BSI/NVVI annual congress 2016

Irma Tindemans, December 6th-9th 2016 – Liverpool, UK

The principle objective of the joint BSI & NVVI congress in Liverpool was to provide a forum to critically assess recent progress in the rapidly moving area of immunology by assembling some of the leading investigators examining pathways of immunity and inflammation. Since I work on the role of the Notch signaling pathway on the pathogenesis of house-dust mite induced allergic airway, I will in this report mainly focus on new findings in the field of lung immunology.

The immune system protects the host from a variety of harmful microbes and eliminates toxic or allergenic substances that enter through mucosal surfaces. Essential to the ability of the immune system to respond to invading pathogens, toxins or allergens is its ability to distinguish self from non-self. The immune system uses both innate and adaptive mechanisms to detect and eliminate antigens. Failure of the immune system in distinguishing self from non-self can lead to autoimmunity, an immune response to harmless antigens can lead to allergies.

The innate immune system acts as a first line of defense against invading pathogens by recognizing pathogen-associated molecular patterns via pattern-recognition receptors (PRRs). One pathogen which is a major health burden, especially in the elder population, is influenza A virus. Iwasaki *et al.* presented that monocytes derived from older individuals (65+ years old) have lower expression of interferon gamma (IFN-γ) compared to monocytes from younger people (20-30 years old). Since the cytokine IFN-γ plays a crucial role in clearing viral infections. this can be an explanation why influenza often causes mortality in the elder population. In a mouse model, Iwasaki *et al.* showed that the PRRs Toll-like receptor 7 (TLR7) and RIG-1, which signals via Mavs, are crucial for the immune system to recognize influenza A virus since TLR7-/-Mavs-/- mice die from influenza infection. This is because these mice lack the capacity to clear the virus. Interestingly, in the absence of caspase 1, TLR7-/-Mavs-/- mice are again protected from influenza A infection (Pang et al., 2013; Pillai et al., 2016).

Upon recognition of antigen, dendritic cells (DCs) get activated and travel to draining lymph nodes to activate naïve T cells. Depending on the signals, naïve T cells can differentiate into several T cell lineages including Th1, Th2, Th9, Th17, Th22, T follicular helper cells (Tfh) and T regulatory cells (Tregs), characterized by their unique cytokine production that is required to provide host protection against specific pathogens. Th2 cells, for example, have an important role in controlling helminth infections. Biased Th2 responses, on the other hand, can lead to allergies and asthma. In contrast, Th1 and Th17 cells were described to mediate autoimmune diseases. In addition, Innate lymphoid cells (ILCs) are a recently identified family of innate immune effector cells that lack antigen-specific receptors (reviewed in (Spits et al., 2013; Tindemans et al., 2014; Walker et al., 2013). In contrast to T cells, ILCs contribute to the first-line immune defense against invading pathogens and have the capacity to quickly produce large amounts of pro-inflammatory cytokines. ILCs have been categorized into three major groups, based on

transcription factor dependency and cytokine production profiles, which closely mirror the various T helper cell subsets. ILC1 consist of NK cells and other IFN-γ-producing innate lymphocytes that express T-bet. ILC2, like Th2 cells, secrete IL-5 and IL-13 in response to stimulation with the cytokines IL-25, IL-33 or thymic stromal lymphopoietin (TSLP), and are crucial to mount a robust Th2 cell response to the protease-allergen papain (Halim et al., 2012; Halim et al., 2014). ILC3 express and require the transcription factor RORγt for their development and for production of IL-17A and IL-22. Interestingly, it has become more and more clear that there is potential plasticity between ILC1s, ILC2s and ILC3s under certain environmental conditions. For example, Hergen Spits (Amsterdam, the Netherlands) showed that a proportion of CD127+ ILC1 is derived from ILC3 and that this differentiation is reversible under certain culture conditions (Bernink et al., 2015; Bernink et al., 2013). Moreover, IL-12 induced IFN-γ production by ILC2s, which was reversed by IL-4. Lastly, it was shown that eosinophils are capable of producing IL-4, which suggests cross-talk between ILC2s and eosinophils (Bal et al., 2016).

There has been much progress in understanding the development of allergic airway responses. Several mouse asthma models have been developed whereby mice are repeatedly exposed to allergens including ovalbumin (OVA) and House-Dust Mite (HDM). HDM extracts contain allergens and proteases (including Derp1) that are capable to directly stimulate TLR4 on epithelial cells (reviewed in (Lambrecht and Hammad, 2014)). TLR-4 stimulated epithelial produce cytokines including IL-1α, IL25, IL-33, TSLP and GM-CSF which can stimulate ILC2 and dendritic cells which eventually leads to activation of Th2 cells. Clare Lloyd (London, UK) emphasized the importance of IL-33 in allergic asthma by showing that IL-33 exposure in mice leads to allergic airway inflammation, characterized by eosinophilia, airway hyper responsiveness and IL-13 production by ILC2 (Saglani et al., 2013). In addition to IL-33, TGF-β1 produced by epithelial cells is important for IL-13 production by ILC2 for the induction of airway hyperreactivity (Denney et al., 2015). Fungal allergens, including A*lternaria*, can enhance Th2 inflammation by inducing IL-33 production (Snelgrove et al., 2014). Moreover, IL-33 is increased in bronchial biopsies (Saglani et al., 2013) and the number of ILC2 is increased in sputum and blood from children with severe asthma (Nagakumar et al., 2016).

After T cells become activated by DCs, T cells migrate to the edge of lymphoid follicles where helper T cells provide signals for B cells to differentiate into antibody secreting plasma cells. Jackson-Jones *et al*. investigated Fat-associated lymphoid clusters (FALC), which are inducible structures that support rapid B-cell immune. They found that that inflammation of the pleural cavity induces IL-33 production by FALC stromal cells which leads to IL-5 production by ILC2 which is crucial for B1-cell activation and local IgM secretion (Jackson-Jones et al., 2016).

I would like to thank the NVVI, the Netherlands, for giving me the opportunity to attend the NVVI/BSI annual congress. My abstract was selected for an oral presentation, in which I showed the results of interfering with several components of the Notch signaling pathway (including Notch and RBPJκ in T cells and Jagged molecules on DCs and stromal cells) on the pathogenesis of house-dust mite induced allergic airway. After my presentation, I was able to discuss my results with many experts in the field of immunology. In addition, I visited (poster) presentations from other participants who often showed

unpublished data. These discussions gave me many new ideas and insights for new experiments for my research project, such as other cells and molecules that I could look at.

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