CHAPTER 9

Summary
CHAPTER 9

The generation of allergic airway disease requires specific interactions between the initial responder cells (the epithelium), the underlying antigen presenting cells (dendritic cells) and naïve T cells. Chapter 1 provides an in depth literature review exploring the complex relationships between these cells in the lung, and how an inflammatory milieu instigated by one cell type can lead to aberrant adaptive immune responses that manifest in allergic airway disease.

*Airway epithelial NF-κB activation modulates airway inflammation and acute lung injury in mice.*

Chapter 2 documents the characterization of a novel transgenic mouse expressing a CC10-specific, Doxycycline-inducible, constitutively active form of IκKβ (the CAIKKβ mouse). Following Dox administration, these mice activate NF-κB in the airway epithelium, resulting in the recruitment of neutrophils into the lung, upregulation of inflammatory cytokines and chemokines, induction of airway hyperresponsiveness in response to methacholine challenge, and concurrent airway smooth muscle thickening. Chapter 3 examines the role of airway epithelial NF-κB in a model of NO2-induced acute lung injury. We determine that the phenotype induced in the CAIKKβ mouse after 1 week of Dox administration is similar to the acute lung injury seen in mice exposed to 25ppm of nitrogen dioxide (NO2) for 6 hours a day for 3 days. NO2-induced acute lung injury also requires NF-κB activation, as indicated by the results demonstrating that CC10-IκBαSR mice, in which airway epithelial NF-κB expression is repressed, have an ameliorated inflammatory response to NO2 (except at very high NO2 doses).

*Airway epithelial NF-κB activation is sufficient to induce allergic sensitization to an innocuous inhaled antigen in mice.*

Chapter 4 demonstrates that the inflammatory milieu generated by airway epithelial NF-κB activation allows for allergic sensitization to an innocuous inhaled antigen. In this chapter, we begin to elucidate the effect of airway epithelial NF-κB activation on nearby cells: specifically, dendritic cells (DCs). Soluble mediators released by the airway epithelium allow for DC maturation, activation, and effective antigen presentation to CD4+ T cells, resulting in a mixed Th2/Th17 polarization complete with airway eosinophilia and neutrophilia, as well as airway hyperresponsiveness (AHR). We move away from the use of intraperitoneally-injected aluminum hydroxide (Alum) as an adjuvant, and begin to explore sensitization specifically as it takes place in the lung.
Summary

The acute mediator Serum Amyloid A induces NLRP3-dependent allergic airway disease in mice.

Chapters 5 takes a closer look at the NF-κB-regulated, airway epithelial-produced soluble mediators that play a role in our animal models of allergic asthma. Chapter 5 reveals that Serum Amyloid A (SAA) is a potent inducer of inflammation, NLRP3 inflammasome activation, and is an instigator of allergic airway sensitization to OVA. SAA treatment can induce dendritic cells to undergo maturation and activation, and to robustly produce IL-1β, leading to an IL-1 receptor signaling-dependent Th17 phenotype.

Airway epithelial NF-κB activation is sufficient to break inhalational tolerance in mice.

Having demonstrated in Chapter 4 that airway epithelial NF-κB activation allowed for allergic sensitization to an innocuous inhaled antigen in naïve mice, we were left with the question of whether induced NF-κB activation in airway epithelium could promote allergic airway disease in mice that had previously been tolerized to the antigen OVA. Chapter 6 reveals that airway epithelial NF-κB activation can drive allergic airway disease irrespective of previous antigen tolerance. The effects of soluble mediators produced by the airway epithelium on DCs appears to be critical in overcoming tolerance, and there is a key role for IL-4 and IL-1 receptor signaling in generating downstream Th2 and Th17 responses, respectively.

The acute mediator Serum Amyloid A protects dendritic cells from apoptosis, driving CD4+ T cell activation and resistance to glucocorticoid treatment.

Chapter 7 returns to the polarizing effects of SAA and indicates that, in vitro, SAA affords protection against apoptosis. Serum-starved dendritic cells undergo caspase 3-dependent apoptosis that is inhibited in SAA-treated cells. In addition, SAA treatment induces inflammatory cytokine production from serum-starved DCs, including IL-1β, IL-6, and HSP70. Finally, SAA-treated, serum-starved DCs effectively present antigen and drive steroid-refractory IL-17 production from CD4+ T cells.

Closing Remarks

The data presented in this thesis contribute to the understanding of how NF-κB-dependent inflammatory mediators, generated by airway epithelial cells in response to injury or antigenic insult, can modulate surrounding leukocytes and polarize the adaptive CD4+ T cell phenotype in allergic airway disease. From these
studies, we conclude that the inflammatory milieu generated as a consequence of airway epithelial NF-κB activation triggers the maturation and prolongs the survival of dendritic cells, and this in turn results in CD4+ T cells that produce both Th2 and Th17 cytokines. Importantly, we have determined that the generation of this NF-κB regulated response can not only induce sensitization in naïve mice, but also overcome established antigen tolerance. It is the latter situation that likely accounts for the development of allergic airway disease in adults. Therefore, inhibition of select soluble mediators secreted by the epithelium may improve inflammation in asthmatic patients, and may also modulate the patient response to glucocorticoid treatment.