DOI 10.18699/SBB-2022-064

Whole-genome analysis of epigenetic control of human GABAergic interneuron differentiation

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Key words: epigenetics, chromatin, GABAergic neurons, development

Motivation and Aim: GABAergic interneurons play a pivotal role in neural circuitry as they inhibit neural activity via the neurotransmitter gamma-aminobutyric acid (GABA). GABAergic interneurons undergo a complex differentiation process, which, if erroneous, may result in severe developmental abnormalities [1, 2]. They have been actively studied, yet the mechanisms underlying the regulation of their differentiation still remain unclear. Recent studies have revealed the importance of epigenetic control for correct cell differentiation [3]. An important step in analyzing the developmental epigenetic regulation is to target genomic loci with the most prominent epigenetic changes upon differentiation.

Methods and Algorithms: The present work encompasses the data on genome spatial organization, chromatin openness, active enhancers, and gene expression of human embryonic stem cells (hESCs) and medial ganglionic eminence (MGE) progenitor cells. We developed an algorithm that considers the combined data to pinpoint the genes potentially important for GABAergic interneuron differentiation.

Results: Combined epigenetic data demonstrate drastic changes in chromatin organization between hESCs and MGE progenitors. These changes include reorganization of chromatin compartments, topologically associating domains, and chromatin openness. We find novel enhancers of *FOXG1* and *SOX6*, transcription factors known to be involved in GABAergic interneuron differentiation. Analysis of epigenetic landscape suggests novel genes that might be involved in differentiation of hESCs into MGE progenitors.

Conclusion: The transition from hESCs to MGE progenitors is accompanied by the dramatic changes in the epigenetic landscape that potentially mediate the differentiation process. These findings shed light on epigenetic control of GABAergic interneuron differentiation and may be further used to diagnose the interneuron dysfunction.

Acknowledgements: The study is supported by the RSF grant 21-74-10102. This is a joint study with Dr. Ana Pombo lab at Max Delbruck Center for Molecular Medicine, Berlin, Germany.

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