Integration of chromatin structure dynamics in the regulatory network governing cell fate acquisition

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Cell fate acquisition and transition are fundamental processes in the ontogeny of multicellular organisms and aberrations along these processes can generate pathologies [1]. Previously we have defined the dynamic gene-regulatory networks underlying endodermal and neuronal differentiation induced by the morphogen all-trans retinoic acid (RA) [2]. Here we assessed the contribution of the chromatin interactome to commitment and selective acquisition of these two cell fates.

To understand the molecular features of the particular biological system and to predict its response to effectors we have developed a regulatory network approach that integrates transcription factor-target gene (TF-TG) relationships, chromatin states (TF ChIP-seq and FAIRE-seq) and chromatin conformation (HiC) data. Using this approach, we reconstructed Gene Regulatory Network that indicated key regulatory elements responding to the initial signal of RA, driving neuronal and endodermal cell differentiation.

We observed previously unrecognized highly dynamic re-wiring of chromatin interactome during cell differentiation. Long-range chromatin interactions are massively reorganized, erasing the majority of the interactome of undifferentiated cells and establishing new interactions already 6 hours after RA treatment.

Our data reveal an enormous capacity of the morphogen to reorganize long- range chromatin interactions as a means to “read” distant epigenetic signals to drive cell fate acquisition and suggest that the differential establishment of chromatin contacts directs the acquisition of the two cell fates.

References:

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