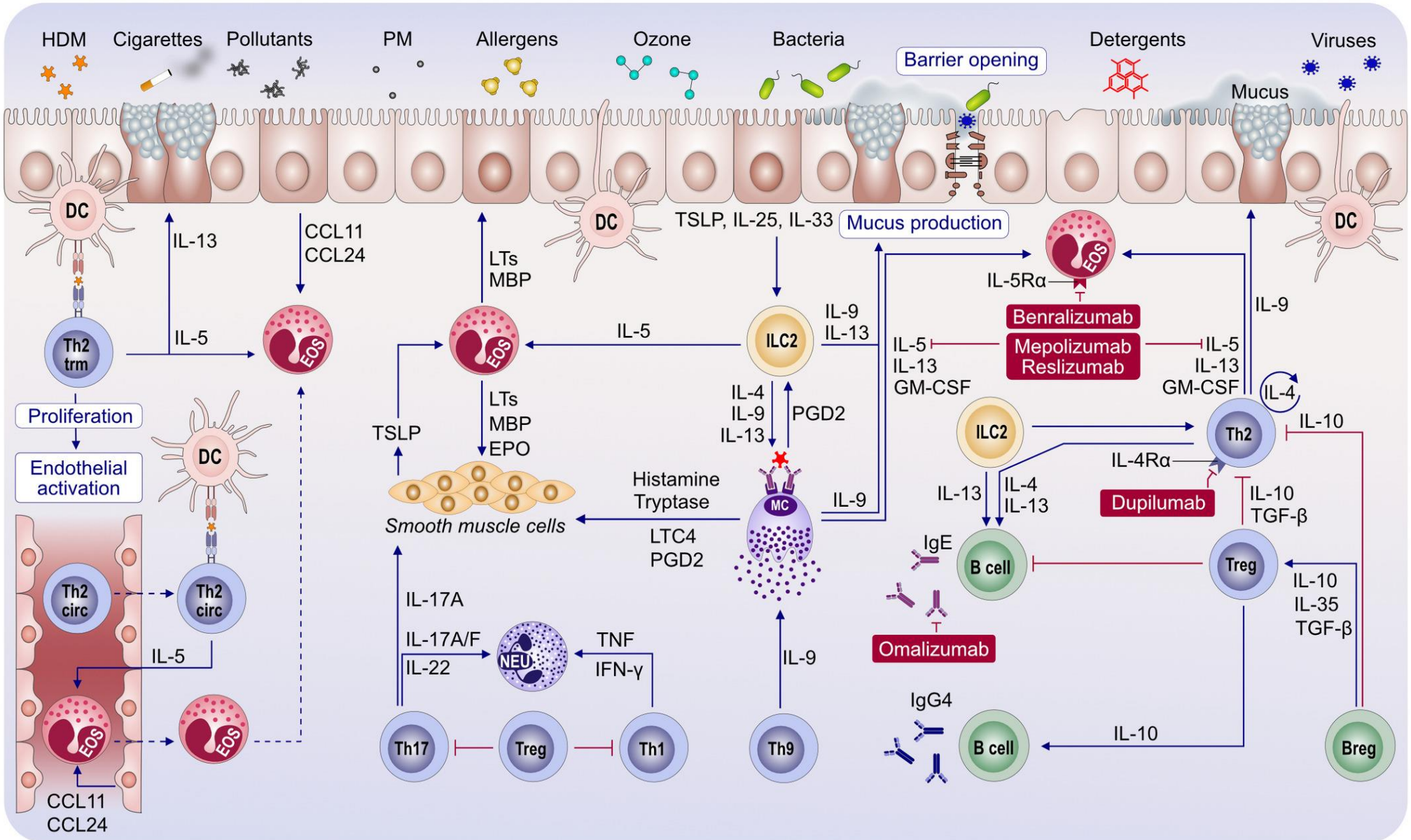
Advances in Understanding of Asthma

Source: Lacin Cevhertas, Ismail Ogulur, Debbie J. Maurer et al. Advances and recent developments in asthma in 2020. Allergy (European J of Allergy and Clinical Immunology) 75 (12)Dec 2020. **https://doi.org/10.1111/all.14607**



Allergy, Volume: 75, Issue: 12, Pages: 3124-3146, First published: 30 September 2020, DOI: (10.1111/all.14607)

The external environment can impair the epithelial barrier. The disrupted barrier allows the penetration of the substances through the tissues where they encounter the antigen-presenting cells. Additionally, submucosal DCs (Dendritic cells) can gain access to outside the epithelium by screening with their dendrites. Activated or damaged epithelial cells stimulate DCs through their secreted cytokines: TSLP, IL-25, IL-33. After capturing the antigen, DCs migrate through the lymphatics to regional lymph nodes and prime the naïve T cells. The differentiation into Th2 cells is driven mainly by IL-4. Mature DCs and TSLP (pleiotropic cytokine), IL-25, and IL-33 directly or indirectly stimulate tissue-resident ILC2s. Th2 cells and ILC2 secrete mainly IL-5, IL-9, and IL-13 but also small amounts of IL-4. While IL-5 stimulates eosinophils, IL-9 and IL-13 induce mucus production and activation of epithelium and mast cells. IL-4 and IL-13 are involved in the opening the epithelial barrier, activation of the endothelium, and migration of Th2 cells, ILC2, and eosinophils and IgE class switching in B cells. After the sensitization of mast cells due to the binding of specific IgE to FcεR, upon cross-linking of IgE, they get activated and release histamine, tryptase, prostaglandins, leukotrienes, and cytokines, which leads to smooth muscle contraction, mucus production, and increased vascular permeability. While Th2-resident memory cells proliferate close to airways, circulating memory Th2 (**T helper 2**) cells traffic into the lung parenchyma and initiate a perivascular inflammation with eosinophil and $CD4^+$ T-cell recruitment, further augmenting type 2 cytokine production within the lung. Eosinophils crosstalk with the resident tissue cells through their secreted leukotrienes and specific proteins such as MBP and EPO. Furthermore, several substances, such as bacteria and mold-derived molecules in allergens, can induce Th17 and neutrophil recruitment. Immune regulation mechanisms prevent type 1, type 2, and type 17 response through Breg and Treg cells and particularly IL-10, IL-35, and TGF-β. In addition, IgG4 has a blocking antibody function for IgE binding to allergens. Several drugs target type 2 cytokines or their receptors signaling: the IL-5 pathway (benralizumab, mepolizumab, reslizumab), the IL-4 and IL-13 pathway (dupilumab), and IgE pathway (omalizumab). **Breg: B regulatory cell; Circ: circulating; DC: dendritic cell; EOS-eosinophil; EPO - eosinophil peroxidase; GM-CSF: granulocyte-macrophage colony-stimulating factor; HDM: house dust mite; IFN-γ, interferon-γ; Ig, immunoglobulin; IL, interleukin; IL-4Rα, interleukin 4 receptor alpha; ILC2, innate lymphoid cell 2; LT - leukotriene; MBP - major basic protein; MC - mast cell; NEU - neutrophil; PGD2- prostaglandin D2; PM-particulate matter; TGF-β- tumor growth factor-β; Th2 Trm: T helper 2 tissue-resident memory; TNF - tumor necrosis factor; Treg, T regulatory cell; TSLP - thymic stromal lymphopoietin**