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The Dynamic Epigenetic Landscape of the Retina During Development, Reprogramming, and Tumorigenesis

Highlights

- Changes in histone modifications were more prominent than those in DNA methylation
- Epigenetic changes were more prevalent at differentiation genes than progenitors
- The retinoblastoma epigenome resembles the retina at a developmental transition
- Histone modifications are important for neuronal epigenetic memory in iPSCs

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In Brief

Aldiri, Xu, and colleagues show in this article how the epigenome of the mouse and human retina changes during development in coordination with transcriptional programs. They also relate those developmental changes to retinoblastoma and epigenetic memory in retina-derived iPSCs.

Aldiri et al., 2017, Neuron *94*, 550–568
May 3, 2017
http://dx.doi.org/10.1016/j.neuron.2017.04.022

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The Dynamic Epigenetic Landscape of the Retina During Development, Reprogramming, and Tumorigenesis

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http://dx.doi.org/10.1016/j.neuron.2017.04.022

SUMMARY

In the developing retina, multipotent neural progenitors undergo unidirectional differentiation in a precise spatiotemporal order. Here we profile the epigenetic and transcriptional changes that occur during retinogenesis in mice and humans. Although some progenitor genes and cell cycle genes were epigenetically silenced during retinogenesis, the most dramatic change was derepression of cell-type-specific differentiation programs. We identified developmental-stage-specific super-enhancers and showed that most epigenetic changes are conserved in humans and mice. To determine how the epigenome changes during tumorigenesis and reprogramming, we performed integrated epigenetic analysis of murine and human retinoblastomas and induced pluripotent stem cells (iPSCs) derived from murine rod photoreceptors. The retinoblastoma epigenome mapped to the developmental stage when retinal progenitors switch from neurogenic to terminal patterns of cell division. The epigenome of retinoblastomas was more similar to that of the normal retina than that of retina-derived iPSCs, and we identified retina-specific epigenetic memory.

INTRODUCTION

Changes in gene-expression programs mark progression from proliferating multipotent progenitor cells to terminally differentiated neurons. Recent studies of neurogenesis of human and mouse cortices (Lister et al., 2013), mouse photoreceptors (Mo et al., 2016), other mature neuronal classes (Mo et al., 2015), and neurons produced from stem cells in organoid cultures (Ziller et al., 2015) shed light on the changes that occur in the epigenome with the combination of transcriptome analysis, DNA methylation, and (in some studies) histone modification. The cell-type-specific epigenome of differentiated cells is thought to be relatively stable once established during development and is also thought to be a major barrier to reprogramming differentiated cells, such as neurons, into induced pluripotent stem cells (iPSCs) (Orkin and Hochedlinger, 2011). For some cell types, the resulting iPSCs retain an epigenetic memory of their cellular origins (Hiler et al., 2015; Kim et al., 2010) that can influence subsequent lineage-specific differentiation.

Developmental changes in the epigenome are also central to human disease. For example, childhood cancers are developmental tumors that arise during crucial periods of development. Neuroblastomas arise of the sympathoadrenal lineage (Cheung and Dyer, 2013), rhabdomyosarcomas emerge from the muscle lineage (Kashi et al., 2015), and osteosarcomas form during the period of rapid bone growth in adolescence (Kansara et al., 2014). Genomic characterization of more than 2,000 childhood cancers revealed that virtually every class of epigenetic