

Session Two

**GENE ENVIRONMENT INTERACTIONS
IN ATOPIC ECZEMA: IMPLICATIONS
FOR TREATMENT**

Dr. Michael Cork

4:30 pm - 5:00 pm
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There has been an increasing awareness that breakdown of the skin barrier may be one of the primary events in the development of atopic eczema. A systematic review of IgE measurements in children with atopic dermatitis revealed that in studies in the community up to 66% of the children did not have a raised IgE (specific or non-specific) at the point it was measured (Flohr et al 2004). These are the children with mild moderate intrinsic atopic eczema, which can be regarded as a primary transitory form of the disease (Nowak and Bieber 2003). One suggestion has been that there could be a primary defect in the skin barrier in atopic dermatitis (Elias et al 1999) and this could be part of the explanation for intrinsic 'atopic' dermatitis.

The barrier to the penetration of irritants and allergens into the skin is located in the stratum corneum. The corneodesmosomes lock the corneocytes together and prevent shearing forces dislodging the corneocytes. Corneocytes are shed from the surface of the skin by a process of proteolysis, which is mediated by skin specific proteases, such as stratum corneum chymotryptic enzyme (SCCE). These proteases are inhibited by specific skin protease inhibitors such as 'cystatin A. It is essential that the process of desquamation is tightly regulated in order to prevent premature desquamation and a breakdown of the skin barrier. A breakdown/thinning of the stratum corneum will permit the penetration of irritants and allergens, which in turn can lead to the development of flares of AD.

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We have previously demonstrated that in children with intrinsic AD there is a strong genetic association with an insertion in the 3'UTR of the SCCE gene. (Vasilopoulos et al, 2004). The consequence of this insertion is to increase the levels of SCCE protein in the skin. (Vasilopoulos et al, 2004). This will lead to enhanced breakdown of the skin barrier, allowing the penetration of irritants and allergens, leading to a flare of atopic eczema (Vasilopoulos et al, 2004).

We have recently identified changes in a protease inhibitor gene cystatin A which are strongly associated with atopic eczema (Vasilopoulos et al 2007). This change results in decreased levels of the cystatin A protease inhibitor resulting in an enhanced activity of endogenous proteases such as SCCE and excessive breakdown of the skin barrier. This will allow greater allergen penetration in a similar way to the change in the KLK7 (SCCE) gene. Cystatin A not only inhibits the action of endogenous proteases such as SCCE it also inhibits the action of exogenous proteases derived from house dust mites and staphylococcus aureus. Cystatin A is secreted in eccrine secretions and so its presence in sweat provides a protective shield over the surface of the skin. The variants in the Cystatin A gene result in decreased production of cystatin A and a defective shield of protease inhibitor over the skin surface. This results in enhanced skin barrier breakdown caused by both exogenous proteases (eg Der P1 and staph aureus) and endogenous proteases (eg SCCE). The proteases produced by house dust mites and staphylococcus aureus also act as allergens once they have penetrated through the skin barrier

Another important environmental agent which exacerbates atopic eczema is soap and other detergents. The skin protease SCCE exhibits a neutral pH optimum (Eckholm et al.: 2000). A change from pH 7.5 to 5.5 reduces the SCCE activity by 50% (Egelrud and Hanson; 2004). The normal pH of the skin is 5.5

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but washing with soap or detergents has been shown to raise the pH to 7.5 and higher. This helps explain why soap and detergents can cause a reduction in the thickness of the stratum corneum and induce flares of atopic dermatitis (Cork et al 2006).

The sensitive skin areas such as the face and flexures have a much thinner stratum corneum than other body sites. They therefore have a lower 'skin barrier reserve' to protect them from the environment. Anything that causes a thinning of the stratum corneum is much more likely to result in enhanced irritant and allergen penetration on these sensitive skin sites than elsewhere on the body. This helps explain why these are sites of predisposition to atopic eczema.

Topical corticosteroids are a very important short term treatment of flares of atopic eczema. However prolonged exposure of the skin particularly on sensitive skin sites such as the face can result in thinning of the stratum corneum and enhanced allergen penetration. This is the most likely explanation of the topical corticosteroid addiction phenomenon and rebound. This effective can be caused by even moderate and mild potency TCS on areas such as the eyelids because they start with such a low skin barrier reserve (Cork et al 2007). Pimecrolimus Elidel has no negative effects on the skin barrier (Cork et al 2006).

The new understanding of the central role of skin barrier dysfunction in atopic dermatitis provides an opportunity to use existing products more effectively. Emollients are an important group of products but some crude formulations such as aqueous cream contain surfactants that can exacerbate rather than improve AD. It is important to understand how all-topical formulations interact with the skin barrier and select those that have a positive effect. A combination of emollients, calcineurin inhibitors and irritant and allergen avoidance will reduce the need for TCS and when they are used they will be more

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effective and have less adverse effects because exposure is shorter.

During the first six months of life the immune system is most vulnerable to be switched from TH1 (intrinsic) to TH2 (extrinsic) by allergens. . Restoration of the skin barrier in the first six months of life could reduce the penetration of allergens and as a result decrease TH1 to TH2 switching. This could slow or prevent the progression of the atopic march. An understanding of how environmental factors interact with the immune system through a defective skin barrier will enhance not only the treatment of atopic eczema but may help develop methods to prevent it...

References

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