Epicutaneous immunotherapy is a developing technique, aiming at desensitizing patients with food allergy with less risks that oral ingestion or injection could generate. Several clinical trials have been performed and are currently running, in milk and peanut allergy, assessing the safety of the technique and its efficacy. Preclinical models indicate a major role in the mechanisms of desensitization, for example, Tregs and epigenetic modifications.

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Food allergy is a worldwide issue, with an estimated prevalence of 2–10%, with no treatment currently available. Oral immunotherapy and sublingual immunotherapy have been tested by several authors, in particular for milk, egg and peanut allergy, with significant results in term of desensitization, that is, increase of the dose inducing a reaction during a food challenge, whereas the achievement of sustained unresponsiveness still seems doubtful [1]. The role of skin in allergy has long been considered in terms of sensitization [2–6] and of triggering of acute symptoms, such as urticaria [7] and exacerbation of atopic eczema in IgE-sensitized individuals upon exposure to food antigens [8–12]. Recent data in humans and in animal models that skin may largely be useful to desensitize allergic patients [13] suggesting a major tolerogenic role, for which the cellular or molecular pathways, largely unknown, require in-deep investigation.

The ontogeny of EPIT®
Allergen immunotherapy by subcutaneous administration of an allergen extract in gradual amounts is an effective treatment, with a long-term benefit, for aeroallergen allergy [14], as recognized by WHO [15]. Subcutaneous Immunotherapy (SCIT) has other benefits, such as the prevention of new sensitizations in children monosensitized with house dust mite (HDM) [16] and the development of asthma in children with pollen-induced seasonal rhinoconjunctivitis [17].

Skin may be addressed by its outer layer with the allergen deposited onto the skin instead of being injected intradermally. First clinically successful attempts at desensitization date back to the 50s, when Pautrizel et al. [18], then Blamoutier et al. [19] and Eichenberger and Storck [20] scarified the skin and repeatedly applied drops of extracts of pollen and HDM, until a local reaction appeared. This invasive technique was finally dropped because of it is invasiveness.

More recently, it appeared that an immune reaction may also occur following deposition of an allergen onto intact skin. The local skin immune reaction triggered by diagnostic patch tests was looked for before World War II [21] and further investigated as a model of skin reactivity to HDM in patients with atopic dermatitis (AD) [22]. The so-called atopy patch test [23] proved later on able to show a skin reactivity to food allergens, such as during food allergy associated with AD [24].
and during digestive manifestations of milk allergy [25]. An important step was taken with the development of a ready-to-use patch test [26], specifically designed to diagnose cow’s milk allergy, applied by the parents for their children. The self-application of the patch allowed conceiving a repeated use by patients themselves, thus hipping from a diagnostic device to a therapeutic one.

This observation was the beginning of the so-called epicutaneous immunotherapy, EPIT®, and the development of Viaskin® (DBV Technologies, Paris, France), an epicutaneous delivery system (Figure 1) which allows the allergen to be applied repeatedly onto the intact skin at home, without any subcutaneous injection or instillation through a scarified skin. The technique allows a permanent and long-lasting contact of the allergen with the organism, such as with SCIT or oral immunotherapy (OIT), but without any injection or swallowing of a dangerous allergen, suggesting that a new route for allergen immunotherapy could be considered in the absence of vital risk.

The development of clinical trials Following these steps, EPIT was first attempted in a proof-of-principle study in patients with food allergy. We conducted a 3-month pilot, double-blind placebo controlled (DBPC) trial in 18 children (age 0.8–7.7 years) with milk allergy. Treatment consisted of three 48-h patch applications on the back (skinned milk powder as active substance), three-times a week. This first trial showed that EPIT was safe, virtually devoid of serious systemic adverse events (AE), which differs from subcutaneous and oral immunotherapies requiring expensive evaluation and monitoring during therapy and a drop-out rate approaching 20% due to persistent side effects of therapy [28–32]. In SLIT, due to small and heterogenous studies in food allergy [33,34], it was difficult to draw a clear profile of AEs. Recently, the Fleischer et al. study exhibit a safer safety profile [35]. Less systemic reactions were notified in SLIT than OIT studies, but SLIT was less effective at least in short-term studies [36–38]. AEs with EPIT were mostly local erythema/eczema occurring at application sites and remaining visible for several days. The estimated risk of local eczema was higher in the active group than in the placebo group (odds ratio: 8.20; 95% CI: 2.72–24.5; p < 0.001). The active treatment was thus associated with more frequent complaints for local pruritus and discomfort than placebo, but this did not lead to treatment interruption. Interestingly, local reactions largely varied between patients, even in the active group, but never exceeded local pruritus or local eczema and were easily controlled using local topical medications.

After 3 months, the primary endpoint of the study was the improvement of the cumulative tolerated dose of milk during the food challenges which changed from 1.77 ± 2.98 ml versus 23.61 ± 28.61 ml in the active group versus 4.36 ± 5.87 versus 5.44 ± 5.88 ml with placebo (p = 0.13), exhibiting only a trend toward clinical efficacy. Considerable increases were seen in some individuals. This suggested that the treatment duration, 3 months, was too short for most subjects, which is consistent with the kinetics of other immunotherapy techniques [39]. An important point in this pilot trial was that only one child of the active group slightly decreased his cumulative tolerated dose, strongly suggesting that the technique would not aggravate sensitization, such as reported in animal experiments [40]. These results were considered as paving the way to further investigations of EPIT efficacy and suggested that longer treatment periods might be appropriate.

Interestingly, other attempts at desensitization via the epidermis were carried out in a Swiss research group using allergens deposited on a large patch applied on stripped skin: in order to keep epithelial barrier disruption minimal, Sentis et al. replaced the old skin scarification by a considerably less invasive adhesive tape stripping [41]. The design of the three clinical trials carried out in grass pollen allergy was different from the previous ones [42–35]. The technique comprises a skin preparation with six rounds of skin-stripping with an adhesive tape, and then deposition of the allergen-bearing patch on the stripped skin 12-times for 48 h, in weekly intervals before the pollen season for the first study with a reduction to 8 h of patch application and number of applications for the others. Besides enhancing the penetration of allergens by removing stratum corneum [46], repeated tape stripping is considered by authors as functioning as a ‘physical’ adjuvant through activation of keratinocytes [47,48]. The first pilot trial revealed that patients treated with pollen extract experienced significant alleviation of hay fever symptoms compared with placebo treated patients [41]. Some systemic side effects, correlated with the degree of stratum corneum disruption, were reported, albeit never severe. The local AEs observed were mild local eczematous reactions under the skin patch [41]. Similar results were observed for the two following clinical trials [45]. The technique is promising but authors insist on the need for further research and development, in order to define an optimal regime, balancing clinical efficacy and safety.

In parallel our group developed EPIT with Viaskin on intact skin in a comprehensive clinical plan for patients with peanut allergy. A Phase 1 safety trial in USA included 80 subjects treated with active treatment (peanut protein) and 20 with placebo (age 6–50 years) [49]. Patients had nonsevere or severe
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peanut allergy based on their history of anaphylactic reactions and tolerated doses of peanut protein per patch were as high as 250 μg in children and 500 μg in adolescents and adults. Overall, 3 of 80 subjects receiving active EPIT and 1 of 20 subjects receiving placebo EPIT dropped out prematurely. In this randomized, DBPC study with 2 weeks of patch application, the peanut patch (Viaskin) proved overall well tolerated and convenient.

The efficacy of peanut EPIT was first investigated in the ARACHILD trial, a DBPC Phase 2A study [50]. Fifty-four children with severe peanut allergy (age 5–17 years) were treated with the peanut patch loaded with 100 μg of peanut protein and DBPC oral food challenges (OFC) were conducted at 6–month intervals over a 18–month period to assess the evolution of the cumulative reactive dose, that is, the accumulated amount of peanut protein triggering a clinical reaction. Enrollment was carried out in highly reactive subjects, that is, those with a baseline cumulative reactive dose <300 mg peanut protein. Success following treatment was defined as ≥ten-fold increase in cumulative reactive dose from baseline and/or a reactive dose ≥1 g peanut protein. The study showed consistent and sustained desensitization, with up to 67% responders at 18 months and four subjects reaching 1.1–2.5 g of peanut protein (~4–10 peanuts). Safety data after 18 months were satisfactory and consistent with Phase 1 results. Further to protocol amendment extending the duration of the study, all children were offered 36 months of active treatment (results not yet available).

A large DBPC Phase 2b dose-finding trial [51] involved 22 centers in USA and Europe, enrolled 221 pediatric and adult highly reactive subjects, that is, presenting with a reactive dose ≤300 mg peanut protein during the DBPC OFC. The 12-month treatment allowed comparing the active drug, Viaskin Peanut, loaded with different amounts of peanut protein, to Viaskin placebo. The primary endpoint relied on the comparison of the eliciting dose during the OFC at baseline and after 12 months of treatment: success was defined at 12-month as ≥10-fold increase in eliciting reactive dose from baseline and/or a reactive dose ≥1 g peanut protein. The study was positive: a significant difference was seen at the highest Viaskin dose, 250 μg, with a proportion of responding subjects (50.0%; 28/56 subjects) higher than with placebo (25.0%; 14/56 subjects), p = 0.0108. Viaskin Peanut 250 μg displayed the strongest efficacy in both treatment response rates and evolution of the eliciting doses, compared with Viaskin Peanut 100 μg and 50 μg. Eighteen subjects (32.1%) from the highest dose tolerated equal or more than 1 g peanut protein versus 7 (12.5%) in the placebo group and 23 (41.1%) increased by 10-fold their eliciting dose versus 10 (17.9%). Also, the children subgroup exhibited a higher response rate than the adult and adolescents subgroup, which did not reach statistical significance. Interestingly, a clear dose–response was observed. In good agreement with the clinical observation, a strong
immunomodulation was seen. The active treatment was associated with a robust and sustained increase of median peanut-specific IgG4 titers throughout the study, consistent variations in peanut-specific IgE titers, which increased during the first 3–6 months of treatment then progressively declined toward baseline levels, contrasting with the total absence of variation of the peanut-specific IgG4 and IgE levels in the placebo group. No safety concerns were noted after up to 12 months of peanut EPIT. The most common related reactions were local skin reactions, that is, pruritus, erythema, edema or urticaria at the site of patch application or slightly beyond the patch area. These local skin reactions occurring in 97% of the subjects were mostly mild to moderate in severity. However, these reactions resolved over time and only two subjects (0.9%) dropped out for local AEs (two severe dermatitis). The frequency of occurrence of systemic allergic events, including distal cutaneous reactions, was low (≤2%); none of these reactions being severe. Globally, the compliance of the treatment with Viaskin Peanut was high (>95%). Overall, the study showed evidence that EPIT with Viaskin Peanut was both safe and effective (ClinicalTrials.gov identifier: NCT01675882). A follow-up study is currently ongoing with active treatment in all patients, for two additional years, including assessment of clinical tolerance (ClinicalTrials.gov identifier: NCT01955109). The program of Phase 3 studies in children expected to start treatment as of 1 year of age and adolescents/adults should confirm the safety and efficacy profile of Viaskin Peanut across pediatric age range, and in adults it should also provide data on unresponsiveness after a follow-up period without treatment.

Additionally, the Consortium of Food Allergy Research study group has initiated a randomized controlled study of peanut EPIT planned for 30 months of treatment with enrollment of 75 subjects including young children down to 4 years of age (ClinicalTrials.gov identifier: NCT01904604).

At this stage of development, Peanut EPIT is promising. Some caution is needed. When reviewing these results, it is important remembering how they were obtained (doses, population, treatment, duration, definition of primary criteria).

The mechanisms of action
EPIT using the Viaskin device is backed by a deep investigation of its mechanisms of action in animal models.

The proof of concept of EPIT efficacy in animal models
The first experiments in animals showed that EPIT induces a downregulation of Th2-type response to rebalance the Th2/Th1 tones. In a first preclinical proof of concept, mice sensitized to ovalbumin (OVA), peanut or aeroallergens [52] were allocated to 8 weeks of weekly treatment with EPIT and SCIT and compared with untreated and negative control groups. Plethysmography after allergen aerosols showed decreased airway hyperreactivity with EPIT (p < 0.05 vs the untreated groups) at levels similar to those seen in the SCIT and negative control groups. Levels of specific IgG2a for all allergens significantly increased with EPIT, similarly to SCIT, whereas the IgE/IgG2a ratio decreased. In a large confirmatory preclinical experiment with peanut-allergic mice, EPIT also reversed airway hyperreactivity measured by the invasive method of resistance/compliance, also similarly to SCIT [53]. In all those experiments, Th2 cytokines, eotaxin and eosinophils counts in bronchoalveolar lavage fluid decreased with EPIT and SCIT (p < 0.001 vs sham treatment). In these two studies, no difference was seen between EPIT and SCIT, indicating that EPIT was a good challenger.

In addition to its action on specific IgE, specific IgG2a and organ responses to allergic stimulation, EPIT appears to act on the allergen-specific cellular response. Tissue eosinophilia is a typical feature of AD, the numbers of eosinophils in the skin usually being modest and correlated to disease severity. Indeed, in the model of OVA-sensitized mice [54], application of allergen onto the skin of sensitized untreated mice induced recruitment of eosinophils. This recruitment significantly decreased after repeated applications of allergen using Viaskin.

Interestingly, the efficacy of EPIT on tissue eosinophilia is not limited to the skin but extends to the digestive organs. A model of eosinophilic gastrointestinal disorder may be obtained with mice sensitized by gavages with whole peanut protein extract and cholera toxin, subsequently exposed to peanuts via a specific regimen [55]. Sustained oral exposure to peanuts in sensitized mice leads to severe esophageal eosinophilia and intestinal villus subatrophia, that is, significantly increased influx of eosinophils into the esophageal mucosa (136 eosinophils/mm²) and reduced villus/crypt ratios (1.6 ± 0.15). EPIT of sensitized mice significantly reduced Th2 immunological response (IgE response and splenocyte secretion of Th2 cytokines) as well as esophageal eosinophilia (50 eosinophils/mm², p < 0.05), mRNA expression of Th2 cytokines in tissue – eotaxin (p < 0.05), IL-5 (p < 0.05) and IL-13 (p < 0.05) – and Th2 transcription factor GATA-3 (p < 0.05) and intestinal villus subatrophia.

EPIT requires the integrity of the skin
This epicutaneous desensitization process needs the integrity of the skin barrier (Figure 2). A study directly
addressed this issue [56] and it appeared that the immune response generated by Viaskin was strongly influenced by potential alterations of the skin. When Viaskin has been applied on intact skin, the profile of the immune response generated by the treatment was dominantly Th1/Treg whereas, when Viaskin was applied on stripped skin, it was clearly Th2 oriented. This shed a new light on the role of the skin preparation during EPIT and, at least partially, explained why skin has long been considered a route for sensitization during EPIT and, at least partially, explained why skin has long been considered a route for sensitization rather that for desensitization [3,57–58]. Actually, Strid et al. [5,59–60] and Spergel et al. [2] demonstrated that the application of antigen on previously stripped skin in naive mice was able to switch antigen-specific T helper cell responses from Th1-type to Th2-type responses. The authors showed that epicutaneous immunization on stripped skin converted an established Th1-response (induced by previous subcutaneous injection with adjuvant) into a Th2 response, as demonstrated by the specific reduction of IFN-γ and IgG2a and the enhancement of IL-4 and IgE. Actually, at least on a mouse model of epicutaneous sensitization, skin seems not to be not inherently sensitizing, and it is likely that factors providing adjuvant activity are required for the development of allergic sensitization to food allergens through the skin [61]. Experimental evidence shows that the hapten picroxy chloride applied epicutaneously promotes a Th1 response, whereas following tape stripping of the stratum corneum, skin application stimulates a dominant Th2 response [62].

**The immune structures of the skin able to interact with EPIT**

The necessary integrity of the upper layers of the skin for EPIT to be efficient underlines the need to take into consideration the skin immune system from its very beginning outer layer.

The immune structures of the skin comprise several strata, which are now the focus of a large investigation [63]. The role of this immune system is to sustain tissue integrity by providing immunoprotection and novel modes of immunoregulation, whereas its dysregulation may promote body surface immunopathologies [64]. EPIT, as opposed other immunotherapy techniques does not need any injection or oral intake of the allergen, which is the basis of its safety. EPIT thus functions according to an original mechanism: the allergen, when deposited onto the skin, without any alteration of it, interacts directly with the immune structure able to detect its presence on the skin. It looks like all the different strata of the skin are involved in this process and thus need to be briefly reviewed [64].

Keratinocytes compose a structural barrier and are strongly involved in the provision and regulation of cutaneous immune responses: keratinocytes are capable of producing and secreting a set of diverse immunological agents and their response may be rapid [64]. The ‘inflammasome-type’ response to a stimulus increases in the underlying epidermis elevated levels of TNF-alpha, IL-1alpha, IL-1beta and GM-CSF that collectively contribute to the differentiation and activation of Langerhans cells (LC); i.e., intraepidermal dendritic cells (DC)) [64]. Keratinocytes can produce the chemokines, major recruitment signals for systemic immunocytes [65].

Healthy skin and intact epidermal permeability barrier also depends on key a contribution, secretion by keratinocytes of several serine proteases and inhibitors. The serine protease inhibitor, LEKTI, encoded by the SPINK5 gene (5q32), which hereditary mutations cause Netherton syndrome [66] is critically important in barrier function. Filaggrin is a key component of the epidermal differentiation complex of the stratum corneum of human skin at the epidermal layer level. Mutations leading to loss of function of filaggrin have been shown in patients with atopic eczema [67–69] and are associated with an increased risk of allergy [70–73]. Therapies aiming at restoration of barrier function are thus thought to play a role, not only in the effective treatment of atopic eczema, but also in the prevention of further allergic disease development [74].

LCs, compose ~2–4% of epidermal cells [64], in a contiguous network that interdigitates with keratinocytes, largely in the suprabasal layer [75]. LCs may be regarded as epidermal ‘trash collectors’, clearing the tissue of moieties ranging from toxins through microbes to apoptotic keratinocytes, for which they are equipped with numerous sensors with potent phagocytic and macrophagocytic capacity. In addition, LCs secrete cytokines and other factors, which, in combination with those produced by and/or other myeloid-lineage cells, contribute to the growth and survival of epithelial cells.

As investigated in murine models [76–77], and also in human biopsies [78], dermis contains several identifiable DC subpopulations. They also express microbial sensors and can migrate into the ‘stressed’ epidermis. They may pick up and processing antigens on route to local LNs [79–81] and also receive antigen by ‘hand-off’ from LC migrating through the dermis to the LNs. It thus seems that some or all dermal DC may bear some of the functions classically attributed to LC.

LN are secondary lymphoid organs inside which conventional DCs and plasmacytoid DCs reside throughout their life cycle and where they are denoted as lymphoid tissue–resident DCs to distinguish them.
Figure 2. Mechanism of antigen capture by dendritic cells/Langerhans cells. (A) Antigen delivery by Viaskin® from epidermis to draining lymph nodes for epicutaneous immunotherapy. Antigen is delivered with Viaskin into the epidermis. After 6 h, antigen is captured and processed by LC, which migrate to the lymph nodes. (B) Antigen delivery by subcutaneous injection. Subcutaneous injections delivered the antigen deeply into the dermis. Antigen is captured by dermal dendritic cells, mast cells and resident B cells. It can passively diffuse into the lymph nodes.

DC: Dendritic cell; LC: Langerhans cell.
from tissue-derived, migratory DCs [82]. CD103(+) DCs have the selective ability to promote de novo generation of regulatory T cells via the production of retinoic acid (RA) [83]. RA-producing DCs in the skin LNs seem primarily of the tissue-derived, migratory DC subtype. These RA-producing skin-derived DCs are capable of triggering the generation of regulatory T cells [84].

How EPIT interacts with the skin immune system

The first step in the cascade of events leading to desensitization during EPIT is the capture of the allergen, which is followed by its processing. These different stages of this cascade were studied in animal models, using a Viaskin patch loaded with OVA-labeled with a fluorescent probe. [54]. When thus entering in contact with the intact skin of mice, OVA was neither crossing passively through the skin nor systemically delivered: OVA were locally taken up and internalized by dendritic cells in the superficial layers of the stratum corneum and transported to the draining lymph nodes. This transport was even quicker in sensitized animals than in naive mice [94].

Immunohistology of the skin after epicutaneous application on intact skin clearly showed that OVA appeared mainly in epidermis and was confined to only few cells in the dermis. The delivery of the native allergen by Viaskin actually allows it to concentrate inside the stratum corneum within the vicinity of immunological cells. There, the allergen is captured by dendritic cells, and detected in draining LNs more than 18 h after the application of the Viaskin patch: this shows the existence of an active immune processing of allergen leading to presentation to the immune system.

The phenotype of cells that capture the allergen in the epidermis and dermis was clearly characterized as DCs expressing langherin receptor (CD207), known as LCs, suggesting that the passage is only mediated by these specialized immune cells. More precisely, these LCs were myeloids DCs and could be divided into at least two subpopulations CD205high, CD86high and CD83high mature DCs and a less mature population of CD205low, CD86low and CD83low. Both express comparably high levels of MHC II, which is crucial for antigen presentation, as well as moderate levels of CD80. CD205 is upregulated during activation of DC, plays a role in antigen uptake, processing and presentation and has been implicated in induction of tolerance [85].

This suggests that both cell subpopulations can present the allergen and modulate immune responses toward a different profile of response, although further studies are required to clarify their precise role.

The role of LCs in the mechanism of the skin-induced tolerance to peanut was investigated in a murine model (Langerin-DTA mice) that constitutes defects in LCs. Skin-induced tolerance after application of peanut proteins to structurally intact skin is abrogated if LCs are absent [86], underlying that LCs play an important role in the induction of tolerance by EPIT.

The role of dermis DCs and events taking place in the LNs may play a role in the induction of tolerance to allergens but is not yet evidenced for epicutaneous immunotherapy.

The generation by EPIT of a specific subset of Tregs

It looks very likely that the core of the desensitization process during EPIT relies on the generation of a specific and probably long-lasting population of Treg cells (Figure 3) [87].

In murine peanut-induced eosinophilic disorders, depleting Treg cells with an anti-CD25 antibody erased the effect of EPIT. Moreover, the protection offered by EPIT-induced Treg cells against peanut oral exposure could be adoptively transferred to sensitized but untreated animals. Tregs are able to migrate to the site of allergen exposure, to induce protection from eosinophil recruitment and Th2-induced inflammation and to induce local Tregs in response to allergen stimulation. EPIT actually proved to be beneficial on the different routes of allergen administration: bronchial hyperresponsiveness [53], eosinophils recruitment in skin [54] and on peanut-induced gut inflammation [55]. Therefore, EPIT induces Tregs, in skin or in draining lymph nodes after LC migration, that are able to recirculate and migrate to different tissues, suggesting the induction of a global desensitization.

This Treg cell population seems long lasting as in the same Treg transfer experiment, the Treg level was not modified 8 weeks after the interruption of EPIT and maintained equivalent suppressive in vivo capacity after adoptive transfer into peanut sensitized mice [87]. One clue of the sustainability of the effect was found when the transfer of EPIT-induced Tregs in Foxp3-IREs-mRFP mice induced an increase in mRFP-expressing cells, implying an induction of host Tregs. Activated EPIT-induced Tregs can facilitate Tregs expansion, likely maintaining ‘homeostatic’ Tregs level.

In this murine model of peanut-induced eosinophilic disorders, it has been evidenced that EPIT increases both spleen and mucosal Foxp3+ Tregs but not IL10+ Tregs (Tr1 population). In contrast with other routes of specific immunotherapy, the suppressive activity of EPIT-induced Tregs does not depend on IL-10...
but is partly mediated by CTLA-4, probably by cell–cell contact. CTLA-4 has been shown to act in the regulation of hypersensitivity responses to food allergens \[88\]. Moreover, EPIT may expand Foxp3+ Tregs, of both naive and effector phenotypes. Whereas the naive Tregs subset has been described to preferentially proliferate in vitro, effector Tregs display higher suppressive activity in vivo, but they are prone to die in vitro \[89\].

**Further steps**

Many questions may arise concerning this emerging technique and the current research on animal models opens new perspectives.

One question relates to the level of protection offered and more precisely, the protection against the anaphylactic shock, the ultimate risk in food allergy. Investigating this level of protection in a mouse model provides interesting clues. It thus appears that epicutaneous but not oral immunotherapy induces antigen-specific gastrointestinal Tregs and protects against food-induced anaphylaxis \[90,91\]. This effect might be due to a larger and stronger expression of Tregs gut homing receptors with epicutaneous than with sublingual or oral immunotherapy \[92\].

The induction of naive Tregs by EPIT could participate in the long-term maintenance as well as in a mechanism of prevention of new sensitizations. Indeed, it was shown that EPIT to a first allergen (milk or HDM) resulted in a protective effect against the second sensitization to irrelevant allergens \[90\]. These results appeared very consistent and reproducible whatever the role and order attributed to the different allergens according to experiments. This study also suggests a central role for Tregs in the protection against further sensitizations: adoptive transfer of CD4+CD25+ T cells from animal sensitized and treated with EPIT was as effective as EPIT itself in preventing further sensitizations. Tregs act either directly or indirectly at the site of antigen presentation.
Executive summary

- Epicutaneous immunotherapy (EPIT) is a new technique for immunotherapy, using intact skin as the route for allergen contact with the immune system.
- EPIT avoids any allergen passage into the bloodstream.
- The desensitizing effect of EPIT seems largely born by the generation of allergen specific Tregs.
- EPIT Tregs seem to be long lasting, due to epigenetic changes.
- EPIT might also induce naive Tregs, responsible for the protection against further sensitizations to other allergen.
- Clinical trials are developing and data obtained in peanut allergy indicate a good protection after 12 months of treatment.
- Clinical trials confirm a very good safety profile.
- Based on preclinical results, EPIT might probably be tested in prevention studies.

Conclusion

Following the development of allergen immunotherapy, for which the models remains SCIT, immunotherapy has been investigated using several routes, in the form of OIT and SLIT. SCIT is not applicable in food allergy, OIT seems to alter the quality of life more than the strict elimination diet, with a low level of sustained unresponsiveness at the end of the treatment and SLIT seems to be less effective. The basic novelty of EPIT is its noninvasiveness, avoiding the risk generated by injection or oral ingestion. Interestingly, skin seems to be a powerful organ for desensitization, as proven in animal models and, in humans, at least based on the data available. Further studies are needed to better understand the mechanisms involved, the potency of the technique and its applicability according to ages and the disease to be treated. The development of Viaskin, mostly with an increase dose approach, will be pursue to improve its efficacy in the older and long-term clinical studies will be required to evaluate the potential role of Viaskin in the atopic march.

Expert commentary

Food allergy has evolved from a period of mere surveillance of patients under elimination diet to a more active handling and the development of immunotherapy. Oral immunotherapy has been attempted by several teams, but was disappointing, despite some efficacy, because of the lack of sustained unresponsiveness in the end and because of an altered quality of life, owing to the risk of an acute reaction to the daily dose, triggered by external factors. EPIT is an alternative route, for which the primary rationale was the total absence of vital risk, owing to the absence of allergen ingestion. Clinical trials are developing and will settle the exact place of the technique in the treatment of food allergy.

Future perspective

EPIT is under heavy investigation, both on the preclinical and on the clinical sides of the technique. Results in animal models are promising and the maneuverability of the technique is good, with treatments being feasible at any age, even in young infants, at an age which is the focus of preventive strategies.

Financial & competing interests disclosure

C Dupont declares being the Chairman of the Scientific Advisory Board and a co-founder of DBV Technologies. The other authors work at DBV Technologies. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.
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18 •• Of interest. •• Interesting clinical monitoring that evidence the safety concerns of subcutaneous immunotherapy.
20 •• Oral immunotherapy creates a lot of debate as severe reactions occurred in the different phases of the study even if mostly in the escalation phase.
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• Skin-expressed antigens for dendritic epidermal T cells in mice contribute to Th2 cell polarization.


Epicutaneous immunotherapy for food allergy as a novel pathway for oral tolerance induction

Review


By targeting the Langerhans cells at the surface of the skin, epicutaneous immunotherapy generates long lasting immune changes through Tregs induction.


Epicutaneous immunotherapy to a first allergen, milk or house dust mite, resulted in a protective effect against a further sensitization to an irrelevant allergen.


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