Modelling epigenetic control of lineage fate decisions.

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Abstract
Lineage fate decisions have been shown to be under control of both transcription factor (TF) networks and epigenetic regulation via DNA methylation and histone modifications. In particular, bivalent genes, that are associated with histones that carry both tri-methylation of H3 at lysine 4 (H3K4me3) and at lysine 27 (H3K27me3) but also bivalent domains of H3K4me3/H3K9me3 have been implicated in this process. A mechanistic understanding of the regulation of these genes is currently missing. Here, we provide a computational model of hematopoietic stem cell (HSC) populations which describes their specification into the myeloid and lymphoid lineage based on epigenetic feedback on transcriptional regulation of bivalent genes.
We assume that lineage specification depends on changes in the activity of epigenetic modifiers. Accordingly, we model the specification of HSCs into their differentiated myeloid and lymphoid progeny assuming characteristic changes of histone modifying and DNA methylating enzymes. In our simulations, each cell contains an artificial genome. The expression of this genome depends on the cell's epigenome which is represented by three histone modifications (H3K4me3, H3K9me3 and H3K27me3) cross-talking with DNA methylating enzymes.
While the model is not capable of deciding on whether lineage specification is initiated by TFs or chromatin reorganization, it suggests that intimate feedback loops between these regulatory layers stabilize lineage specific transcriptional programs. Consequently, aberrant expression of epigenetic modifiers will impact cell fate decisions potentially leading to stem cell loss of function. As an example, we demonstrate how disturbed histone modification processes might result in a differentiation block as seen in acute myeloid leukemia. Moreover, we show how accelerated or prolonged proliferation during the highly dynamic progenitor states can destabilize histone modifications and therewith effects DNA methylation and in consequence lineage specification processes.