12
Inflammatory Diseases
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**Mechanisms underlying divergent responses of genetically distinct macrophages to IL-4**

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Mechanisms by which noncoding genetic variation influences gene expression remain only partially understood but are considered to be major determinants of phenotypic diversity and disease risk. Here, we evaluated effects of >50 million SNPs and InDels provided by five inbred strains of mice on the responses of macrophages to interleukin-4 (IL-4), a cytokine that plays pleiotropic roles in immunity and tissue homeostasis. Of >600 genes induced >2-fold by IL-4 across the five strains, only 26 genes reached this threshold in all strains. By applying deep learning and motif mutation analyses to epigenetic data for macrophages from each strain, we identified the dominant combinations of lineage-determining and signal-dependent transcription factors driving IL-4 enhancer activation. We found that the IL-4-induced transcription factor EGR2 is the driver of collaborative and hierarchical transcription factor binding at IL-4-activated enhancers. These studies further revealed mechanisms by which noncoding genetic variation influences absolute levels of enhancer activity and their dynamic responses to IL-4, thereby contributing to strain-differential patterns of gene expression and phenotypic diversity.