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Stiff hands in diabetics correlates with loss of hyaluronan in the basal membrane zone of the skin

Many patients with type 1 diabetes have thick, tight, waxy skin and limited joint mobility, especially of the distal phalanges of the hands, a combination called *cheiroarthropathy*.[1] Affected patients are unable to bring their palms completely together when opposing the hands, the so called "prayers sign". These changes are important also because affected patients have a strongly increased risk of microangiopathy. The biochemical change is not fully understood, but it seems likely that non-enzymatic glycosylation of dermal collagen is one of the underlying causes. In this issue, Bertheim et al. (p. 329) explore another component of the connective tissue, hyaluronan or hyaluronic acid, which is a member of the glycosaminoglycan family of macromolecules and is an important matrix constituent in all layers of the skin (2, 3). By applying a specific probe for hyaluronan, i.e. biotinylated hyaluronan binding protein, to tissue sections of skin biopsy specimens from the dorsum of the hands of healthy controls and patients with various degrees of diabetes-associated cheiroarthropathy, the authors show that a specific staining is obtained which is significantly reduced in the basal membrane zone and papillary dermis of the most severely affected patients. Conversely, the epidermis stained stronger and was thicker in the patients compared to the healthy controls. Since hyaluronan is not only a matrix component important for the water-holding capacity of the skin, but also involved in cell migration, angiogenesis, immune reactions and phagocytosis, a loss of hyaluronan in the upper dermis could have serious consequences for the integrity of the skin and underlying joints in diabetes. However, there are still some question marks to be straightened before this hypothesis can be accepted. For instance, when the total amount of hyaluronan was analyzed in a few skin samples, no significant difference was noted between diabetes patients and healthy controls. It is also not known whether the observed changes are primary or secondary events in the process of developing stiff skin and joints, and how these changes relate to the well-known glycosylation problem in diabetes. Finally, it is still unexplained how changes in the hyaluronan deposition in the basal membrane zone located superficially in the skin might affect the stiffness of underlying tissues and joints.

Does smoking precipitate palmoplantar pustulosis via an autoimmune mechanism in the skin?

It is common knowledge among dermatologists that palmoplantar pustulosis (PPP) is a chronic disease related to psoriasis and associated with a high frequency of smokers ($\geq 95\%$ in some studies). Overrepresentation of PPP patients with autoimmune diseases, especially autoimmune thyroiditis[2] is also seen. However, the pathogenesis of PPP is still unknown. On p. 341 in this issue Hagforsen et al. put forward the interesting hypothesis that smoking exposes autoantigens in the sweat ducts of the palms and soles in PPP-prone patients and thus precipitates an autoimmune loop which leads to chronic stimulation of skin inflammation, leukocyte chemotaxis to the acrosyringium, and epidermal hyperproliferation. The same authors recently showed a strong immunoreactivity of the nicotinic acetylcholine receptor in the acrosyringium of palmar skin (see ref 10 in this article). Specifically, the staining of the α-7 subunit of the receptor was found to be stronger in the skin from PPP patients than in skin from healthy subjects (smokers or non-smokers). In the present study, Hagforsen et al. have gone on to study the serum levels of autoantibodies against the niotinic acetylcholine receptor by comparing patients with PPP and chronic hand eczema, respectively. Nineteen of 45 patients with PPP showed elevated concentrations of the antibodies, compared to none of 23 patients with palmar eczema. The authors then, by indirect immunofluorescence, studied the reactivity of the same patient sera on sections of normal palmar skin. Using skin from healthy non-smokers, 21 (46.7%) of the PPP sera gave positive staining mainly localized to endothelial cells of the papillary dermis. Alternatively, using skin from healthy smokers as substrate many of these sera also reacted with the acrosyringium and sweat glands. This reaction pattern was not seen with sera from hand eczema patients. Based on these and several other observations, Hagforsen et al. propose that smoking facilitates the binding of autoantibodies to endothelial cells and sweat ducts in palmoplantar skin, hence activating inflammation, which eventually results in a pustule formation in the lowest part of the stratum corneum. However, much remains to be studied before any candidate autoantigen(s) has been proven and the concept of smoking-induced PPP can be further exploited.

Anders Vahlquist
Editor-in-Chief

IgE-mediated hypersensitivity against human sweat antigen in patients with atopic dermatitis.

Dr. Hide et al. (p. 335) show in a study of 66 patients with atopic dermatitis, 7 patients with allergic rhinitis and 27 healthy controls that 85% of the patients develop a wheal and flare reaction, if their own sweat is injected intradermally – fully similar to a type I reaction in the skin. Only 11% of control persons had a similar ability to react towards their own sweat. Interestingly, 5 of 7 patients with allergic rhinitis, but not eczema, had the same ability. The authors demonstrate that basophils from atopic patients release histamine *in vitro* when sweat is added, and this is likely happening via IgE on the surface of the basophils. Thus, basophils of atopic patients – irrespective of disease severity and total serum IgE are armed with IgE having reactivity towards sweat antigens, which seem to have a molecular weight of 1.3 to 17 kD. Sweating is known to provoke or worsen itch in atopic eczema patients. The histamine-release could be a contributing factor. However, sweating is associated with an increased skin temperature, which in itself promotes the many biochemical processes going on in atopic eczema skin, including the release of cytokines from activated T lymphocytes. Therefore, the observations of Dr. Hide et al. are interesting, but are likely not the only factors in the itch symptom – as antihistamines are known not to be sufficient for the treatment of itch in atopic dermatitis. It will be interesting to known the exact nature of the sweat antigen(s).

Kristian Thestrup-Pedersen
Section Editor

[1]Fitzpatrick's Dermatology in General Medicine Fifth edition, McGraw-Hill, Editors: Freedberg IM et al., 1999.

[2]Rosen K. Pustulosis palmoplantaris and chronic eczematous hand dermatitis. Treatment, epidermal Langerhans cells and association with thyroid disease. Acta Derm Venereol Suppl 1988; 137: 1 – 52.

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