

Gene Regulation Logic in Activated Macrophages

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Past studies of mammalian genes activated in response to a stimulus have suggested diverse mechanisms through which chromatin structure and nucleosome remodeling events contribute to inducible gene transcription. However, because of this diversity, the logical organization of the genome with respect to nucleosome remodeling and gene induction has remained obscure. With respect to the innate immune system, numerous pro-inflammatory genes are rapidly induced in macrophages in response to microbial infection. Transcription factors such as NF- κ B and AP-1 contribute to the induction of the vast majority of these genes, but because each gene exhibits a unique promoter structure and unique regulatory characteristics, it has been difficult to understand the underlying regulatory logic.

We have found that, in lipopolysaccharide (LPS)-stimulated macrophages, the catalytic BRG1/BRM subunits of the SWI/SNF class of ATP-dependent nucleosome remodeling complexes are not required for the activation of genes that are rapidly induced in the absence of new protein synthesis, referred to as early primary response genes. However, SWI/SNF complexes were consistently required for the activation of primary response genes induced with delayed kinetics, as well as for the activation of almost all secondary response genes, which require new protein synthesis for induction. Surprisingly, a second nucleosome remodeling complex containing the Mi-2 β catalytic subunit was selectively recruited along with the SWI/SNF complexes to the control regions of secondary response and delayed primary response genes, with the Mi-2 β complex acting antagonistically to limit the induction of these gene classes. These results provide initial insight into the differential contributions of nucleosome remodeling complexes to the rapid induction of defined classes of mammalian genes and reveal a robust anti-inflammatory function of Mi-2 β . In more recent studies, specific mechanisms that are responsible for the proper regulation of genes within each class have been uncovered. In particular, the fundamental reason why early primary response genes can be activated in the absence of nucleosome remodeling or new protein synthesis has been elucidated and a transcription factor required for nucleosome remodeling and transcription at a large fraction of late primary response genes has been identified.

References:

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