Oral Mucosa in Food Allergy

Subjects: Dentistry, Oral Surgery & Medicine

Contributor: Cristina Gomez-Casado

Oral mucosa remodeling has been recently proven to be a feature of severe allergic phenotypes and autoimmune diseases. This remodeling process includes epithelial barrier disruption and the release of inflammatory signals.

oral mucosa food allergy diagnosis treatment

1. Introduction

The oral mucosa or mucosal lining consists of primarily non-keratinized stratified squamous epithelia and a highly vascularized connective tissue called the lamina propria, which underlies the epithelia [1]. The oral mucosa is an immunocompetent site, whose function is primarily tolerogenic [1][2][3]. It lines the inside of the mouth and therefore acts as a physical barrier; nevertheless, it also contains immune cells that help maintain mucosal homeostasis [1]. Therefore, an intact and fully functional oral mucosa is crucial to prevent immune reactions to innocuous environmental antigens [4].

In several allergic and autoimmune diseases, the oral mucosa has been proven to undergo a remodeling process. This remodeling is characterized by a leaky epithelial barrier, a fibrotic lamina propria, the release of inflammatory mediators, and the recruitment of immune infiltrate [5][6][7].

2. Oral Mucosa

2.1. Structure of the Oral Mucosa

Despite the continuous exposition of the oral mucosa to external stimuli, pathological events are not so frequently seen. This is due to the anatomical and physiological features of the oral mucosa and possibly to the limited exposition time to external stimuli. The oral mucosa comprises three layers: the epithelium, the basement membrane, and the lamina propria, and contains active networks of extracellular matrix, different cell types, and neuro-vascular systems [8].

Interestingly, oral mucosa structure varies along its location within the oral cavity, but three main types of mucosa can be recognized based on their morphology and specific pattern of differentiation: keratinized stratified squamous epithelium- masticatory mucosa, which covers the hard palate and gingiva; non-keratinized stratified squamous epithelium- lining mucosa, on the underside of the tongue, the inside of the lips, cheeks, the floor of the mouth, and the alveolar ridge; and the specialized mucosa of the dorsal surface of the tongue [8][9][10].

The oral epithelium is the superficial layer that separates the environment from underlying tissues. It is a stratified squamous epithelium consisting of cells tightly attached to each other and arranged in layers. It possesses structural properties such as stratification and cornification of the keratinocytes and specific cell-to-cell interactions to maintain its barrier function [8][9][10]. The keratinized type contains four layers of cells: the basal layer, spinous layer, granular layer, and the superficial layer (keratinized layer). Keratinocytes are born and proliferate in the basal layer and undergo terminal differentiation as they migrate to the surface where they die. Thus, the outermost cell layer is dead cells. Conversely, the surface cells of non-keratinized epithelia are living cells without keratin. Moreover, the non-keratinized oral epithelium has no granular layer [8][9][10].

The integrity of the epithelial barrier is a key factor to avoid uncontrolled antigen penetration. Oral epithelium integrity is maintained through highly specific junctional complexes between epithelial cells. Three types of epithelial cell junctions have been described: tight junctions (TJs), gap junctions (GJs), and anchoring junctions [10][11][12][13]. Tight junctions form the closest cell–cell interactions in the apical area of oral epithelial cells, working as a restrictive gate for the passage of water, electrolytes, and other small molecules. They consist of a number of transmembrane proteins, including occludin, claudin, and immunoglobulin-like surface, as well as cytoplasmic molecules such as zonula occludens (ZO) [10][11]. Gap junctions are composed of hemichannels called connexons which are regulated by several factors, including pH, calcium concentration and posttranslational modifications. Thus, they provide direct communication between adjacent cells and the exchange of small molecules and ions. Anchoring junctions are classified as adherens junctions (AJs), desmosomes, and hemi-desmosomes [12]. Adherens juntions are protein complexes situated below TJs that strongly hold cells. Whereas, AJs are composed by cadherins, such as E-cadherin, that connect to the actin cytoskeleton by catenins; desmosomes link two cells together by the intermediate filament cytoskeleton, becoming the adhesive bonds that give mechanical strength to tissues. Moreover, desmosomes act as surface receptors that mediate cellular differentiation and proliferation. Adhesion between the epithelium and connective tissue is provided by hemidesmosomes (half of a desmosome), which link the intermediate filament network of epithelial cells to the underlying basement membrane [11][12]. Since the structure and functions of all of the abovementioned cell–cell junctions are key to preserve epithelial barrier integrity, their disruption has been linked to infections, autoimmune diseases, allergies, and cancer disorders [11][14][15][16][17][18][19]. Epithelial cells in the mucosa, which were initially thought to be just inert barriers, are now known to play a key role in the immune-protective system of the mucosa [2][20][21][22]. Epithelial cells can react to external stimuli by synthesizing cytokines, adhesion molecules, growth factors, chemokines, and matrix metalloproteases [10]. Likewise, inflammatory factors, such as IFNγ and TNFα, have been reported to disrupt epithelial integrity through downregulation of TJ proteins, increasing epithelial permeability [23][24][25][26][27][28]. Generation of epithelium-derived cytokines, such as thymic stromal lymphopoietin (TSLP), IL-25, and IL-33, leads to Th2 immunity [29].

The basement membrane or basal lamina is a thin layer composed of collagen and laminin situated between the epithelium and lamina propria. It appears as a structureless band and includes glycogen, muco-substances, glycolipids, and phospholipids [8].

The lamina propria is the underlying connective tissue and consist of networks of fibers arranged in groups and a ground substance composed of water, glycoproteins, and proteoglycans, and serum-derived proteins. Moreover, it contains a variety of cells, blood vessels, and neural elements [8][30]. Fibroblasts are the principal cell of the lamina propria, whose main function is maintaining tissue integrity by secreting fibers and ground substance [8][30].

2.2. Oral Mucosa-Associated Immune System

The oral mucosa is an immunocompetent site [3][31] that displays lymphoid tissue foci where antigen-presenting cells (APCs) and lymphocytes co-localized in the lamina propria [1][3][31]. In homeostatic conditions, the lamina propria harbors small numbers of lymphocytes and dendritic cells (DC), which can become the dominant cell type in chronic conditions. Whereas, in response to infection (acute condition), the recruitment of polymorphonuclear leukocytes (mainly neutrophils), monocytes, and macrophages represents an important component of the innate immune response [1]. Macrophages of the lamina propria are scavengers of damaged tissue and foreign material. Additionally, they can present the processed ingested material to T cells and produce cytokines and chemokines that stimulate fibroblast proliferation and collagen production necessary for repair [1][8]. Primarily located adjacent to the basement membrane of endothelial cells, mast cells containing granules with histamine, heparin, and cytokines are found. Their migration is influenced by the synthesis of mast cell growth factor by endothelial cells and keratinocytes [1][8].

In response to any insult, the abundant vasculature ensures the recruitment of inflammatory cells. In turn, the oral epithelium responds to irritation by an increase in cell proliferation and hyper-keratinization. Moreover, the oral epithelium reacts to microorganisms by secreting antimicrobial peptides, antimicrobial proteins (lytic enzymes), chemokines, cytokines, and neuropeptides. These molecules are also produced by polymorphonuclear cells, myeloid cells, keratinocytes, and fibroblasts. Similarly, capillaries of the lamina propria express adhesion molecules which facilitate the trafficking of leukocytes from the blood [1][8][10].

The tolerogenic properties of the oral mucosa seem to rely on their specific types of APC, which are differently distributed along mucosal sites [1][3][32]. In mice, four subtypes of oral CD11c+ DCs have been identified depending on the expression of CD103, Ep-CAM (epithelial cell adhesion molecule), and langerin+ (Ln+) surface markers: interstitial DCs (iDCs), Langerhans cells (Ln+Ep−CAM+), Ln+ iDCs (CD11c+Ep−CAM+), CD103+ iDCs (CD11c+) [32]. The CD103+ DCs may also express CD207 and are the main migratory subtype able to cross-present viral and self-antigens, critical for the initiation of CD8+ T cell responses [33]. Plasmacytoid DCs (B220+120G8+) have been also found on the sublingual mucosa area [34]. Notably, CD11c−CD11b+ APCs (presumably macrophages) can be detected in low numbers in the buccal mucosa but predominate in the mucosa of the sublingual area [34].

In human oral mucosa, Langerhans cells (Ln+CD1a+) represent the predominating APC population, but myeloid DCs have also been detected [35]. They constitutively express FcεRI and display upregulated levels of co-inhibitory molecules (B7-H1 and B7-H3), but a decrease in the co-stimulatory molecule expression CD86. Moreover, oral Langerhans cells express MHC class II and the CD83 maturation marker. All these features contribute to oral Langerhans cells' induction of T regulatory (Treg) cells and the secretion of IL-10 and TGFβ, which explain their role as tolerogenic cells [35]. Oral and epidermal Langerhans cells, which are constantly exposed to microbial

stimuli, express similar levels of the CD83 maturation marker, suggesting a state of maturation associated with tolerance induction [35]. Analysis of the gingiva identified Ln+DCs in the mucosal epithelium and CD209+ DCs in the lamina propria, which are considered the equivalent of dermal DCs. Contrary to the findings in mice, plasmacytoid DCs characterized by CD123+ are rarely detected in healthy human oral mucosa, although their number increases upon inflammation [36][37].

Within the gingiva, T cells, B cells, and innate lymphoid cells (ILCs) can be detected in healthy conditions [38]. ILCs present in the oral mucosa may help maintain barrier function and protect against pathogenic infections [39]. However, the homeostatic role of B cells and ILCs in oral immune responses to commensals and dietary antigens is still unclear. On the contrary, many studies have described the presence and role of different T cell populations. At murine and human gingiva mucosa, resident memory T cells (mainly CD4+), IL-17 secreting cells (both Th17 and T cell receptor (TCR) γδ T cells), and resident Foxp3+ regulatory T cells (Tregs) have been detected [38][40][41]. Oral T memory cells provide defense against pathogens, while Tregs participate in oral tolerance [1]. Regarding the origin of gingival Tregs, some studies indicate CCR4/CCL22-controlled Treg trafficking [42][43], and a recent investigation revealed that oral murine CD103−CD11b+ DCs possessed the necessary properties to induce Foxp3+ Treg cells [44]. They could show that oral murine CD103−CD11b+ DCs transport sublingual antigens to submandibular lymph nodes and induce antigen-specific Treg cells.

3. Oral Mucosa in Food Allergy

The interaction between epithelial and immune cells at the mucosal linings has been proven to be critical in the onset and maintenance of allergic inflammation [5]. Therefore, an intact and fully functional mucosal barrier is considered crucial in the maintenance of mucosal homeostasis, as it protects the host immune system from the exposure to allergenic molecules and noxious environmental triggers [21]. The oral mucosa is the first immune tissue that encounters allergens upon ingestion of food. Oral exposure to allergens is complex in terms of immunological effects. In the relatively short time that food proteins are in the mouth, they should be bio-accessible. Therefore, the bio-accessibility of allergens at this stage may be a determinant for sensitization [45]. The continuous exposure of the oral mucosa to environmental triggers (antigens, allergens, or contaminants) induces a remodeling process in the oral epithelial barrier. This remodeling is maintained over time. An impaired oral mucosal barrier can therefore facilitate allergen access. Additionally, the damaged epithelium secretes the alarmins IL-25, IL-33, and TSLP. This triggers a local inflammatory immune response characterized by increased expression of pro-inflammatory cytokines and higher numbers of immune cells being recruited to the oral mucosa [5]. The chronic exposure to the allergen and its access to the mucosa-associated immune system together with the sustained local inflammation is reflected systemically, e.g., by increased IL-33 plasma levels [5][46]. This results in a positive feedback loop promoting further remodeling and inflammatory events in an otherwise pro-tolerogenic environment.

Food allergy is defined as “an adverse health effect resulting from a specific immune response that occurs reproducibly on exposure to a particular food” [47] that is causing a growing clinical problem. IgE-mediated reactions usually occur within two hours (they can even occur after few minutes) of ingestion of food and affect the

skin, gastrointestinal tract, respiratory tract, and, less frequently, the cardiovascular system. In the most severe cases of anaphylaxis, multiple organ systems are involved and may include cardiovascular collapse.

It is currently not understood why some people develop allergic sensitization to foods while most people are immunologically tolerant, but the evidence suggests that environmental factors are important. The increased exposure to biological and chemical air pollutants such as protease enzymes, tobacco, or particulate matter (the so called exposome) has been proven responsible for disrupting the integrity of the epithelial barrier by degrading the intercellular junctions and triggering epithelial alarmin release [48]. The epithelial disruption leads to Th2 immune responses responsible for allergy development [49][50][51]. The “barrier regulation” hypothesis [52] postulates that allergic sensitization begins with the damage of the epithelial barrier [48][53]. Individuals with food allergies have their barrier permeability increased [54][55][56]. Thus, barrier impairment may itself lead to a predisposition toward atopy [57].

Moreover, the route of exposure is another crucial factor in food allergy. Food allergens brought in contact by non-oral routes contribute to allergic sensitization. In fact, epidemiological studies in humans indicate that non-oral contact with food allergens is correlated with the risk of a child developing food allergy [58][59][60]. In addition, symptomatic food allergy is often observed when a child eats the allergenic food for the first time, which is consistent with a previous sensitization phenomenon by non-oral routes [31]. Although there is growing evidence to support a disrupted and inflamed skin barrier as being responsible for the development of food sensitization [61], results from a large randomized controlled trial for the prevention of food allergy were negative [62]. The BEEP (Barrier Enhancement for Eczema Prevention) evaluated whether applying petrolatum-based oils or moisturizers from the first few weeks of life could prevent atopic dermatitis and food allergy and, on the contrary, found an increased rate of infections and a trend toward increased food allergy in the intervention group [62][63], in accordance with the PreventADALL trial on atopic dermatitis [63]. The role of epicutaneous sensitization in the development of food allergy has been extensively reviewed recently [57]. Regarding molecular mechanisms, allergic sensitization is thought to require the activity of T cells that express Th2 cytokines, such as IL-4 and IL-13. However, the exact nature of the T cell support required for the allergen-specific B cells to turn into the IgE-producing plasma cells in humans has not been described yet. Similarly, it is not clear to what extent the change to IgE class occurs in various tissues of the body. In addition, other cell types, such as tissue-resident mast cells, secrete IL-4, IL-13, and other cytokines that can influence the differentiation of B cells [64]. High titers of allergen specific IgE antibodies of high affinity are often detected in patients with symptomatic allergy. These antibodies bind to FcεRI in tissue-resident mast cells and circulating basophils, where they are involved in early or immediate hypersensitivity responses when interacting with allergens. It has also been reported that allergen-specific IgE may contribute to the pathogenesis of allergies by facilitating antigen presentation and epitope spread by means of the uptake of antigen–IgE complexes by the low-affinity IgE receptor, CD23, present on DCs, B lymphocytes, and other APCs [65][66][67][68]. IgE can also help transport the antigen from the lumen via CD23 receptors on the surface of epithelial cells, as it has been shown in the human gut, in cultures of human respiratory epithelial cells [69], and in a mouse model of allergy [70].

In the case of profilin sensitization, the oral mucosa has been proven to be altered and is associated with disease progression [71][72][73][74][75][76]. Profilin is a pollen aeroallergen that normally plays a limited role as a food allergen because it is easily degraded by proteases and acidic conditions. However, it can sensitize some pollen allergic individuals in areas of high allergen exposure. In the study by Rosace et al. [5], grass pollen allergic patients from overexposed areas in Spain were subjected to an oral challenge with profilin. The observed reactions ranged from local reactions such as oral allergy syndrome (OAS), angioedema, and oral pruritus, to severe systemic reactions such as urticaria and asthma. The patients that were allergic to profilin presented a progressive oral mucosal remodeling, characterized by decreased expression of TJ (claudin-1 and occluding) and AJ (E-cadherin) proteins, which led to a leaky epithelial barrier, increased angiogenesis and acanthosis, and augmented collagen deposition in the lamina propria. These processes have been previously associated with mucosal remodeling [77][78][79] and are comparable with those described from patients with other inflammatory pathologies [80][81]. In addition, an increased IL-33 expression was also observed in the severe allergic patients, i.e., those orally sensitized to profilin with a clinical history of severe allergic reactions. The epithelial damage might be associated with the IL-33–dependent ILC2 population located in the mucosal epithelium [82][83][84]. As profilin is present in all vegetables, it would contribute to sustaining the inflammatory allergic response, thereby causing allergic reactions to food [85]. This suggests that oral epithelial remodeling could be a key process for the acquisition of a severe allergic phenotype in patients with profilin-mediated food allergy.

In addition, the bio-accessibility of allergens at the oral cavity may be key to induce oral remodeling and allergic reactions. Allergen bio-accessibility may be modulated by the composition, volume, and pH of saliva [45]. Koppelman et al. [45] investigated the release of peanut allergens from lightly roasted peanut flour in the saliva in different conditions. The allergens Ara h2 and Ara h6, which are the most potent peanut allergens [86][87][88], were rapidly released from the food matrix, while Ara h1 and Ara h3 were poorly released. Therefore, Ara h2 and Ara h6 may be the first peanut allergens that individuals are exposed to upon ingesting lightly roasted peanut flour and may trigger immune responses in the oral mucosa. It remains to be determined whether this is also the case for other peanut-containing foods. Their early release provides them with the unique opportunity to interact with the oral mucosal immune system, which, in the case of accidental ingestion of hidden peanut allergens, can provoke life-threatening anaphylactic reactions in peanut-allergic patients [89][90][91].

References

1. Moutsopoulos, N.M.; Konkel, J.E. Tissue-Specific Immunity at the Oral Mucosal Barrier. Trends Immunol. 2018, 39, 276–287.
2. Leoni, G.; Neumann, P.-A.; Sumagin, R.; Denning, T.L.; Nusrat, A. Wound repair: Role of immune–epithelial interactions. Mucosal Immunol. 2015, 8, 959–968.
3. Novak, N.; Haberstok, J.; Bieber, T.; Allam, J.-P. The immune privilege of the oral mucosa. Trends Mol. Med. 2008, 14, 191–198.

4. Moutsopoulos, N.M.; Moutsopoulos, H.M. The oral mucosa: A barrier site participating in tissue-specific and systemic immunity. Oral Dis. 2018, 24, 22–25.
5. Rosace, D.; Gomez-Casado, C.; Fernandez, P.; Perez-Gordo, M.; del Carmen Dominguez, M.; Vega, A.; Belver, M.T.; Ramos, T.; Vega, F.; Marco, G.; et al. Profilin-mediated food-induced allergic reactions are associated with oral epithelial remodeling. J. Allergy Clin. Immunol. 2019, 143, 681–690.e1.
6. Sanchez-Solares, J.; Delgado-Dolset, M.I.; Mera-Berriatua, L.; Hormias-Martin, G.; Cumplido, J.A.; Saiz, V.; Carrillo, T.; Moreno-Aguilar, C.; Escribese, M.M.; Gomez-Casado, C.; et al. Respiratory allergies with no associated food allergy disrupt oral mucosa integrity. Allergy 2019, 74, 2261–2265.
7. Sanchez-Solares, J.; Sanchez, L.; Pablo-Torres, C.; Diaz-Fernandez, C.; Sørensen, P.; Barber, D.; Gomez-Casado, C. Celiac Disease Causes Epithelial Disruption and Regulatory T Cell Recruitment in the Oral Mucosa. Front. Immunol. 2021, 12.
8. Squier, C.; Brogden, K.A. Human Oral Mucosa: Development, Structure and Function; John Wiley & Sons, Ltd.: West Sussex, UK, 2013; ISBN 9781118710470.
9. Shetty, S.; Gokul, S. Keratinization and its Disorders. Oman Med. J. 2012, 27, 348–357.
10. Groeger, S.; Meyle, J. Oral Mucosal Epithelial Cells. Front. Immunol. 2019, 10, 208.
11. Samiei, M.; Ahmadian, E.; Eftekhari, A.; Eghbal, M.A.; Rezaie, F.; Vinken, M. Cell junctions and oral health. EXCLI J. 2019, 18, 317–330.
12. Wan, H.; Gadmor, H.; Brown, L. Anchoring junctions in the oral mucosa: Adherens junctions and desmosomes. In Oral Mucosa in Health and Disease; Springer: Cham, Switzerland, 2018; pp. 31–51.
13. Liu, W.; Cui, Y.; Wei, J.; Sun, J.; Zheng, L.; Xie, J. Gap junction-mediated cell-to-cell communication in oral development and oral diseases: A concise review of research progress. Int. J. Oral Sci. 2020, 12, 17.
14. Ewert, P.; Aguilera, S.; Alliende, C.; Kwon, Y.-J.; Albornoz, A.; Molina, C.; Urzúa, U.; Quest, A.F.G.; Olea, N.; Pérez, P.; et al. Disruption of tight junction structure in salivary glands from Sjögren's syndrome patients is linked to proinflammatory cytokine exposure. Arthritis Rheum. 2010, 62, 1280–1289.
15. Martin, T.A.; Mansel, R.E.; Jiang, W.G. Loss of occludin leads to the progression of human breast cancer. Int. J. Mol. Med. 2010, 26, 723–734.
16. Dos Reis, P.P.; Bharadwaj, R.R.; Machado, J.; Macmillan, C.; Pintilie, M.; Sukhai, M.A.; Perez-Ordonez, B.; Gullane, P.; Irish, J.; Kamel-Reid, S. Claudin 1 overexpression increases invasion

and is associated with aggressive histological features in oral squamous cell carcinoma. Cancer 2008, 113, 3169–3180.

17. Villaret, D.B.; Wang, T.; Dillon, D.; Xu, J.; Sivam, D.; Cheever, M.A.; Reed, S.G. Identification of genes overexpressed in head and neck squamous cell carcinoma using a combination of complementary DNA subtraction and microarray analysis. Laryngoscope 2000, 110, 374–381.
18. Groeger, S.E.; Meyle, J. Epithelial barrier and oral bacterial infection. Periodontology 2000 2015, 69, 46–67.
19. Henriquez, O.A.; Den Beste, K.; Hoddeson, E.K.; Parkos, C.A.; Nusrat, A.; Wise, S.K. House dust mite allergen Der p 1 effects on sinonasal epithelial tight junctions. Int. Forum Allergy Rhinol. 2013, 3, 630–635.
20. Golebski, K.; Röschmann, K.I.L.; Toppila-Salmi, S.; Hammad, H.; Lambrecht, B.N.; Renkonen, R.; Fokkens, W.J.; van Drunen, C.M. The multi-faceted role of allergen exposure to the local airway mucosa. Allergy 2013, 68, 152–160.
21. Steelant, B.; Farré, R.; Wawrzyniak, P.; Belmans, J.; Dekimpe, E.; Vanheel, H.; Van Gerven, L.; Kortekaas Krohn, I.; Bullens, D.M.A.; Ceuppens, J.L.; et al. Impaired barrier function in patients with house dust mite-induced allergic rhinitis is accompained by decreased occludin and zonula occludens-1 expression. J. Allergy Clin. Immunol. 2016, 137, 1043–1053.e5.
22. Lambrecht, B.N.; Hammad, H. Allergens and the airway epithelium response: Gateway to allergic sensitization. J. Allergy Clin. Immunol. 2014, 134, 499–507.
23. Edelblum, K.L.; Turner, J.R. The tight junction in inflammatory disease: Communication breakdown. Curr. Opin. Pharmacol. 2009, 9, 715–720.
24. Capaldo, C.T.; Nusrat, A. Cytokine regulation of tight junctions. Biochim. Biophys. Acta Biomembr. 2009, 1788, 864–871.
25. Van Deventer, S.J.H. Anti-TNF antibody treatment of Crohn’s disease. Ann. Rheum. Dis. 1999, 58 (Suppl. 1), i114–i120.
26. Abe, A.; Takano, K.; Kojima, T.; Nomura, K.; Kakuki, T.; Kaneko, Y.; Yamamoto, M.; Takahashi, H.; Himi, T. Interferon-gamma increased epithelial barrier function via upregulating claudin-7 expression in human submandibular gland duct epithelium. J. Mol. Histol. 2016, 47, 353–363.
27. Mei, M.; Xiang, R.-L.; Cong, X.; Zhang, Y.; Li, J.; Yi, X.; Park, K.; Han, J.-Y.; Wu, L.-L.; Yu, G.-Y. Claudin-3 is required for modulation of paracellular permeability by TNF-α through ERK1/2/slug signaling axis in submandibular gland. Cell. Signal. 2015, 27, 1915–1927.
28. Baker, O.J.; Camden, J.M.; Redman, R.S.; Jones, J.E.; Seye, C.I.; Erb, L.; Weisman, G.A. Proinflammatory cytokines tumor necrosis factor-alpha and interferon-gamma alter tight junction

structure and function in the rat parotid gland Par-C10 cell line. Am. J. Physiol. Cell Physiol. 2008, 295, C1191–C1201.

29. Roan, F.; Obata-Ninomiya, K.; Ziegler, S.F. Epithelial cell–derived cytokines: More than just signaling the alarm. J. Clin. Investig. 2019, 129, 1441–1451.
30. Moharamzadeh, K.; Brook, I.M.; Van Noort, R.; Scutt, A.M.; Thornhill, M.H. Tissue-engineered Oral Mucosa: A Review of the Scientific Literature. J. Dent. Res. 2007, 86, 115–124.
31. Berin, M.C.; Sampson, H.A. Mucosal Immunology of Food Allergy. Curr. Biol. 2013, 23, R389–R400.
32. Hovav, A.-H. Dendritic cells of the oral mucosa. Mucosal Immunol. 2014, 7, 27–37.
33. Henri, S.; Poulin, L.F.; Tamoutounour, S.; Ardouin, L.; Guilliams, M.; de Bovis, B.; Devilard, E.; Viret, C.; Azukizawa, H.; Kissenpfennig, A.; et al. CD207+ CD103+ dermal dendritic cells cross-present keratinocyte-derived antigens irrespective of the presence of Langerhans cells. J. Exp. Med. 2010, 207, 189–206.
34. Mascarell, L.; Lombardi, V.; Louise, A.; Saint-Lu, N.; Chabre, H.; Moussu, H.; Betbeder, D.; Balazuc, A.-M.; Van Overtvelt, L.; Moingeon, P. Oral dendritic cells mediate antigen-specific tolerance by stimulating TH1 and regulatory CD4+ T cells. J. Allergy Clin. Immunol. 2008, 122, 603–609.e5.
35. Allam, J.-P.; Stojanovski, G.; Friedrichs, N.; Peng, W.; Bieber, T.; Wenzel, J.; Novak, N. Distribution of Langerhans cells and mast cells within the human oral mucosa: New application sites of allergens in sublingual immunotherapy? Allergy 2008, 63, 720–727.
36. Santoro, A.; Majorana, A.; Roversi, L.; Gentili, F.; Marrelli, S.; Vermi, W.; Bardellini, E.; Sapelli, P.; Facchetti, F. Recruitment of dendritic cells in oral lichen planus. J. Pathol. 2005, 205, 426–434.
37. Jotwani, R.; Cutler, C.W. Multiple Dendritic Cell (DC) Subpopulations in Human Gingiva and Association of Mature DCs with CD4+ T-cells in situ. J. Dent. Res. 2003, 82, 736–741.
38. Dutzan, N.; Konkel, J.E.; Greenwell-Wild, T.; Moutsopoulos, N.M. Characterization of the human immune cell network at the gingival barrier. Mucosal Immunol. 2016, 9, 1163–1172.
39. Panda, S.K.; Colonna, M. Innate Lymphoid Cells in Mucosal Immunity. Front. Immunol. 2019, 10, 861.
40. Dutzan, N.; Abusleme, L.; Bridgeman, H.; Greenwell-Wild, T.; Zangerle-Murray, T.; Fife, M.E.; Bouladoux, N.; Linley, H.; Brenchley, L.; Wemyss, K.; et al. On-going Mechanical Damage from Mastication Drives Homeostatic Th17 Cell Responses at the Oral Barrier. Immunity 2017, 46, 133–147.
41. Park, J.Y.; Chung, H.; Choi, Y.; Park, J.H. Phenotype and Tissue Residency of Lymphocytes in the Murine Oral Mucosa. Front. Immunol. 2017, 8, 250.

42. Glowacki, A.J.; Yoshizawa, S.; Jhunjhunwala, S.; Vieira, A.E.; Garlet, G.P.; Sfeir, C.; Little, S.R. Prevention of inflammation-mediated bone loss in murine and canine periodontal disease via recruitment of regulatory lymphocytes. Proc. Natl. Acad. Sci. USA 2013, 110, 18525–18530.
43. Araujo-Pires, A.C.; Vieira, A.E.; Francisconi, C.F.; Biguetti, C.C.; Glowacki, A.; Yoshizawa, S.; Campanelli, A.P.; Trombone, A.P.F.; Sfeir, C.S.; Little, S.R.; et al. IL-4/CCL22/CCR4 Axis Controls Regulatory T-Cell Migration That Suppresses Inflammatory Bone Loss in Murine Experimental Periodontitis. J. Bone Miner. Res. 2015, 30, 412–422.
44. Tanaka, Y.; Nagashima, H.; Bando, K.; Lu, L.; Ozaki, A.; Morita, Y.; Fukumoto, S.; Ishii, N.; Sugawara, S. Oral CD103−CD11b+ classical dendritic cells present sublingual antigen and induce Foxp3+ regulatory T cells in draining lymph nodes. Mucosal Immunol. 2017, 10, 79–90.
45. Koppelman, S.; Smits, M.; Tomassen, M.; de Jong, G.; Baumert, J.; Taylor, S.; Witkamp, R.; Veldman, R.; Pieters, R.; Wichers, H. Release of Major Peanut Allergens from Their Matrix under Various pH and Simulated Saliva Conditions—Ara h2 and Ara h6 Are Readily Bio-Accessible. Nutrients 2018, 10, 1281.
46. Sugita, K.; Steer, C.A.; Martinez-Gonzalez, I.; Altunbulakli, C.; Morita, H.; Castro-Giner, F.; Kubo, T.; Wawrzyniak, P.; Rückert, B.; Sudo, K.; et al. Type 2 innate lymphoid cells disrupt bronchial epithelial barrier integrity by targeting tight junctions through IL-13 in asthmatic patients. J. Allergy Clin. Immunol. 2018, 141, 300–310.e11.
47. Boyce, J.A.; Assa'ad, A.; Burks, A.W.; Jones, S.M.; Sampson, H.A.; Wood, R.A.; Plaut, M.; Cooper, S.F.; Fenton, M.J.; Arshad, S.H.; et al. Guidelines for the diagnosis and management of food allergy in the United States: Report of the NIAID-sponsored expert panel. J. Allergy Clin. Immunol. 2010, 126, S1–S58.
48. Celebi Sözener, Z.; Cevhertas, L.; Nadeau, K.; Akdis, M.; Akdis, C.A. Environmental factors in epithelial barrier dysfunction. J. Allergy Clin. Immunol. 2020, 145, 1517–1528.
49. Moran, T.P. The External Exposome and Food Allergy. Curr. Allergy Asthma Rep. 2020, 20, 37.
50. Agache, I.; Miller, R.; Gern, J.E.; Hellings, P.W.; Jutel, M.; Muraro, A.; Phipatanakul, W.; Quirce, S.; Peden, D. Emerging concepts and challenges in implementing the exposome paradigm in allergic diseases and asthma: A Practall document. Allergy 2019, 74, 449–463.
51. Gómez-Casado, C.; Díaz-Perales, A. Allergen-Associated Immunomodulators: Modifying Allergy Outcome. Arch. Immunol. Ther. Exp. 2016, 64, 339–347.
52. Wesemann, D.R.; Nagler, C.R. The Microbiome, Timing, and Barrier Function in the Context of Allergic Disease. Immunity 2016, 44, 728–738.
53. Akdis, C.A. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions? Nat. Rev. Immunol. 2021.

54. Järvinen, K.M.; Konstantinou, G.N.; Pilapil, M.; Arrieta, M.-C.; Noone, S.; Sampson, H.A.; Meddings, J.; Nowak-Węgrzyn, A. Intestinal permeability in children with food allergy on specific elimination diets. Pediatr. Allergy Immunol. 2013, 24, 589–595.
55. Dupont, C.; Barau, E.; Molkhou, P.; Raynaud, F.; Barbet, J.P.; Dehennin, L. Food-Induced Alterations of Intestinal Permeability in Children with Cow's Milk-Sensitive Enteropathy and Atopic Dermatitis. J. Pediatr. Gastroenterol. Nutr. 1989, 8, 459–465.
56. Andre, C.; Andre, F.; Colin, L.; Cavagna, S. Measurement of intestinal permeability to mannitol and lactulose as a means of diagnosing food allergy and evaluating therapeutic effectiveness of disodium cromoglycate. Ann. Allergy 1987, 59, 127–130.
57. Brough, H.A.; Nadeau, K.C.; Sindher, S.B.; Alkotob, S.S.; Chan, S.; Bahnson, H.T.; Leung, D.Y.M.; Lack, G. Epicutaneous sensitization in the development of food allergy: What is the evidence and how can this be prevented? Allergy 2020, 75, 2185–2205.
58. Fox, A.T.; Sasieni, P.; du Toit, G.; Syed, H.; Lack, G. Household peanut consumption as a risk factor for the development of peanut allergy. J. Allergy Clin. Immunol. 2009, 123, 417–423.
59. Brough, H.A.; Santos, A.F.; Makinson, K.; Penagos, M.; Stephens, A.C.; Douiri, A.; Fox, A.T.; Du Toit, G.; Turcanu, V.; Lack, G. Peanut protein in household dust is related to household peanut consumption and is biologically active. J. Allergy Clin. Immunol. 2013, 132, 630–638.
60. Hernández-Ramírez, G.; Pazos-Castro, D.; Gómez Torrijos, E.; Yuste Montalvo, A.; Romero-Sahagun, A.; González-Klein, Z.; Jimeno-Nogales, L.; Escribese, M.M.; Extremera Ortega, A.; Nuñez-Borque, E.; et al. Group 1 allergens, transported by mold spores, induce asthma exacerbation in a mouse model. Allergy 2020, 75, 2388–2391.
61. Tsakok, T.; Woolf, R.; Smith, C.H.; Weidinger, S.; Flohr, C. Atopic dermatitis: The skin barrier and beyond. Br. J. Dermatol. 2019, 180, 464–474.
62. Chalmers, J.R.; Haines, R.H.; Bradshaw, L.E.; Montgomery, A.A.; Thomas, K.S.; Brown, S.J.; Ridd, M.J.; Lawton, S.; Simpson, E.L.; Cork, M.J.; et al. Daily emollient during infancy for prevention of eczema: The BEEP randomised controlled trial. Lancet 2020, 395, 962–972.
63. Skjerven, H.O.; Rehbinder, E.M.; Vettukattil, R.; LeBlanc, M.; Granum, B.; Haugen, G.; Hedlin, G.; Landrø, L.; Marsland, B.J.; Rudi, K.; et al. Skin emollient and early complementary feeding to prevent infant atopic dermatitis (PreventADALL): A factorial, multicentre, cluster-randomised trial. Lancet 2020, 395, 951–961.
64. Mukai, K.; Tsai, M.; Saito, H.; Galli, S.J. Mast cells as sources of cytokines, chemokines, and growth factors. Immunol. Rev. 2018, 282, 121–150.
65. Burton, O.T.; Oettgen, H.C. Beyond immediate hypersensitivity: Evolving roles for IgE antibodies in immune homeostasis and allergic diseases. Immunol. Rev. 2011, 242, 128–143.

66. Gould, H.J.; Sutton, B.J. IgE in allergy and asthma today. Nat. Rev. Immunol. 2008, 8, 205–217.

67. Selb, R.; Eckl-Dorna, J.; Neunkirchner, A.; Schmetterer, K.; Marth, K.; Gamper, J.; Jahn-Schmid, B.; Pickl, W.F.; Valenta, R.; Niederberger, V. CD23 surface density on B cells is associated with IgE levels and determines IgE-facilitated allergen uptake, as well as activation of allergen-specific T cells. J. Allergy Clin. Immunol. 2017, 139, 290–299.e4.

68. Oettgen, H.C.; Burton, O.T. IgE receptor signaling in food allergy pathogenesis. Curr. Opin. Immunol. 2015, 36, 109–114.

69. Palaniyandi, S.; Tomei, E.; Li, Z.; Conrad, D.H.; Zhu, X. CD23-Dependent Transcytosis of IgE and Immune Complex across the Polarized Human Respiratory Epithelial Cells. J. Immunol. 2011, 186, 3484–3496.

70. Yu, L.C.H.; Yang, P.-C.; Berin, M.C.; Di Leo, V.; Conrad, D.H.; Mckay, D.M.; Satoskar, A.R.; Perdue, M.H. Enhanced transepithelial antigen transport in intestine of allergic mice is mediated by IgE/CD23 and regulated by interleukin-4. Gastroenterology 2001, 121, 370–381.

71. Barber, D.; Díaz-Perales, A.; Villalba, M.; Chivato, T. Challenges for Allergy Diagnosis in Regions with Complex Pollen Exposures. Curr. Allergy Asthma Rep. 2015, 15, 496.

72. Barber, D.; de la Torre, F.; Lombardero, M.; Antépara, I.; Colas, C.; Dávila, I.; Tabar, A.I.; Vidal, C.; Villalba, M.; Salcedo, G.; et al. Component-resolved diagnosis of pollen allergy based on skin testing with profilin, polcalcin and lipid transfer protein pan-allergens. Clin. Exp. Allergy 2009, 39, 1764–1773.

73. Ruiz-García, M.; García del Potro, M.; Fernández-Nieto, M.; Barber, D.; Jimeno-Nogales, L.; Sastre, J. Profilin: A relevant aeroallergen? J. Allergy Clin. Immunol. 2011, 128, 416–418.

74. Asero, R.; Tripodi, S.; Dondi, A.; Di Rienzo Businco, A.; Sfika, I.; Bianchi, A.; Candelotti, P.; Caffarelli, C.; Povesi Dascola, C.; Ricci, G.; et al. Prevalence and Clinical Relevance of IgE Sensitization to Profilin in Childhood: A Multicenter Study. Int. Arch. Allergy Immunol. 2015, 168, 25–31.

75. Mastrorilli, C.; Tripodi, S.; Caffarelli, C.; Perna, S.; Di Rienzo-Businco, A.; Sfika, I.; Asero, R.; Dondi, A.; Bianchi, A.; Povesi Dascola, C.; et al. Endotypes of pollen-food syndrome in children with seasonal allergic rhinoconjunctivitis: A molecular classification. Allergy 2016, 71, 1181–1191.

76. Santos, A.; Van Ree, R. Profilins: Mimickers of Allergy or Relevant Allergens. Int. Arch. Allergy Immunol. 2011, 155, 191–204.

77. Tsuchiya, T.; Nishimura, Y.; Nishiuma, T.; Kotani, Y.; Funada, Y.; Yoshimura, S.; Yokoyama, M. Airway remodeling of murine chronic antigen exposure model. J. Asthma 2003, 40, 935–944.

78. Van Bruaene, N.; Derycke, L.; Perez-Novo, C.A.; Gevaert, P.; Holtappels, G.; De Ruyck, N.; Cuvelier, C.; Van Cauwenberge, P.; Bachert, C. TGF-beta signaling and collagen deposition in

chronic rhinosinusitis. J. Allergy Clin. Immunol. 2009, 124, 253–259.

79. Takabayashi, T.; Kato, A.; Peters, A.T.; Hulse, K.E.; Suh, L.A.; Carter, R.; Norton, J.; Grammer, L.C.; Cho, S.H.; Tan, B.K.; et al. Excessive fibrin deposition in nasal polyps caused by fibrinolytic impairment through reduction of tissue plasminogen activator expression. Am. J. Respir. Crit. Care Med. 2013, 187, 49–57.
80. Elia, C.S.A.; Renata, M.E.; Benito, A.S.M.; Vitorino, M.S.; Maria, G.R. Oral epithelial changes in HIV-positive individuals. Pathol. Res. Pract. 2013, 209, 399–403.
81. Dodani, K.; Anumala, N.; Avula, H.; Reddy, K.; Varre, S.; Kalakonda, B.B.; Arora, N.; Suri, C.; Avula, J.K. Periodontal findings in patients with oral submucous fibrosis and comet assay of affected gingival epithelial cells. J. Periodontol. 2012, 83, 1038–1047.
82. Porsbjerg, C.; Baines, K.; Gibson, P.; Bergqvist, A.; Erjefält, J.S.; Sverrild, A.; Backer, V. IL-33 is related to innate immune activation and sensitization to HDM in mild steroid-free asthma. Clin. Exp. Allergy 2016, 46, 564–574.
83. Rak, G.D.; Osborne, L.C.; Siracusa, M.C.; Kim, B.S.; Wang, K.; Bayat, A.; Artis, D.; Volk, S.W. IL-33-Dependent Group 2 Innate Lymphoid Cells Promote Cutaneous Wound Healing. J. Investig. Dermatol. 2016, 136, 487–496.
84. Martinez-Gonzalez, I.; Steer, C.A.; Takei, F. Lung ILC2s link innate and adaptive responses in allergic inflammation. Trends Immunol. 2015, 36, 189–195.
85. Alvarado, M.I.; Jimeno, L.; De La Torre, F.; Boissy, P.; Rivas, B.; Lázaro, M.J.; Barber, D. Profilin as a severe food allergen in allergic patients overexposed to grass pollen. Allergy 2014, 69, 1610–1616.
86. Peeters, K.A.B.M.; Koppelman, S.J.; van Hoffen, E.; van der Tas, C.W.H.; den Hartog Jager, C.F.; Penninks, A.H.; Hefle, S.L.; Bruijnzeel-Koomen, C.A.F.M.; Knol, E.F.; Knulst, A.C. Does skin prick test reactivity to purified allergens correlate with clinical severity of peanut allergy? Clin. Exp. Allergy 2007, 37, 108–115.
87. Porterfield, H.S.; Murray, K.S.; Schlichting, D.G.; Chen, X.; Hansen, K.C.; Duncan, M.W.; Dreskin, S.C. Effector activity of peanut allergens: A critical role for Ara h 2, Ara h 6, and their variants. Clin. Exp. Allergy 2009, 39, 1099–1108.
88. Kulis, M.; Chen, X.; Lew, J.; Wang, Q.; Patel, O.P.; Zhuang, Y.; Murray, K.S.; Duncan, M.W.; Porterfield, H.S.; Burks, A.W.; et al. The 2S albumin allergens of Arachis hypogaea, Ara h 2 and Ara h 6, are the major elicitors of anaphylaxis and can effectively desensitize peanut-allergic mice. Clin. Exp. Allergy 2012, 42, 326–336.
89. Wüthrich, B. Lethal or life-threatening allergic reactions to food. J. Investig. Allergol. Clin. Immunol. 2000, 10, 59–65.

90. Bock, S.A.; Muñoz-Furlong, A.; Sampson, H.A. Fatalities due to anaphylactic reactions to foods. J. Allergy Clin. Immunol. 2001, 107, 191–193.
91. Sampson, H.A.; Mendelson, L.; Rosen, J.P. Fatal and Near-Fatal Anaphylactic Reactions to Food in Children and Adolescents. N. Engl. J. Med. 1992, 327, 380–384.

Retrieved from https://encyclopedia.pub/entry/history/show/29625