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# Cross-Linking of Elafin/SKALP to Elastic Fibers in Photodamaged Skin: Too Much of a Good Thing?

Joost Schalkwijk[1]

**Muto *et al.* report that UVA light induces the expression of elafin, a potent elastase inhibitor, in skin fibroblasts. Elafin binds to elastic fibers by transglutaminase-mediated cross-linking and protects against proteolytic breakdown. Decreased degradation could contribute to accumulation of elastotic material in photodamaged skin. Elastase and its locally produced inhibitors play a role in actinic elastosis.**

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The fibrillary basophilic material present in the upper dermis of photodamaged skin is largely composed of elastic material. It is unclear to what extent this accumulation is caused by increased synthesis of elastin or by breakdown of existing and nascent elastic fibers, or by a relative decrease of collagen (Lewis *et al.*, 2004; Sellheyer, 2003).

The paper by Muto *et al.* (2007, this issue) contains two interesting new findings. First, it shows that the serine protease inhibitor elafin (Wiedow *et al.*, 1990), otherwise known as skin-derived antileukoproteinase (SKALP) (Molhuizen *et al.*, 1993), can be expressed by mesenchymal cells. This is a surprising finding, as it was assumed that elafin expression was strictly limited to epithelial cells (Pfundt *et al.*, 1996). The authors confirm previous findings that resting skin fibroblasts *in vivo* and *in vitro* are negative for elafin, but they show that UVA irradiation (and not UVB) induces elafin expression in these cells. Second, it is shown that elafin binds to elastic fibers *in vivo* and *in vitro*, thereby protecting against elastase-mediated breakdown. Elafin is a member of the trappin gene family (Schalkwijk *et al.*, 1999). The proteins encoded by the trappin family are characterized by a proteinase-inhibiting whey acidic protein (WAP) domain and a domain that contains the consensus GQDPVK hexapeptide motifs that are excellent substrates for transglutaminases (Molhuizen *et al.*, 1993). Muto *et al.* (2007) show that, *in vitro*, elafin can be cross-linked to elastic fibers, while retaining its proteinase-inhibiting activity. Immunohistochemical analysis of skin biopsies from photodamaged skin showed strong elafin staining associated with the elastotic material. The accumulation of elastase inhibitors on elastic fibers is not unprecedented, as the association of another WAP domain protein, secretory leukocyte protease inhibitor (SLPI), has been documented in connective tissue of the lung (Kramps *et al.*, 1989) and skin (Wingens *et al.*, 1998).

On the basis of their findings, Muto *et al.* (2007) speculate that elafin binding to elastic fibers is a protective response against undesirable degradative action of elastolytic enzymes such as neutrophil elastase derived from the infiltrating cells after UV irradiation (Hawk *et al.*, 1988). The authors argue that the accumulation of elastotic material in photodamaged skin is caused by decreased degradation of elastic fibers rather than by overproduction of elastic fibers. The findings in this paper are novel and exciting. I think, however, that the data are open to other interpretations than those offered by the authors. It is indeed very likely that elafin expression by fibroblasts after UVA exposure is a protective mechanism against unwanted breakdown of extracellular matrix molecules. I also agree with the authors that the accumulation of elastotic material in photodamaged skin could be the consequence of a protective mechanism gone awry. Normal turnover of collagens and elastin is limited, and regeneration of fully matured elastic fibers after skin injury happens very slowly, if at all. Teleologically speaking, our skin has ample reason to protect its elastic fibers,

[1]*Department of Dermatology, Radboud University Nijmegen Medical Centre, Nijmegen Centre for Molecular Life Sciences, Nijmegen, The Netherlands*

*Correspondence: Dr Joost Schalkwijk, Department of Dermatology, Radboud University Nijmegen Medical Centre, Nijmegen Centre for Molecular Life Sciences, PO Box 9101, 6500 HB Nijmegen, The Netherlands. E-mail: J.Schalkwijk@ncmls.ru.nl*

and secretion of an elastase inhibitor following an insult (excessive UV light) makes sense. Chronic exposure to UV light would cause sustained production of elafin, and the action of transglutaminases will result in an irreversible covalent binding with elastic fibers.

> Teleologically speaking, our skin has ample reason to protect its elastic fibers.

Although this would position the protease inhibitor in exactly the right place to do its job, it also comes with a cost: modification of glutamines and lysines in the elastic fiber constituents. Accumulation of these modifications could in the end severely compromise the biochemical and cell-biological properties of these elastic fibers, including resistance to breakdown and normal turnover, propensity to aggregate, and activation of fibroblasts to increase tropoelastin synthesis. The assertion by Muto *et al.* (2007) that fiber-associated elafin protects against breakdown does not, in itself, explain why there is a strong increase of elastic fiber material in photodamaged skin. There are, however, some lessons to be learned from a mouse model. Chronic UV irradiation of hairless mice is a model for actinic elastosis (Starcher and Conrad, 1995). It was shown, however, that mice that lack neutrophil elastase do not accumulate elastic fibers; this suggests a role for elastase not only in breakdown but also in increased production of elastic fibers. There is no mouse ortholog for the human elafin gene, but mice do have SLPI, which probably has the same function. Taken together, these observations suggest that elastase activity promotes elastin synthesis, possibly in an indirect way following the release of breakdown products of the elastic fibers. This process could be controlled to some extent by the local induction of elastase inhibitors such as elafin (Muto *et al.*, 2007) and SLPI (Wingens *et al.*, 1998). When these safeguards fail, excess elastase activity cannot be controlled. Speculatively, elastic fibers altered by transglutaminase-mediated cross-linking and increased elastin production will in the end lead to the elastotic material seen in photodamaged skin.

## CONFLICT OF INTEREST

The author states no conflict of interest.

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# Opioids and the Skin: "Itchy" Perspectives beyond Analgesia and Abuse

Martin Schmelz[1] and Ralf Paus[2]

**Opioids are intimately linked to central pain inhibition and their abuse potential. Thus, peripheral opioid receptors in the skin have been studied initially with a focus on their peripheral analgesic properties. Recent results, however, clearly indicate that opioids play a specific role in skin homeostasis by modulating keratinocyte differentiation, wound healing, and inflammatory responses.**

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Traditionally, opioid research is focused on the powerful inhibition of central pain pathways by opioid receptor ligands, an effect that has been clinically exploited for centuries. Like the habitual abuse of exogenous opioids — a matter of much scientific scrutiny and heated political debate — analgesic therapy with exogenous opioids has long been known to be associated with intense generalized pruritus (Twycross *et al.*, 2003; Gutstein and Akil, 2001). And yet, this ancient lead toward the peripheral activities of opioids has

[1]*Department of Anesthesiology–Mannheim, University of Heidelberg, Heidelberg, Germany.* [2]*Department of Dermatology, University Hospital Schleswig-Holstein, University of Lübeck, Lübeck, Germany*

*Correspondence: Prof. Martin Schmelz, Department of Anesthesiology–Mannheim, University of Heidelberg, Theodor Kutzer Ufer 1-3, 68135 Mannheim, Germany. E-mail: Martin.schmelz@anaes.ma.uni-heidelberg.de*