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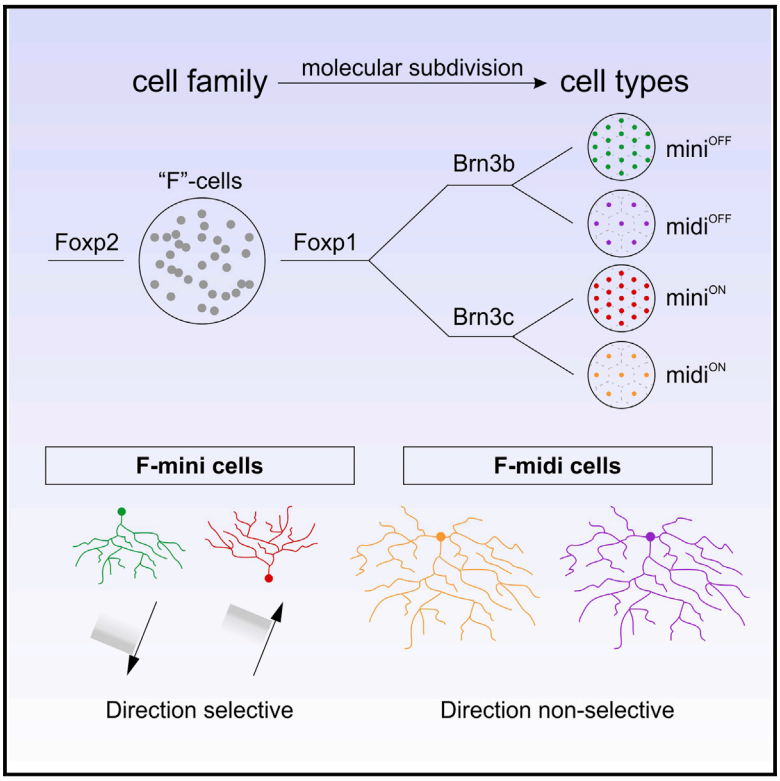
Two Pairs of ON and OFF Retinal Ganglion Cells Are Defined by Intersectional Patterns of Transcription Factor Expression

Graphical Abstract



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In Brief

The visual system depends upon the functioning of >30 retinal ganglion cell (RGC) types, many of which remain poorly characterized. Using intersectional labeling techniques in mouse and primate retina, Rousso et al. identify F-RGCs: two pairs of related cells that vary in size, distribution, and selectivity to directional motion.

Highlights

- Foxp2 expression marks F-RGCs, two mini and two midi types comprising two pairs
- Intersectional expression of *Foxp* and *Brn3* genes uniquely identifies each F-RGC type
- The two F-mini RGC types are unusually small, abundant, and direction selective
- Combinatorial expression of *Foxp* and *Brn3* genes also marks RGC types in macaque retina

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Two Pairs of ON and OFF Retinal Ganglion Cells Are Defined by Intersectional Patterns of Transcription Factor Expression

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SUMMARY

Visual information is conveyed to the brain by axons of >30 retinal ganglion cell (RGC) types. Characterization of these types is a prerequisite to understanding visual perception. Here, we identify a family of RGCs that we call F-RGCs on the basis of expression of the transcription factor *Foxp2*. Intersectional expression of *Foxp1* and *Brn3* transcription factors divides F-RGCs into four types, comprising two pairs, each composed of closely related cells. One pair, F-mini^{ON} and F-mini^{OFF}, shows robust direction selectivity. They are among the smallest RGCs in the mouse retina. The other pair, F-midi^{ON} and F-midi^{OFF}, is larger and not direction selective. Together, F-RGCs comprise >20% of RGCs in the mouse retina, halving the number that remain to be classified and doubling the number of known direction-selective cells. Co-expression of *Foxp* and *Brn3* genes also marks subsets of RGCs in macaques that could be primate homologs of F-RGCs.

INTRODUCTION

The vertebrate retina contains five neuronal classes: photoreceptors that transduce light into electrical signals, interneurons (bipolar, horizontal, and amacrine cells) that process the information, and retinal ganglion cells (RGCs) that transmit it to the rest of the brain through the optic nerve (Figure 1A) (Masland, 2012; Sanes and Zipursky, 2010). Each class is divided into multiple types, enabling the complex computations that result in different RGCs being tuned to distinct visual features such as contrast, color, or motion in a specific direction (Berson, 2008; Sanes and Masland, 2015). A full accounting of the types of RGCs and their functional properties is therefore prerequisite to understanding how the visual system works.

Initial classification schemes for RGCs in mice were based on their morphological properties (Badea and Nathans, 2004; Coombs et al., 2007; Kong et al., 2005; Sun et al., 2002; Völgyi et al., 2009), leading to identification of ~20 RGC types. Recently, these methods have been supplemented by molecular, genetic, and functional approaches (Badea and Nathans, 2011; Baden et al., 2016; Dhande and Huberman, 2014; Huberman et al., 2008; Kim et al., 2008; Tien et al., 2015), increasing the estimated number of RGC types to >30. Nonetheless, the total number is unclear, and nearly half of all RGCs in mice remain unknown or unclassified (Sanes and Masland, 2015).

To identify novel RGC types, we analyzed combinatorial expression of transcription factors (TFs), a strategy that has been useful for defining cell types in other parts of the CNS (Catela et al., 2015; Lodato and Arlotta, 2015). We screened retinas for expression of ~40 TFs and found that the forkhead/winged-helix domain protein Foxp2 was expressed by 20%–25% of RGCs, few (if any) of which corresponded to previously known types. Combinatorial co-expression of Foxp1 and the Pou4f factors, Brn3a-c, divided Foxp2^{+} RGCs (F-RGCs) into four discrete types that differ in size, dendritic lamination, and physiological responsiveness. They comprise a pair of small and abundant direction-selective RGCs, F-mini^{ON} and F-mini^{OFF}, and a pair of larger, less numerous, direction-non-selective RGCs, F-midi^{ON} and F-midi^{OFF} ("ON" and "OFF" refer to predominant responsiveness to increases and decreases in illumination level, respectively). F-RGCs comprise more than 20% of RGCs in the mouse retina, halving the number of RGCs that remain to be classified and characterized in mouse and doubling the number of known direction-selective RGCs.

Our molecular, morphological, and physiological analyses revealed several noteworthy features of F-RGCs. First, F-mini and F-midi RGCs each comprise an ON and OFF pair. Their relationship is reminiscent to the paramorphic pairs described in other species, which are defined as "neuronal cell types differing from one another mainly at the level of dendritic stratification but otherwise more similar to one another than to other types" (Berson, 2008). Paramorphism is a common feature of RGCs in many species (Berson, 2008; Famiglietti, 2004, 2005; Famiglietti and Kolb, 1976; Isayama et al., 2009) but has not been explored extensively in mice; F-RGCs enable future studies into its developmental origin. Second, the F-mini RGCs are direction selective. The computation of directional motion by retinal neurons is a topic of intense current interest. Most studies have focused on ON-OFF direction-selective RGCs (ooDSGCs), which acquire direction selectivity from starburst amacrine cells (Borst and Helmstaedter, 2015; Vaney et al., 2012). The F-mini RGC dendrites overlap little with those

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