Sample Abstract

Astr is a gene controlling an IL4 regulatory activity that cell autonomously controls TH2 bias, the propensity of naïve CD4 cells to develop into IL4 secreting TH2 cells (). ASTR was first identified as a Myc-induced nuclear factor (). It belongs to the XXX protein family whose hallmark ZZ domain was shown recently in multiple family members to possess histone demethylase activity (). *Astr* is induced rapidly in naive T helper cells to levels that are inversely correlated with those of IL4, being high in low-TH2 biased strains and low in high-TH2 biased strains, suggesting an IL4/TH2 inhibitory role (). Consistent with this, transient reporter assays demonstrated that ASTR can dampen transcription from the *Il4* gene. In humans, as in mice, IL4 and TH2 cells critically impact a wide array of diseases, a prime example of which is bronchial asthma where genetic association studies have repeatedly identified both the gene locus encoding IL4 and IL13 (5q25-31) and several mutations in the IL4 receptor alpha chain as strong disease risk factors. Together, these data support the central hypothesis of this proposal that **in T cells, ASTR represses IL4 expression, thereby critically influencing TH2 development and TH2-dependent disease**. We will test this hypothesis by determining: (1) the role of ASTR in regulating IL4 and TH2 bias in human and mice T helper cells; and (2) whether *ASTR* contributes to bronchial asthma. These studies will further our understanding of the molecular and genetic basis for IL4/TH2-dependent disease and lead to identification of novel targets for diagnostic and therapeutic intervention.

Aim 1. Determine if ASTR repress *IL4* and diminish TH2 bias in T helper cells.

To determine the necessary and sufficient role of ASTR in repressing IL4 in human and mouse T helper cells, we will: (**1A**) perform transcriptional analyses using blood obtained from healthy volunteers to determine whether in activated T helper cells an inverse correlation exists (as it does in mice) between variation in ASTR and *IL4* expression levels; (**1B**) determine whether ASTR over-expression is sufficient to repress *IL4* expression in differentiating naïve T helper cells; (**1C**) determine whether ASTR directly binds to human and mouse *IL-4* promoter; and (**1d**) determine whether ASTR is required to maintain *IL4* expression at a low level in differentiating naïve T cells.

Aim 2. Does *ASTR* carry risk-conferring alleles for human bronchial asthma?

To determine whether *ASTR* modulates bronchial asthma, we will utilize a mouse model of bronchial hypersensitivity in which the amounts of functional ASTR expressed in T cells can be inducibly and temporally modulated. Severity and kinetics of disease induction resulting from the quantitative modulation of *ASTR* will be correlated with alterations in IL-4 and IgE production. Using ASTR small molecule inhibitors we will confirm the results from the genetic studies pharmacologically.