

Improving the treatment of atopic eczema through an understanding of gene – environment interactions

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Historically, eczema has been thought of as principally an allergic 'atopic' disease, hence the name atopic eczema.

Atopy is the tendency to produce 'allergic' IgE antibodies instead of 'non-allergic' IgM antibodies. These antibodies may be non-specific or specific, reacting against particular allergens such as grasses and pets.

Two forms of atopic eczema have been recognised. One form is called 'extrinsic' (allergic) atopic eczema, in which there are both raised non-specific IgE and specific IgE antibodies. The other is called 'intrinsic' (non-allergic) atopic eczema, which is not associated with a raised non-specific or specific IgE. It had previously been thought that the majority (c. 80%) of children with atopic eczema had extrinsically induced allergic atopic eczema, with the remaining 20% having non-allergic atopic eczema.

However, a recent systematic review of all studies of IgE levels in children with atopic eczema demonstrated that in children from the community up to 66% had the non-allergic form of atopic eczema,¹ inviting the question whether the use of 'atopic' in atopic eczema is appropriate. The majority of children with non-allergic atopic eczema have mild/moderate clinical symptoms, as do the majority of children with atopic eczema in the community.

If most children with mild/moderate atopic eczema are non-allergic by not having raised IgE levels, why do they have eczema? Although the majority of scientists studying atopic eczema have historically thought that the main cause was raised allergic IgE antibodies, a couple of groups have suggested that the primary problem is in the skin barrier.²

The structure of the epidermal part of the skin is illustrated in Fig. 1. Skin cells (keratinocytes) divide at

the bottom of the epidermis in order to produce a supply of new skin cells.

The new skin cells then start to mature (differentiate) as they move up through the skin. At the top of the skin, the skin barrier (stratum corneum) is formed. The skin barrier protects the body from the environment and normally prevents the penetration of irritants and allergens through the skin. The skin cells in the stratum corneum are locked together by structures called corneodesmosomes and the skin cells are surrounded by lipid bi-layers.

The stratum corneum can be visualised as being similar to a brick wall (Fig. 2), with the skin cells analogous to the bricks and the lipid lamellae analogous to the cement.³ The stability of tall brick walls is maintained by passing iron rods through holes in the bricks. These iron rods are analogous to the corneodesmosomes, because they hold the bricks/skin cells together (Fig. 2b). The iron rods allow the skin to resist shearing forces. The cement protects the skin cells and the iron rods (Fig. 2c) from the environment. A strong skin barrier is essential to protect the body from the

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penetration of irritants and allergens.

In order to maintain a

constant thickness of the stratum corneum barrier, skin cells must be shed from the surface of the skin (Fig. 1). The skin cells can only be shed after the corneodesmosomes (iron rods) have been broken down (rusted) (Fig. 3a). The iron rods are broken down by chemicals called proteases.

This then allows skin cells to be shed from the skin surface (Figs 1, 3a). This process is called proteolysis and leads to shedding of the skin cells from the surface of the skin (desquamation). In normal skin the rusting (proteolysis) of the iron rods only occurs near the surface of the skin (Fig. 3a). As a result, a thick skin barrier is maintained and this prevents the penetration

Figures 1–11 are on pages 11–13.

of irritants and allergens (Fig. 3). In atopic eczema, the skin barrier is thinner than that in normal skin.⁴ The skin barrier is also a lot more vulnerable to irritation by substances such as soap and detergents.

Another observation that focused our attention on the skin barrier was that the skin barrier was thinnest in the skin sites that were most vulnerable to atopic eczema (Fig. 4). Skin sites such as the face and the flexures have the thinnest skin barrier and these sites are most often affected by atopic eczema. In the skin sites where the stratum corneum is very thin, such as the face, there is very little barrier reserve. This means that, if the barrier is damaged, it will be easy for irritants and allergens to penetrate through the further-thinned skin barrier and trigger a flare of the eczema.

The prevalence of atopic eczema has increased relentlessly over the past 50 years from 4% in the 1940s to more than 25% today.⁵ The genes that predispose to atopic eczema have not changed over the past 60 years, but our environment has changed considerably.⁶ One example is the exposure to soap and surfactants where the use of products such as bubble baths to wash babies has increased substantially over the past 60 years.⁶ Surfactants are used to make dirt soluble and allow it to be washed off the skin. Soap and surfactants have been shown to cause a reduction in the thickness of the stratum corneum by 40%.⁴ They are also known to break down the lipid lamellae (cement).

Atopic eczema has a strong genetic component. If a child has one parent with atopic eczema, they will have a 20% chance of developing eczema themselves, but if both parents have (or had) atopic eczema, then the risk increases to 50%.

Several genes that predispose to atopic eczema have been identified, but they are most relevant to extrinsic (allergic) rather than intrinsic (non-allergic) eczema.^{7,8} In view of the evidence, implicating breakdown of the skin barrier as a very important event in the development of atopic eczema, we looked at genes that regulate the strength of the skin barrier in normal controls, and in children with atopic eczema.⁹

The skin cells (corneocytes) in the upper part of the skin barrier (Fig. 5) are locked together by corneodesmosomes (iron rods). These are broken down

by chemicals called proteases, such as stratum corneum chymotryptic enzyme (SCCE) (Fig. 5). These proteases are inhibited by skin protease inhibitors (e.g. SKALP). In normal skin there are low levels of the proteases (e.g. SCCE) and so the skin barrier is thick and can resist the penetration of irritants and allergens (Fig. 6a).

We found that in children with non-allergic atopic eczema there was a change in the SCCE protease gene.⁹ The most likely consequence of this change in the SCCE gene was to produce higher levels of the SCCE protease.⁹ This would lead to premature breakdown of the corneodesmosomes leading to a breakdown of the skin barrier (Fig. 6b), allowing the penetration of irritants and allergens that would trigger a flare of the atopic eczema. The lipid lamellae (cement) are also incomplete in atopic eczema, which contributes further to the barrier breakdown.

Another very important gene involved in the regulation of the skin barrier in atopic eczema, is the SPINK V protease inhibitor gene. This was previously reviewed in Exchange by Cookson & Moffat.¹⁰

Soap and surfactants have been shown to thin the skin barrier and induce a flare of atopic eczema. The normal pH of the skin is 5.5, but exposure to soap and surfactants will raise this to 7.5 and higher.

The protease SCCE is pH sensitive and becomes more active at a pH of 7.5. If the skin pH is raised from 5.5 to 7.5, this results in a 50% increase in the activity of the SCCE protease (Fig. 6c).

The consequence is a greater breakdown of the skin barrier and enhanced penetration of irritants and allergens: a very good example of a gene–environment interaction leading to the development of atopic eczema. Returning to the brick wall model (Fig. 3), in normal skin the levels of protease activity are low and so the iron rods are only rusted near the surface of the skin. This allows the normal process of shedding of skin cells from the skin surface but maintains a strong skin barrier (Fig. 3a). In a child predisposed to atopic eczema, the iron rods are rusted all the way down through the skin barrier (Fig. 3b) as a result of the increased skin protease activity. If this child is then exposed to soap or surfactants, these enhance the rusting process and the brick wall falls apart (Fig. 3c). This in turn allows the penetration of other irritants and

'The prevalence of atopic eczema has increased relentlessly'

allergens (Fig. 3d) that trigger a flare of the eczema. In addition, the lipid lamellae (cement) are incomplete in atopic eczema and this is exacerbated by exposure to soap and detergents.

Some emollient soap substitutes, such as aqueous cream, also contain surfactants. If aqueous cream is inappropriately used as a 'leave-on' emollient cream, it can irritate the skin of children with atopic eczema and make it worse rather than better. In an audit of children attending a paediatric dermatology clinic, using aqueous cream caused irritant reactions in more than 50% of the children.¹¹ We now understand why aqueous cream causes this problem. The surfactants it contains interact with at least one of the genes that lead to skin-barrier breakdown in atopic eczema. This can then lead to skin-barrier breakdown and a flare of the eczema.

Improving the treatment of atopic eczema

Our increasing understanding of how the skin barrier breaks down in atopic eczema reinforces the importance of skin-barrier maintenance and repair as a first-line treatment of atopic eczema (Fig. 7). It is important to use an intensive emollient routine to restore the skin barrier, consisting of emollient cream or ointment, emollient soap substitutes and emollient bath/shower products.^{12, 13, 14} This has been called a 'complete emollient therapy regimen'.¹⁵ Emollients provide an oily layer over the surface of the skin, which acts as an artificial skin barrier. Some constituents of emollients may also mimic the defective lipid lamellae in atopic eczema.¹² Emollients therefore produce a partial repair of the skin barrier (Fig. 8) and are a very important treatment to prevent flares of atopic eczema.

Identification of irritants and allergens and their avoidance is an important second step in the management of atopic eczema. Avoidance of irritants such as soap and detergents is important to all children with atopic eczema because these agents interact with the changes in the genes that cause skin-barrier breakdown. Some allergens, such as those from house-dust mites, may be important amongst all children with atopic eczema because they also interact with the skin barrier.¹⁶ Other allergens, such as those from the diet, may be important in some children and not in others.

Treatment of flares forms the third line of treatment of atopic eczema (Fig. 7). The more attention that is paid to the first two steps of eczema management, the less

often flares of atopic eczema will occur. The calcineurin inhibitors pimecrolimus (Elidel™) and tacrolimus (Protopic™) have been an important advance in the

'Avoidance of irritants such as soap and detergents is important'

treatment of atopic eczema and have a good safety profile. Topical corticosteroids are a safe and effective treatment if the appropriate potency is used in short courses. Combining emollients and pimecrolimus can reduce the number of flares of atopic eczema and the need for topical corticosteroids.¹⁷

The key to the best management of atopic eczema is to focus on the three lines or steps of treatment (Fig. 7). If more attention is paid to steps (a) and (b), then the fewer the flares that will need treatment at step (c). It is also very important for the management of atopic eczema (and any skin problems) to take time: time to listen, time to teach and time to demonstrate how to use treatments such as emollients. We have shown that the delivery of this type of education programme to children with atopic eczema (and their parents), by specialist dermatology nurses, produces a substantial improvement in the control of the eczema.¹⁸ We have developed a series of cartoons called 'Skin Wars', to explain to children with eczema (and their parents!) how eczema develops and how to treat it.¹³ Figure 9 is one of our cartoons from 'Skin Wars', which explains to the child that soap and surfactants can break down their skin barrier and can be thought of as 'baddies'. What they need to do is get rid of all the baddies and replace them with the 'goodies' – emollients that help to repair the skin barrier. The skin's response to topical products is very individual and we let children pick their favourite emollients from a tray of all the emollients in the British National Formulary. A particular emollient may cause a skin reaction in some children and so the child and parent can pick emollients that best suit their own skin. We also give advice regarding the choice of many other factors in the child's environment – for example, washing powders, clothing and design of their bedrooms.

Future of treatment for atopic eczema

Although emollients are a very effective treatment for flares of atopic eczema when used in large quantities, they do not completely repair the skin barrier. This is because they do not inhibit the increased levels of proteases present in the skin of children with atopic eczema.



We are developing a new class of treatment for atopic eczema – the skin protease inhibitors (SPI) – in collaboration with York Pharma. This product inhibits the increased levels of proteases present in the skin of children predisposed to atopic eczema (Fig. 10). The new treatment has all the positive effects of an emollient, combined with the anti-protease action, in order to produce a more complete repair of the skin barrier (Fig. 10). The SPI would be combined with emollient wash/bath/shower products to improve the repair of the skin barrier and reduce the number of flares of atopic eczema.

Atopic eczema develops before atopic asthma and hay fever, and this cascade of events has been called the ‘atopic march’ (Fig. 11). One hypothesis is that the defective skin barrier in a baby at risk of developing atopic eczema at birth can allow the penetration of allergens, which shift the baby’s immune system from non-allergic to allergic and therefore increase the chance of them developing asthma, hay fever and food allergies^{16, 19, 20} (Fig. 11).

Babies who are predisposed to develop atopic eczema include those who have changes in their SCCE protease gene.⁹ Restoration of the skin barrier of these babies in the first 6 months of life, with skin protease inhibitors and emollient wash products, could reduce the penetration of irritants and allergens and help to reduce the severity of (or prevent) atopic asthma and allergic rhinitis. Any new intervention such as the SPIs should be combined with all the existing treatments, and education for atopic eczema (Fig. 7), in order to produce the greatest improvement in the control of atopic eczema.

The completely new approach to the treatment of atopic eczema would be treating babies who were predisposed to, but who had not yet developed, atopic eczema. This will require the development of a diagnostic test to predict which babies are predisposed to develop atopic eczema. It is likely that these tests will become available within the next 5 years. The future of treatment for atopic eczema, asthma and related diseases will be in identifying those who are at risk before they develop these conditions and then by intervening to prevent the development or reduce the severity of these diseases.

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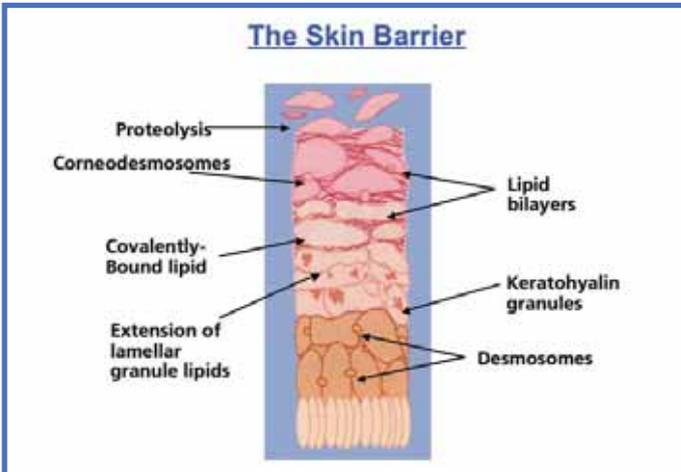


Fig. 1: The skin barrier is located in the top of the skin. The skin cells are locked together by structures known as corneodesmosomes. Near the surface of the skin, the corneodesmosomes are broken down, allowing the skin cells to be shed from the surface of the skin. This process is essential in order to maintain a constant skin thickness. The process must not occur too quickly because this would result in a skin barrier that was too thin to resist the penetration of irritants and allergens. Once irritants and allergens have penetrated through the defective barrier, they can trigger a flare of the eczema.

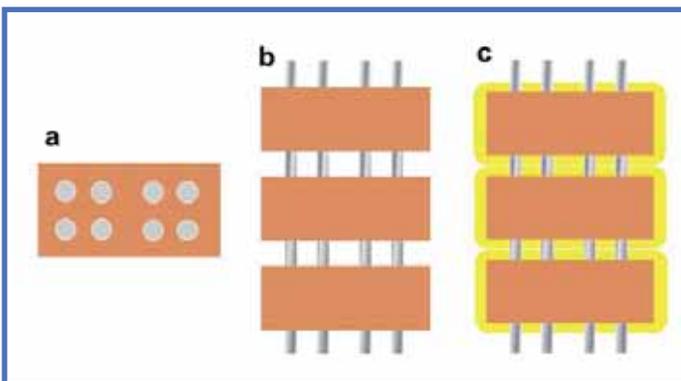


Fig. 2: The upper part of the skin forms a barrier that protects the individual from their environment. This barrier can be visualised like a brick wall, with the skin cells analogous to the bricks and the lipid layers analogous to the cement. In tall brick walls, iron rods are passed down through holes in bricks in order to give the wall much greater strength. These iron rods are analogous to the corneodesmosomes that lock the skin cells together.

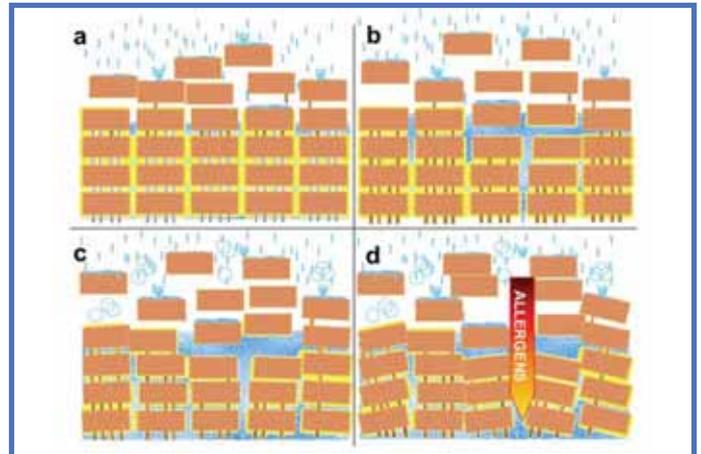


Fig. 3: In normal skin (3a) the iron rods (corneodesmosomes) are normal throughout the stratum corneum (top layer of skin). At the surface of the skin, the corneodesmosomes start to break down, the normal process of shredding skin cells from the surface (desquamation). This can be visualised as analogous to the iron rods rusting. The normal process of rusting can be enhanced if the surface of the skin is washed with soap, because this increases the activity of the chemicals (proteases) that break down the iron rods.

In a child predisposed to atopic eczema, it can be visualised that the iron rods (corneodesmosomes) are rusted all the way down through the skin barrier (3b) as a result of the increased amount of chemicals (proteases) that break down the iron rods. If the child is then exposed to soap, this enhances the rusting process and the brick wall falls apart (3c). This then allows the penetration of other irritants and allergens that trigger a flare of the eczema (3d).

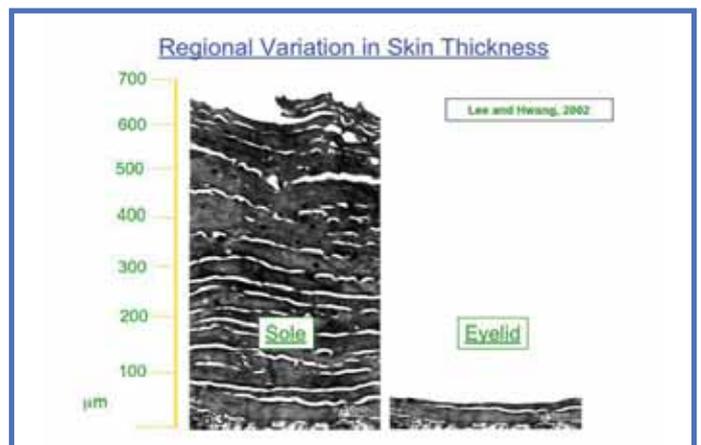


Fig. 4: The thickness of the upper part of normal skin

(stratum corneum) is not the same in the skin from different body sites. The thinnest stratum corneum is found in the eyelids, rest of the face and flexures. Interestingly, these skin sites are those that are most likely to develop atopic eczema. At the other end of the spectrum, the sole of the foot has the thickest stratum corneum.

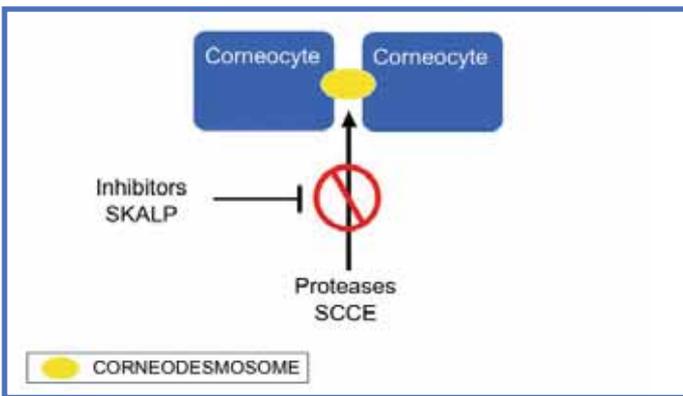


Fig. 5: The skin cells (corneocytes) are locked together by corneodesmosomes (iron rods). Chemicals called proteases, e.g. stratum corneum chymotryptic enzyme (SCCE) break down these corneodesmosomes. Inhibitors such as SKALP inhibit these proteases.

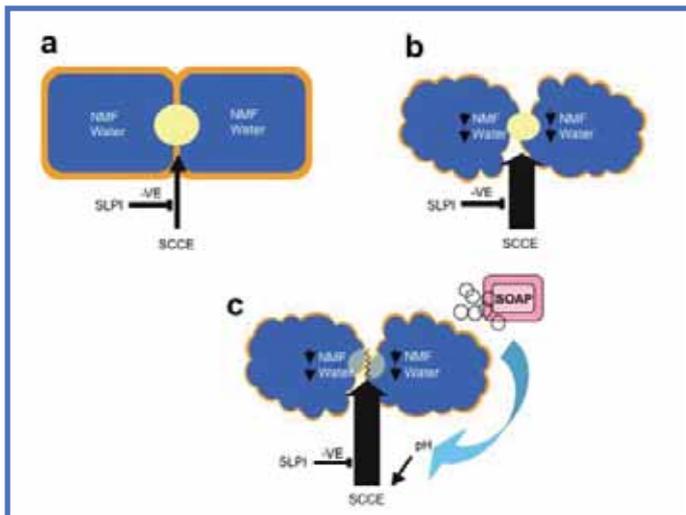


Fig. 6: In normal skin (6a) there are low levels of the proteases (e.g. SCCE) and so the skin barrier is thick and can resist the penetration of irritants and allergens.

In children with atopic eczema there is a change in the SCCE protease gene. The most likely consequence of this change in the SCCE gene is to produce higher levels of the SCCE protease. This leads to premature breakdown of

the skin barrier (6b). This then allows the penetration of irritants and allergens that trigger a flare of the atopic eczema.

Soap has been shown to thin the skin barrier and induce a flare of atopic eczema. The normal pH of the skin is 5.5, but exposure to soap can raise this to 7.5 and higher. The protease SCCE works best at pH 7.5, so putting soap on the skin will enhance the breakdown of the corneodesmosomes, leading to greater penetration of irritants and allergens (6c).

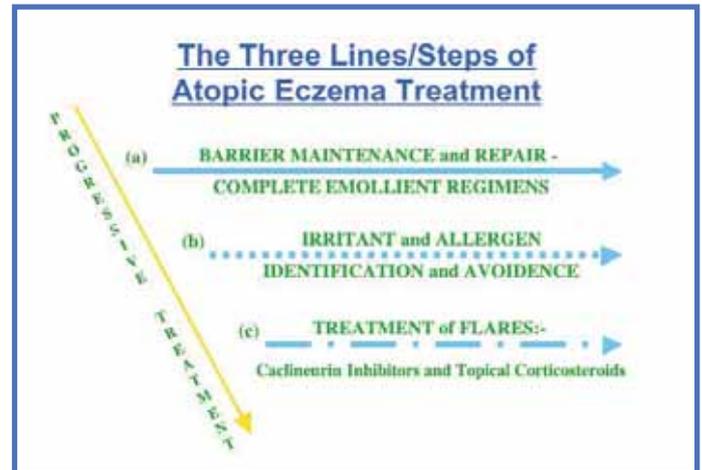


Fig. 7: The treatment of atopic eczema can be divided into three steps. The more effort that is put into the first steps – (a) barrier maintenance and repair and (b) irritant and allergen identification and avoidance – the lower the number and severity of the flares that will require treatment under step (c).

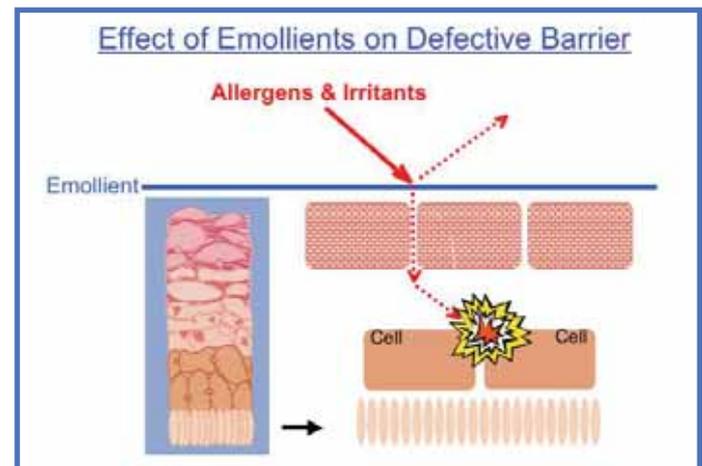


Fig. 8: Emollients produce a partial repair of the defective skin barrier in atopic eczema and, as a result,

reduce the number of flares of the eczema. If emollients are applied in large quantities and at frequent intervals, the degree of barrier repair can be increased significantly. The emollient forms an oily layer that traps water underneath it, which can then pass back into the skin cells to regenerate them. Ingredients of some emollients can also mimic the deficient cement (lipid lamellae) in atopic eczema.

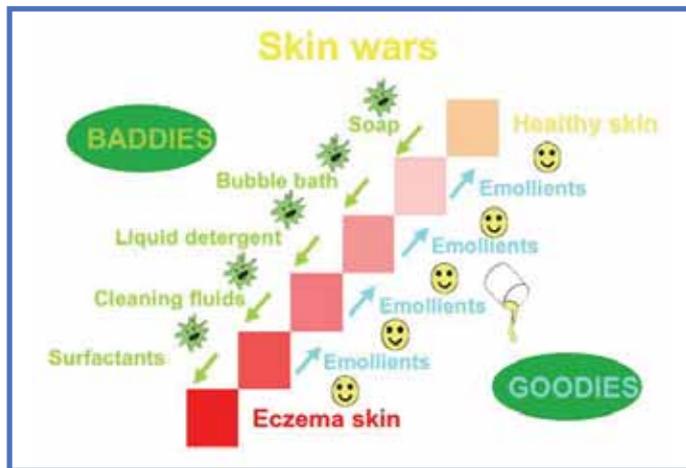


Fig. 9: The key to the management of atopic eczema is to spend time to educate. 'Skin Wars' are a series of cartoons we have developed to explain to children with eczema (and their parents) how eczema develops and how to treat it. These cartoons explain to the child how soap can break down their skin barrier and can be thought of as 'baddies'. What they need to do is get rid of all the baddies and replace them with the 'goodies': emollients, which help to repair the skin barrier.

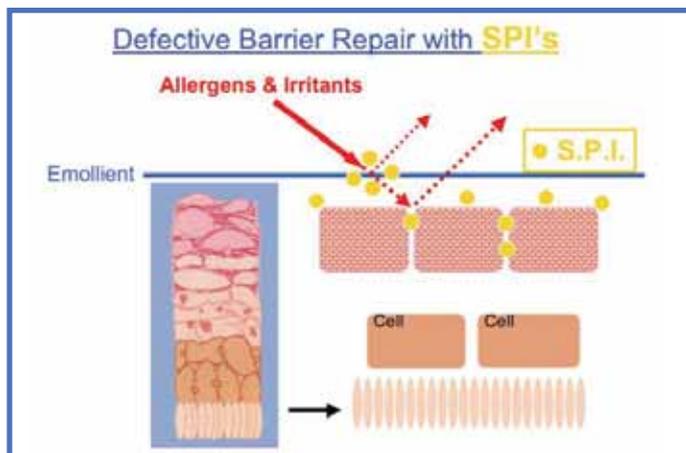


Fig. 10: Skin protease inhibitors (SPI) are a new type of treatment that is being developed for atopic eczema. The

SPI combine all of the positive features of emollients, with ingredients that inhibit proteases on and in the skin. The SPI can therefore contribute to the repair of the defective iron rods (corneodesmosomes) in the skin of children with atopic eczema.

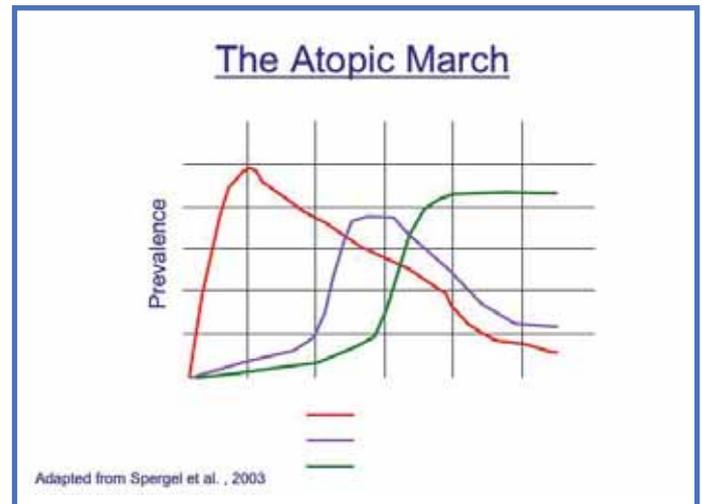


Fig. 11: The 'atopic march' indicates the progression in some children – first they develop atopic eczema, then atopic asthma and then hay fever. This has led to the hypothesis that the development of atopic eczema in some way makes a child more likely to develop asthma and hay fever. There is increasing evidence that the first event in this atopic march is a predisposition to a defective skin barrier. This defective skin barrier then allows the penetration of irritants and allergens, which trigger the development of atopic eczema. The same allergens can shift the immune system of babies from non-allergic to allergic and so lead to the development of asthma and hay fever.

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