Title: Integrative analysis of the epigenetic regulation of neutrophil differentiation

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Abstract

Neutrophils are short-lived blood cells that play a critical role in host defense against infection. In the context of the BLUEPRINT consortium, a complete set of reference epigenomes was generated for the full neutrophil differentiation lineage, including bone marrow progenitors ((pro)myelocytes, metamyelocytes, band form and segmented) and mature blood circulating neutrophils. Here we provide an integrative view of the epigenetic regulation of neutrophil differentiation, focused in the interplay between neutrophil chromatin states, DNA methylation and RNA expression.

By mapping chromatin state transitions to genes, we identified genes that are affected by chromatin state transitions at specific stages of differentiation (here called transition-specific genes) and genes that are affected by chromatin remodelling through all stages of differentiation (here called differentiation-dynamic genes).

Differentiation-dynamic genes are enriched for neutrophil-specific functions, including GTPase and hydrolase activities, vesicle mediated transport and programmed cell death. These genes are expressed at relatively high levels throughout differentiation

On the other hand, transition-specific genes show specific functions associated at each stage of differentiation, including cell cycle arrest, cellular antimicrobial responses and regulation of RNA processing. Genes with transition-specific chromatin state changes are mostly correlated with down-regulated expression in the first stages of differentiation, while those with state changes in the segmented to mature transition are associated to increases in gene expression, with an enrichment in functions related to neutrophil changes during terminal differentiation and mature neutrophil activation, such as the regulation of RNA processing, the negative regulation of metabolic processes and the regulation of IL-12 biosynthesis.

Chromatin state transitions were found to be consistent with the observed expression changes, with a predominance of repressed to active chromatin state transitions in up-regulated genes and of active to repressed states in downregulated genes. Finally, we also mapped differentially methylated regions (DMRs). DNA methylation in the first transition correlates with gene up-regulation and with chromatin state changes, suggesting a role for DNA methylation changes in the early stages of neutrophil development.

In summary, our integrative analyses show how changes at different epigenomic layers may orchestrate the formation of mature neutrophils.