The role of enhancers in the early stages of monocyte-to-macrophage differentiation.

Yi Xu[1] , Vanessa Meyer[1] and Nikki Gentle[1]
[1] School of Molecular and Cell Biology, University of the Witwatersrand.

Monocytes, key mediators of both adaptive and innate immune responses, can migrate from the blood into tissues and differentiate into tissue-resident macrophages that display distinct, heterogeneous phenotypes and functions, often decidedly different from those of their progenitors. This process of monocyte-to-macrophage differentiation, though well studied, is not yet entirely understood. Promonocytic cell lines treated with phorbol 12-myristate 13-acetate (PMA) are widely used as an in vitro model for studying monocyte-to-macrophage differentiation. We therefore used this model to evaluate the relationship between changes in gene expression and chromatin accessibility in the early stages of differentiation, in order to better understand the impact of regulatory elements on this process. To this end, we identified genes significantly differentially expressed (DEGs) in response to treatment of THP-1 cells with 162 nM PMA for 24 hours - representative of an early time point in the process of monocyte-to-macrophage differentiation. Changes in chromatin accessibility that correlated with these changes in gene expression were then identified using ATAC-seq data. A total of 2870 DEGs (1436 up-regulated and 1434 down-regulated) were identified in PMA-treated cells relative to untreated cells. Significant changes in chromatin accessibility were detected within the promoter regions of 5% of these genes and within known enhancer elements proximal to 20% of these genes. In general, increased chromatin accessibility at enhancer regions correlated with increased gene expression, while decreased chromatin accessibility in these regions was not associated with any significant change in gene expression. Collectively, these results suggest a role for the regulation of enhancer accessibility in monocyte-to-macrophage differentiation.

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