach Delivery: Increased Solute Uptake Points to a Defective Skin Barrier in Atopic Dermatitis

W.H. Irwin McLean[1] and Peter R. Hull[1]

**Evidence is now emerging for enhanced penetration of chemical solutes into uninvolved skin of atopic dermatitis patients. Along with the recent discovery of prevalent null mutations in the gene encoding filaggrin, a protein essential for stratum corneum formation, these data point to an innate epidermal-barrier defect in atopy.**

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Atopic dermatitis (AD, "eczema") has increased in prevalence in recent decades; it now affects 15%–20% of children in the developed world alone and affects all races to differing degrees. The disease is a classical complex trait — it is clearly highly heritable but with reduced penetrance, and there is strong evidence for environmental influences (Morar *et al.*, 2006). Furthermore, the disease impacts on other areas of medicine, as a high percentage of eczema patients develop a range of additional allergic conditions, including food allergies, asthma, and rhinitis, often occurring in a temporal "program" known as the atopic march (Spergel and Paller, 2003). AD causes considerable morbidity and significantly affects quality of life. This is particularly the case for severe AD persisting into adulthood. Establishing the contributing etiological factors for this complex disease — both genetic predisposing factors and environmental trigger factors — is of paramount importance in the development of new, possibly more effective treatments and/or preventative regimens. Given that the skin is inflamed within an AD lesion, there is an obvious immunological component in the disease; however, recent evidence coming from both molecular genetics and functional analysis strongly suggests that a skin barrier defect is the necessary cause in a considerable proportion of atopy cases.

Although there is considerable functional evidence for impaired skin barrier function within active lesional skin of AD patients, as seen, for example, by increased trans-epidermal water loss, the situation has been less clear in studies of uninvolved skin, where the results have been somewhat contradictory. Ivone Jakasa and colleagues in Amsterdam and Rome (2007) present conclusive, statistically significant evidence for enhanced uptake of an entire series of polyethylene glycols, covering molecular weights in the range 150–590 daltons, in non-lesional skin of AD patients. This result is further supported by recently published evidence from the same research group for enhanced uptake of sodium lauryl sulfate in non-lesional AD skin, based on the use of similar methods (Jakasa *et al.*, 2006). Genji Imokawa's group and collaborators in Japan, using a photoacoustic spectography system, showed enhanced penetration of both a lipophilic and a hydrophilic dye through clinically normal skin of AD patients as compared with control subjects. In addition, they showed a significant correlation between penetration rates for the hydrophilic dye and elevated IgE levels for patients with severe AD (Hata *et al.*, 2002). Together, these reports strongly support the hypothesis that patients with AD have an inherent skin barrier defect, probably due to one or a combination

[1]*Epithelial Genetics Group, Human Genetics Unit, Division of Pathology and Neuroscience, University of Dundee, Ninewells Hospital and Medical School, Dundee, United Kingdom*

*Correspondence: Prof. W.H. Irwin McLean, Human Genetics Unit, Ninewells Hospital and Medical School, Dundee DD1 9SY, United Kingdom. E-mail w.h.i.mclean@dundee.ac.uk*