Epigenomic Regulation of Human Macrophages by Interferon-gamma

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Interferon-gamma (IFN-γ) is a pleiotropic cytokine that regulates immune responses involved in host defense and inflammation. The mechanisms underlying how IFN-γ stimulates gene expression to activate macrophages and the functions of these genes are well established. However, the precise role of IFN-γ in gene repression is largely unknown. Here, we show that IFN-γ represses gene expression by inactivation and disassembly of enhancers bound by the transcription factor MAF. We used integrated and unbiased genome-wide approaches combining RNA-seq, ATAC-seq, and ChIP-seq to analyze transcriptomic and epigenomic alterations in primary human macrophages treated with IFN-γ. We identified novel ‘disassembled’ enhancers that exhibit coordinated suppression of binding by MAF, lineage-determining transcription factors, and chromatin accessibility upon IFN-γ stimulation. Interestingly, disassembled enhancers associated with IFN-γ-repressed genes had ‘M2’-like homeostatic/reparative functions. In rheumatoid arthritis macrophages, MAF and MAF-binding disassembled enhancers-associated genes were downregulated, suggesting a new disease-associated ‘negative IFN-γ signature’. These results illuminate a novel regulatory mechanism by which IFN-γ disassembles a subset of MAF-bound enhancers to repress M2 gene expression to promote macrophage activation by IFN-γ in immunity and chronic inflammation.