T cell interaction with epithelial cells

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In chronic allergic inflammation, dermis in the atopic dermatitis skin and submucosa in the asthmatic lung act like a peripheral lymphatic organ, where dendritic cells, T cells and B cells contact each other. This is followed by a second step of antigen-presentation and activation in the inflamed tissue. Immune system cells and their cytokines interact with resident tissue cells, which leads to a series of tissue events after the activation, and proinflammatory cytokine and chemokine release from both sides. **Some of these events seem to be part of the immune pathology, such as basement membrane thickening, epithelial death, desquamation and spongiosis, however, they also act as mechanisms that control the severity of tissue inflammation. These can be listed as: keep away effects; wash away effects and suppression and regulation of T cells, B cells and dendritic cells.**

“Keep away” effects play a role in allergen ignorance by decreasing the allergen burden. They are lamina reticularis thickening and allergen-specific secretory IgA, in addition to cough and mucociliary activity. “Wash away“ effects to decrease the intensity of inflammation are epithelial apoptosis, spongiosis, leakage and wash of proinflammatory cytokines away from the tissues and transmigration of the inflammatory cells towards the lumen. Direct “suppression” of allergen-specific T cells and proinflammatory dendritic cells as well as “regulation” of B cells in the direction of non-inflammatory antibody isotypes (more IgG4 and IgA, less complement activating antibodies and IgE) are also observed.

**Allergen ignorance (keep the allergens away from subepithelial tissues)**

The most common features of proteins that make them allergens are their properties to overcome immunological ignorance, such as high expression (dose), resistance to digestion (stability) and structural features and related factors including enzymatic activity in the tissues to initiate an immune response.

Several essential tissue events play a role in immune tolerance to allergens. Basement membrane (*lamina reticularis*) thickening, allergen-specific secretory IgA, ciliary movements and cough can be listed as tissue events that try to keep the allergens away from submucosal immune system cells (keep away effects). The airway wall in asthma is usually characterized by increased thickness and markedly and permanently reduced airway caliber. It appears that the immune system naturally tries to decrease allergen burden before the initiation of a visible disease and continues to do so during allergic inflammation. A major T regulatory (T\textsubscript{Reg}) cell cytokine, TGF-β is a potent regulator of fibroblast and myofibroblast function and controls the production of several extracellular matrix proteins, including collagens, proteoglycans and tenascin. The thickening of the subepithelial lamina reticularis in bronchial asthma has been related to an increase in fibroblasts in correlation with
TGF-β expression. Lamina reticularis thickening starts very early in asthma, and is detectable even at the time of first diagnosis, suggesting that a mechanical barrier between mucosal allergens, activated epithelium and inner tissues i.e. immune system cells in the submucosa occurs with the aim of down-regulation of the allergen-induced inflammatory response. These mechanisms resemble features of immune response to chronic helminth infections in order to decrease antigenic burden of the helminths and mechanically keep them away from tissues. For example, keeping them in fibrous sacks etc.

**Tissue factors that decrease the intensity of inflammation (death of highly activated inflammatory cells and wash away of their cytokines)**

Activated T cells interact with resident tissue cells and also other migrating inflammatory cells in allergic inflammation. They activate bronchial epithelial cells, smooth muscle cells, macrophages, fibrocytes in the asthmatic lungs, and epidermal keratinocytes and fibrocytes in the allergic skin. Epithelial-cell activation followed by apoptosis (activation-induced cell death) seems to be one of the hallmarks of visible pathology in the asthmatic lung and atopic dermatitis skin. It involves two stages. First, activation of epithelial cells and release of pro-inflammatory cytokines/chemokines takes place (pro-inflammatory stage). This is followed by eventual death of highly activated bronchial epithelial cells and skin keratinocytes, which lead to desquamation of dead epithelial cells in asthma (shedding), spongiosis in eczema. Since the dead epithelial cell loses its contacts with the inner tissue and its contribution to inflammation does not exist anymore, this seems to be the anti-inflammatory stage.

After the apoptosis of keratinocytes and formation of spongiosis, wash away of inflammatory cells and cytokines takes place. Transepidermal water loss in atopic dermatitis is together with wash away from the dermis to the surface of skin to decrease the amount of cytokines and chemokines in the inflammatory area. In asthma, transmigration of inflammatory cells away from the tissues toward the lumen is an important event that counteracts with the inflammatory burden. Although bronchoalveolar lavage cell count is a marker of tissue inflammation in asthma models, it has to be noted here that it represents a natural mechanism to decrease the number of activated inflammatory cells in submucosa. Cells that leave the tissues toward lumen are not inflammatory anymore and can be cleared away from the inflamed lung inside the sputum.

**Suppression and regulation of allergen-specific immune response**

The overall evaluation of the studies on T and B cell response against allergens suggest that immunological ignorance and active suppression are not entirely distinct, but rather, represent linked mechanisms of peripheral tolerance. If a detectable immune response is mounted, allergen-specific T regulatory 1 (Tr1) cells represent the dominant T cell subset against allergens in healthy immune response and after allergen-specific immunotherapy. These cells suppress allergen-specific Th1- and Th2-like T cells and down-regulate inflammatory dendritic cells.

In healthy individuals, the antibody response against allergens varies between no response to IgG4 dominating allergen-specific antibodies in the presence or absence of low amounts of IgE. The induction of non inflammatory IgG4 and IgA type antibodies against allergens represent an important allergen tolerance mechanism by blocking of allergen entry at mucosal surfaces, interference with surface IgE cross-linking of mast cells and basophils and inhibition of antigen capture by IgE in B cells and dendritic cells. Tr1 cells do not only suppress allergen-specific immune response development, but also regulate B cells by induction of IgG4 by IL-10. In addition, antigen-specific secretory IgA plays a role in ignorance of food and aeroallergens.
IL-10 and Tr1 cells directly and indirectly suppress mast cells, basophils, eosinophils and resident tissue cells and contribute to the maintenance of peripheral tolerance and down-regulate thresholds of proinflammatory events in the tissues. Furthermore, there is increasing evidence on the immune regulatory (suppressive) properties of IL-10-secreting B cells and IL-10-secreting mast cells.

Conclusion

The interaction of the activated immune system cells with resident tissue cells results in inflammation. However, many aspects of this inflammation regulate and decrease the burden of allergen exposure as well as the burden of inflammation. These can be listed as direct “suppression” of allergen-specific Th1 and Th2 cells; “regulation” of B cells in the direction of non-inflammatory antibody isotypes; “keep away” effects that play a role in allergen ignorance and “wash away” effects to decrease the intensity of inflammatory cells and cytokines.

Some of these events seem to be part of the immune pathology, such as basement membrane thickening, epithelial death, desquamation and spongiosis, however, they are actually mechanisms that control the severity of tissue inflammation and damage.