**DNA methylation and histone markers associated with higher incidence for asthma**

Asthma is a heritable, multifaceted airway inflammatory disease afflicting approximately 8% of the USA population (Yang and Schwartz, 2012). The disease has steadily increased in prevalence and severity in the last couple of decades (Eder *et al*., 2006). There are various lines of evidence suggesting that epigenetics may have a role to play in the pathophysiology of asthma. Epigenetic modifications are inheritable from one generation to another. Similarly, there is a 36-79% likelihood of a child inheriting asthma if one parent is also afflicted with the disease (Yang and Schwartz, 2012). Comparable to epigenetic mechanisms, asthma displays a parent-specific transmission pattern, with an affected mother more likely to pass on the disease than an affected father (Moffat and Cookson, 1998).

In addition, epigenetic mechanisms have been shown to regulate transcriptions factors which are necessary in T cell differentiation into T cell subtypes (Fields *et al*., 2002; Lee *et al*., 2006; Webster *et al*., 2007). Asthma is recognized as an immune-mediated inflammatory disease characterized by the skewing of naïve T-cell differentiation into the Th2 phenotype (Lloyd and Hessel, 2010). The irregular shift in the proportion of the Th2 cell population along with increased expression of its associated cytokines (IL-4, IL-5, IL-13) has been demonstrated to drive airway inflammation (Lloyd and Hessel, 2010). CD4+ T lymphocyte cultures from hosts with bronchial asthma exhibited a strong degree of DNA demethylation at the IL-4 promoter when treated with an allergen relative to control cultures not treated with allergenic stimulation (Kwon *et al*., 2008). Also, histone tail modifications commonly associated with transcriptional activation such as H3K4me3 are found at IL-4 regulatory regions of Th2 cell genomes but not Th1 cell genomes (Wei *et al*., 2009). It's possible that these mechanisms are epigenetically transmitted from generation to generation, leading to higher incidence of asthma in children with an affected parent. I hypothesize that cultured naive T cell lymphocytes exposed to allergenic stimulation will exhibit a lower degree of DNA methylation and histone repressive marks like H3K27me3 than control cultures at genes necessary for Th2 cell differentiation such as IL-4, IL-5, and IL-13. I predict the same results to occur for genes which regulate the Th2 cell differentiation mechanism such as STAT6, GATA-2, TBET, and EZH2.

To test this hypothesis, I want to compare DNA methylation and H3K27me3 modifications between a WT mouse strain and a mouse strain which serves as a model for asthma. The acute model for asthma would require exposing mice to an allergen two hours each day for 14 days. The chronic model for asthma involves treating mice to an allergen for two hours each day for six weeks. I would like to first establish that my asthma model is viable by investigating whether allergen exposure will lead to Th2 cell differentiation. I want to isolate T cell populations from my mouse strains and use FACS to determine what percentage of the population has developed into the Th2 lineage. I expect that my asthmatic mice strains will have T cell populations that will be further skewed towards Th2 cell differentiation whereas my WT strain will exhibit a balance between Th1 and Th2 cell differentiation. Furthermore, I want to culture T lymphocyte populations and compare them for DNA methylation and H3K27me3 modifications at the regulatory regions of Th2 cell differentiation genes. I predict that T lymphocytes derived from the asthma model strains will exhibit less DNA methylation and H3K27me3 markers as compared to T lymphocytes from the WT strain. If there is a difference in methylation and H3K27me3 modifications between the asthma model and the WT strain, I want to investigate whether these modifications are inherited by the next generation. I want to expose my acute and chronic asthma model strains to an allergen for several generations of mice, and obtain T lymphocytes cultures from each generation. I will compare these T lymphocytes to T lymphocytes obtained from successive WT generations to determine if any methylation or histone tail modifications are epigenetically inherited.

 Asthma is a complex disease influenced by both environmental and genetic factors. Therefore, identifying and elucidating epigenetic mechanisms driving asthmatic inflammation may leave the environmental influence issue unaddressed. However, there is hope that understanding these mechanisms can result in more effective therapeutic strategies for chronic forms of asthma.

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