Elucidating the Role of Epigenetic Memory in the Pathogenesis of Allergic Inflammation in a model of Eosinophilic Esophagitis

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Introduction

Eosinophilic Esophagitis (EoE) is a disease that is driven by IL-13 mediated allergic inflammation and is characterized by transcriptional changes known as the EoE transcriptome. Previous work in the lab has shown epigenetic regulation is a mechanism by which gene expression is controlled. Literature has shown gene expression can be regulated by various epigenetic mechanism such as DNA methylation, snRNAs, histone, and histone marks. Epigenetics allows a link between the environmental and genetic components of EoE. Elucidating the epigenetic signature of IL-13 response is essential for further understanding EoE pathogenesis. Our study focuses on exploring the dynamics of epigenetic changes in the promoters of EoE hallmark transcriptional target genes in the context of IL-13 mediated response in TE-7 human esophageal epithelial cells.

Hypothesis

We hypothesized that the transcriptional response to IL-13 is accompanied by rapid but transient epigenetic changes in the promoters of target genes. Epigenetic changes may remain in the promoters of some IL-13-responsive genes following IL-13 withdrawal and thereby allow a faster transcriptional response to recurrent IL-13 stimulation by a mechanism known as "short-term" epigenetic memory.

Methods

We developed 4 novel approaches for modeling IL-13 induction of EoE. Quantitative real time PCR focused on the promotes of IL-13 inducible genes, along with chromatin immunoprecipitation with specific antibodies were used to assess the transcriptional responses to IL-13 stimulation

Results

We have demonstrated that epigenetic response to IL-13 is time- , dose- and signal dependent and is rapidly normalized following IL-13 withdrawal. By analyzing transcriptional response of prominent IL-13 targets to IL-13 re-stimulation we did not observe improved expression in the cells previously exposed to IL-13.

Conclusion

These data do not support the existence of short-term epigenetic memory at least for the tested target genes. A limitation of this study was that only IL-13 highly inducible genes were studied and a cancerous esophageal adenocarcinoma cell line was used which could display different memory as opposed to primary cells or immortalized (EPC2) epithelial cells. To more comprehensively examine short-term memory, our strategy must change to use of a genome wide transcriptional approach, with further epigenetic analysis of marks known to confer memory such as H3K4me1.Our study provide the framework for understanding complex relationships between environmental stimuli and allergic responses.

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