Aberrant Splicing Of Histone Modification Genes Affects Asthma Pathogenesis And Severity

Aim Alternative splicing represents a mechanism for increasing the diversity of proteins. However, an imbalance in splice variant expression can lead to disease development or impact on severity. Dendritic cells (DC) function is affected in asthmatic patients. This influences the immune response in asthmatics and their respond to stimuli. The purpose of this research was to assess the overall gene expression and alternative splicing events in immature Monocyte-derived DC (imMoDC) in healthy subjects and mild and severe asthmatics.

Methods Exon array analysis was performed using total RNA isolated from imMoDC of mild and severe asthmatics and healthy controls. RT PCR was used to confirm the existence of newly identified splice variants.

Results The 10 genes found to have the most significant splice variants associated with Asthma and Asthma phenotypes had functional roles in a variety of disease and cellular mechanisms such as histone modifications, dendritic cell differentiation, development of dendrites, NFκB and p53 pathways, GPCR signaling and cell cycle progression. Two genes SETD7 and KDM6A associated with histone methylation marks known to have a co-localised, bivalent priming effect on gene expression of a subset of genes including central immune genes. We identified novel splice variants of these genes. Splicing events were confirmed, and found to cause a loss of functional SET domains or 3'UTR predicted miRNA binding sites. Furthermore, expression of these splice variants may influence asthma severity.

Conclusions These differential splicing events between asthma phenotypes represent a novel regulatory chromatin model of epigenetic control of the immune system, offering exciting new insights into the interface of the epigenetic and genetic landscape of the disease. Understanding regulatory mechanisms underlying the methylation in asthma, this research has the potential to facilitate development of a new approach in the field of pharmacogenetics in asthma treatment.