

2 March 2020

Dear Editor,

It is our pleasure to hereby submit a manuscript entitled *“Combined analysis of single cell RNA-Seq and ATAC-Seq data reveals regulatory toggles operating in native and iPS-derived retina.”* for publication in Nature Communications.

In this paper we report single cell RNA sequencing of murine native and iPS-derived neuroretina at four matched developmental stages spanning the emergence of the major retinal cell types. Moreover, we generate bulk ATAC-Seq data for three of the corresponding developmental stages both for native retina and organoids. The major contribution of this work - in our opinion - is the discovery of “regulatory toggles” that lock the transcriptomes of cells in mutually exclusive cell states through the operation of sets of activators and repressors. We reveal this by applying a novel approach in which we look for correlations across cell-types of vectors of enrichment/depletion for binding motifs corresponding to transcription factors that are dynamically regulated during retinal development. We make the unexpected observations that as much as halve of the transcription factors act mainly as repressors in the retina.

We further compare the developmental trajectories and associated transcriptomes between native retina and organoids and identify a number of differences that provide valuable insights with regards to perturbed biological pathways, transcription factors and regulatory toggles, which are complementing other recent publications in the field. We are providing evidence for the unsuspected origin of a new family of Trb1+ ganglionic cells as well as the re-specification of amacrine into both horizontal and photoreceptor precursor cells.


We strongly believe that this work will be of interest to the broad readership of Nature Communications.

We look forward to your response and remain,

Yours sincerely,



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