Asthma has become an epidemic, affecting 300 million people worldwide. Airway inflammation, smooth muscle constriction, airflow obstruction and mucous hypersecretion are clinical hallmarks of asthma, originating from complex interactions between inflammatory cells, their secreted mediators, airway epithelium and smooth muscle cells. Asthma is well-known as the result of sensitization to a variety of environmental allergens and is typically associated with cytokines secreted by T_H2 helper cells and with resulting eosinophilia. Severe asthmatics however, who typically respond poorly to currently available asthma medications, suffer from neutrophil-predominant disease, associated with another subset of T helper cells - called T_H17 cells. T_H17 cells produce major pro-inflammatory cytokine, interleukin 17 (IL-17), that up-regulates neutrophil-mobilizing cytokines (**Fig. 1A**). While IL-17 is required for host defense against extracellular microorganism it also has been linked to the development and pathogenesis of many autoimmune disorders.

The molecular mechanisms of IL-17 signaling remained elusive for many years. Recently, we and others have demonstrated that while IL-17 activates target gene transcription (often via transcription factor NFκB), it primarily acts at the post-transcriptional level, by stabilizing messenger RNAs (mRNAs). The lifespan of messenger RNA is increasingly recognized as a principal determinant of gene expression. While during inflammation many genes exhibit a significant increase in transcription, their mature mRNAs frequently exhibit remarkably short half-lives, that need to be prolonged to enable robust protein translation.

In effort to decipher signaling events downstream of the IL-17 receptor, we found several factors necessary for IL-17-mediated mRNA stabilization (**Fig. 1B**). We have discovered that upon IL-17 stimulation, Act1 was phosphorylated by inducible kinase IKKi and then formed complex with TRAF2/TRAF5 to prevent mRNA degradation. More recently, we found that the RNA-binding protein, HuR (human antigen R), plays a critical role in IL-17 signaling. We found that upon IL-17 stimulation HuR was polyubiquitinated by Act1, the key adaptor molecule in IL-17 mediated signaling. This induced subsequent binding of HuR to its target mRNAs, which, in turn, increased their stability as well as translation efficiency. We found that deletion of HuR in the *in vivo* inflammation model led to diminished production of IL-17-induced proinflammatory cytokines and attenuated neutrophilia. Taken together, our results demonstrated for the first time the critical role of HuR in IL-17 signaling and hinted that it may play an important role in the pathogenesis of severe asthma.

Now, we propose to test the potential role of HuR in the pathogenesis of this disease. We plan to specifically delete HuR in two cell types critical for asthma pathogenesis - airway epithelial and smooth muscle cells. Subsequently, we will challenge HuR-deficient and control cells with IL-17 and analyze gene expression, identify direct RNA targets of HuR and assess smooth muscle cells activation. Physiologically relevant model is necessary to mimic complex multifactorial disease such as asthma. Therefore, we propose to validate the role of HuR using an *Aspergillus*-induced severe asthma mouse model; *Aspergillus fumigatus* is a ubiquitous fungal organism that is associated with allergic sensitization and severe asthma in humans.

To summarize, our study will shed light on the role of HuR in IL-17-associated severe asthma pathogenesis and ultimately may allow the development of novel therapies.

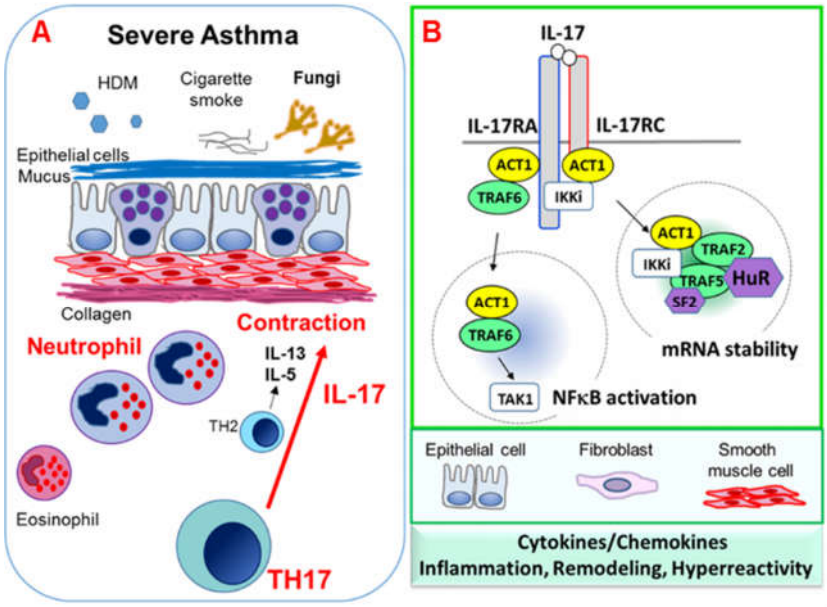

***Figure 1**. (**A**) T_H17 cells and associated cytokine IL-17 play a significant role in neutrophil-predominant disease. IL-17 exerts its impact on multiple aspects of asthma pathogenesis, including inflammatory response of epithelial cells, collagen deposition, smooth muscle cell hyperplasia and smooth muscle contraction. (**B**) IL-17R adaptor protein Act1 interacts with TRAF6 and HuR/TRAF2/5 to induce transcriptional and post-transcriptional control of inflammatory gene expression.*