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The developing ocular lens: A practical paradigm for probing chromatin landscape and gene expression

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Gene accessibility integrated with the gene expression (Buenrostro et al., 2018) provide a powerful approach to uncover how nascent cells become functional tissues. A critical question is whether chromatin landscape markers and/or chromatin states are relevant to functional cell types. An excellent paradigm for addressing this question and demystifying the differentiation process is the well-studied ocular lens (Bloemendal, 1985; Coulombre and Coulombre, 1963; Piatigorsky, 1981).

A recent report by Disatham and colleagues (this volume) using ATAC-seq analysis of the early embryonic lens together with a related study in mice (Zhao et al., 2019) make a significant beginning to address this question. ATAC-seq (Assay for Transposase Accessible Chromatin sequencing (Buenrostro et al., 2015); data have the ability to provide panoramic, yet precise views of the open chromatin, regulatory elements, enhancers and active genes, providing an excellent moniker for cell identity (Corces et al., 2016).

The phenotype of a functional lens is transparency. It is composed of an anterior epithelium that differentiates on its edges into long elongated fiber cells, which make >90% of the volume of this tissue. The transition from the epithelium to fiber cells entails high expression of crystallins, proteins that generate transparency (Andley, 2007; Bassnett and Sikic, 2017). Every fiber cell has an identity characterized by its spatial state and specific gene activity that is innate to its refractive ability. At one temporal stage, the lens contains undifferentiated epithelial cells, nascent fiber cells (in the equatorial region), differentiating fibers in the cortical region (a transition zone of physiological/morphological activity) and terminally differentiated fiber cells in the center, the future visual axis. Each one of these cell states is highly accessible, attesting to the completeness of this paradigm.

In this recent paper, the Kantorow laboratory (Disatham et al.) have performed genome-wide analysis of four distinct, isolated, regions/states of differentiation in the chicken embryo lens by ATAC-seq and RNA-seq, correlating the accessibility data with expression profiling of 10, 000 genes. They examine epithelial cells at the lens surface, all the way to terminally differentiated fibers in its center. Fifty percent of the genes specific for a region show high Pearson correlation ($r = >0.7$) with altered chromatin accessibility; as the differentiation proceeds, the chromatin landscape changes. Two cytoskeleton protein genes (BFSP1 and BFSP2) that contribute to the structure of the lens and two transcription factors (PAX-6, epithelium preferred and HSF4, nascent fiber cell preferred) exemplify the rich information about the chromatin states and the gene activities, highlighting the "quality of accessibility" and therefore, the regulatory motifs and transcription factors not previously known or considered. Further, this regional accessibility is corroborated by the expression patterns of chromatin remodeling genes. A pioneering effort as this one not only exposes technical and conceptual lacunae, it also opens up the future challenges. The amount of information in the Disatham et al. manuscript is impressive and a good beginning. A caveat is that the regional data may mask significant heterogeneity, as revealed by single cell spatial analysis in the mouse lens (Gangalum et al., 2018). In the future, it would be appropriate to focus on distal and the proximal landscape features, which may relate to differential gene expression in different cell-types. In the end, this information will be essential to an understanding of how a gene activity may relate to its phenotype; this is not only true for a fiber cell in the lens, but also for a transformed cell in a tumor.

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