Prevention of atopic dermatitis
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Abstract
Atopic dermatitis now affects one in five children, and may progress to asthma and hay fever. In the absence of effective treatments that influence disease progression, prevention is a highly desirable goal. The evidence for most existing disease prevention strategies, such as avoidance of allergens and dietary interventions, has been unconvincing and inconsistent. Fresh approaches to prevention include trying to induce tolerance to allergens in early life, and enhancing the defective skin barrier to reduce skin inflammation, sensitisation and subsequent allergic disease. Early and aggressive treatment of atopic dermatitis represents another possible secondary prevention strategy that could interrupt the development of autoimmunity, which may account for atopic dermatitis persistence. Large scale and long term randomized controlled trials are needed to demonstrate that these ideas result in clinical benefit.

Introduction
Atopic dermatitis, also known as atopic eczema or just “eczema” [1], is a very common skin condition characterized by skin inflammation and itching that typically starts in early life [2,3]. Atopic dermatitis is associated with dry skin and a tendency towards asthma and hay fever [4,5] and now affects around 20% of children in developed and developing countries [6,7]. Data from the International Study of Asthma and Allergies in Childhood (ISAAC) suggests that atopic dermatitis is increasing (Figure 1), especially in younger children [8]. Genetic factors that determine skin barrier integrity and skin inflammation seem to be important [9,10], but so too is the environment, given the rapid rise in prevalence, and the observation that atopic dermatitis seems to be more common in wealthier, smaller and more educated families [11]. Lack of stimulation of the immune system by microbes at an early age because our children are “too clean” (the hygiene hypothesis) or failure of a balanced gut flora to mature may also be important [12,13]. Whilst some people with atopic dermatitis are clearly allergic to foods and house dust mites, recent studies suggest that the role of allergy in atopic dermatitis might have been overemphasized [14,15]. Current treatments, although quite effective [16], are still geared towards treatment of symptoms and visible signs rather than fundamentally altering the course of disease.

In the absence of disease-modifying treatment, attention needs to focus on disease prevention, especially as this might also prevent progression to asthma and hay fever (the “atopic march”). Yet an overview of seven systematic reviews, which included 39 trials on 11,897 participants, concluded that none of the previously tested interventions could be shown to conclusively prevent atopic dermatitis [17]. The possibility that atopic dermatitis may be prevented in a subgroup of infants at high risk of disease by exclusive breastfeeding or the introduction of prebiotics (nutrients that encourage beneficial gut bacteria) was based on limited evidence with potential flaws, [17] although more recent evidence for some probiotics (beneficial live gut bacteria) during and after pregnancy show some promise [18]. Instead of continuing to examine strategies that have been tried for disease
prevention over the last 40 years, fresh approaches for disease prevention, stimulated by recent advances in our understanding of atopic dermatitis, are needed.

**Recent advances**

**Be more tolerant**

Although there is little doubt that some individuals with atopic dermatitis are truly allergic to substances such as house dust mite protein, longitudinal studies reveal allergen sensitization is probably a consequence, not a cause, of atopic dermatitis [19]. This idea is bolstered by findings that genetic syndromes defined by a loss of immune tolerance have eczema as a feature [20]. Consequently, instead of trying to rid the environment of allergens, maybe a better approach would be to try and induce tolerance by exposure to allergens or endotoxins at an early stage of immune development [13]. Peanut allergy might serve as a good model in this regard. In Israel for example, where peanut consumption is much higher than the UK, peanut allergy seems to be much less common [21], an observation that has stimulated a research group to test the hypothesis that introduction of peanuts into the diet in early life can reduce peanut allergy [22].

Gut parasites are another potentially interesting area to explore given that our immune system lived with them for millions of years before their relatively recent eradication. It is possible that this eradication of gut parasites has contributed to the increase in allergic disease due to insufficient immune stimulation of the right sort [23,24], and that the reintroduction of extracts from gut parasites in early life might tip the abnormally tilted atopic dermatitis immune response back into one of allergen tolerance [25].

**Turning everything inside-out**

Research into the causes of atopic dermatitis has been dominated over the last 40 years by a preoccupation with allergy and the immune responses of the skin, gut, lungs and blood. Yet one of the hallmarks of atopic dermatitis is the presence of generally dry skin even in the absence of inflammation [26], an observation that stimulated researchers in Dundee to look at the genes that may be responsible for other dry skin conditions such as ichthyosis [10]. They found that mutations of genes that code for filaggrin – a key protein in the outer skin that maintains skin barrier function – are a strong predictor of atopic dermatitis, especially more severe, chronic atopic dermatitis and associated asthma [27,28]. So the world of atopic dermatitis research is turning its attention away from the inside of the body to the dry skin on the outside. We speculate that exposing children born with atopic dermatitis and defective skin barriers to frequent cleansing with alkaline soaps, bubble baths and shampoos leads to a breach of the skin barrier and low grade inflammation, which can then develop a life of its own through the process of autoimmunity [29,30], (figure 2). The defective skin barrier might also permit allergic sensitization to occur as allergens are introduced more easily to antigen presenting cells in the skin [31]. If this is true, then enhancing the skin barrier function in babies born to parents with allergic disease by limiting the assault of skin cleansers coupled with liberal use of emollients could prevent the development of atopic dermatitis and even the
progression to asthma. Our Barrier Enhancement for Eczema Prevention (BEEP) pilot study has provided an encouraging signal, which our group now plans to test on a much larger scale [32]. It is likely that many new “designer” skin barrier repair products with various claims will emerge over the next 10 years [33,34]. Only large scale randomized controlled trials will definitely show whether they do any good, and whether they are any better than simple, cheaper emollients [35].

Nip it in the bud

Even if atopic dermatitis cannot be prevented in the primary sense, it may still be possible to reduce disease severity through a strategy of early aggressive treatment when atopic dermatitis first appears. It is known that the constant scratching associated with atopic dermatitis may expose parts of skin to cells that can trigger an autoimmune response, which could result in a more widespread and persistent disease [30], (figure 3). So interrupting that chain of events by clamping down early on atopic dermatitis is an avenue worth exploring. Others have also suggested exploring disease modifying strategies in atopic dermatitis to break, stop or reverse atopic dermatitis and associated asthma, in a way that is heavily informed by biomarkers [36]. Other forms of secondary prevention such as “weekend” therapy (applying topical treatments for two consecutive days each week once the disease is under control) had been shown to have a large impact on reducing disease flares [37]. Whether the length and intensity of inducing the initial remission is important for long term control needs to be tested. The emergent theme seems to be one of not “chasing” atopic dermatitis but instead one of getting control then keeping control [38].

Future directions

Although atopic dermatitis prevention has not been a very fruitful area of research in the sense that the same interventions have been explored repeatedly and inconclusively [17], recent gene discoveries coupled with different ways of thinking about disease progression has produced new ideas for primary and secondary disease prevention [10,36]. The dry skin seen in atopic dermatitis,
which has been recognized clinically yet largely ignored by science for many years [39], has undergone a sharp revival of interest with the discovery of mutations in the filaggrin gene. We predict this will result in studies that evaluate the potential protective effect of skin barrier enhancement in high-risk and even low-risk infants. Such intervention studies are not without their challenges. For example, defining a new case of atopic dermatitis as opposed to transient irritant eczema (which commonly occurs in infants) is tricky [40], as will be the problem of how to avoid contamination of a control group if word gets out that emollients from birth might prevent eczema. Selecting which emollient(s) have true barrier enhancement properties and those that are also acceptable for long term use for families whose babies do not appear to have a problem in the first place is also challenging, especially as, paradoxically, some emollients can impair rather than repair the skin barrier [41].

With regards to those studies that focus on inducing allergen tolerance at a young age, attention needs to be paid to the timing, amount and type of exposures to induce such tolerance and whether such tolerance leads to clinical benefit in terms of less atopic dermatitis and associated diseases. It is also unclear whether the conventional strategy of targeting a high risk population in atopic dermatitis prevention (children of parents who have atopic disease), is correct as such a policy could miss around 40% of potentially preventable cases if the same risk factors operate [42]. Perhaps it would be more cost-effective to adopt a whole population-based approach in countries with high levels of atopic dermatitis, although a much stronger evidence base would be required before such a public health approach could be entertained. Or perhaps the way forward is in the opposite direction, i.e. personalized medicine, so that prevention strategies for childhood disease are governed by genetic tests and biomarkers that determine disease risk. One thing is for certain, the whole field of atopic dermatitis prevention is exploding with new ideas. The biggest challenge will be to evaluate these ideas properly in large prospective randomized controlled trials.

Disclosures
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