

Teneurin-3 Specifies Morphological and Functional Connectivity of Retinal Ganglion Cells in the Vertebrate Visual System

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SUMMARY

A striking feature of the CNS is the precise wiring of its neuronal connections. During vertebrate visual system development, different subtypes of retinal ganglion cells (RGCs) form specific connections with their corresponding synaptic partners. However, the underlying molecular mechanisms remain to be fully elucidated. Here, we report that the cell-adhesive transmembrane protein Teneurin-3 (*Tenm3*) is required by zebrafish RGCs for acquisition of their correct morphological and functional connectivity in vivo. Teneurin-3 is expressed by RGCs and their presynaptic amacrine and postsynaptic tectal cell targets. Knockdown of Teneurin-3 leads to RGC dendrite stratification defects within the inner plexiform layer, as well as mistargeting of dendritic processes into outer portions of the retina. Moreover, a subset of RGC axons exhibits tectal laminar arborization errors. Finally, functional analysis of RGCs targeting the tectum reveals a selective deficit in the development of orientation selectivity after Teneurin-3 knockdown. These results suggest that Teneurin-3 plays an instructive role in the functional wiring of the vertebrate visual system.

INTRODUCTION

In the vertebrate retina, retinal ganglion cells (RGCs) develop stereotypic dendritic arborization patterns and make specific synaptic connections with amacrine and bipolar cells in the inner plexiform layer (IPL) (Masland, 2012). The formation of such precise connections is critical for the processing of visual information and the generation of feature selectivity in RGCs (Golisch and Meister, 2010; Wässle, 2004). A key structural characteristic of visual circuits is the organization of connections into precise laminae (Roska and Werblin, 2001; Sanes and Zipursky, 2010). Recent studies have shown that the assembly of neuropil strata in the IPL is regulated by both adhesive (Yamagata and Sanes, 2008) and repulsive transmembrane proteins (Matsuoka et al.,

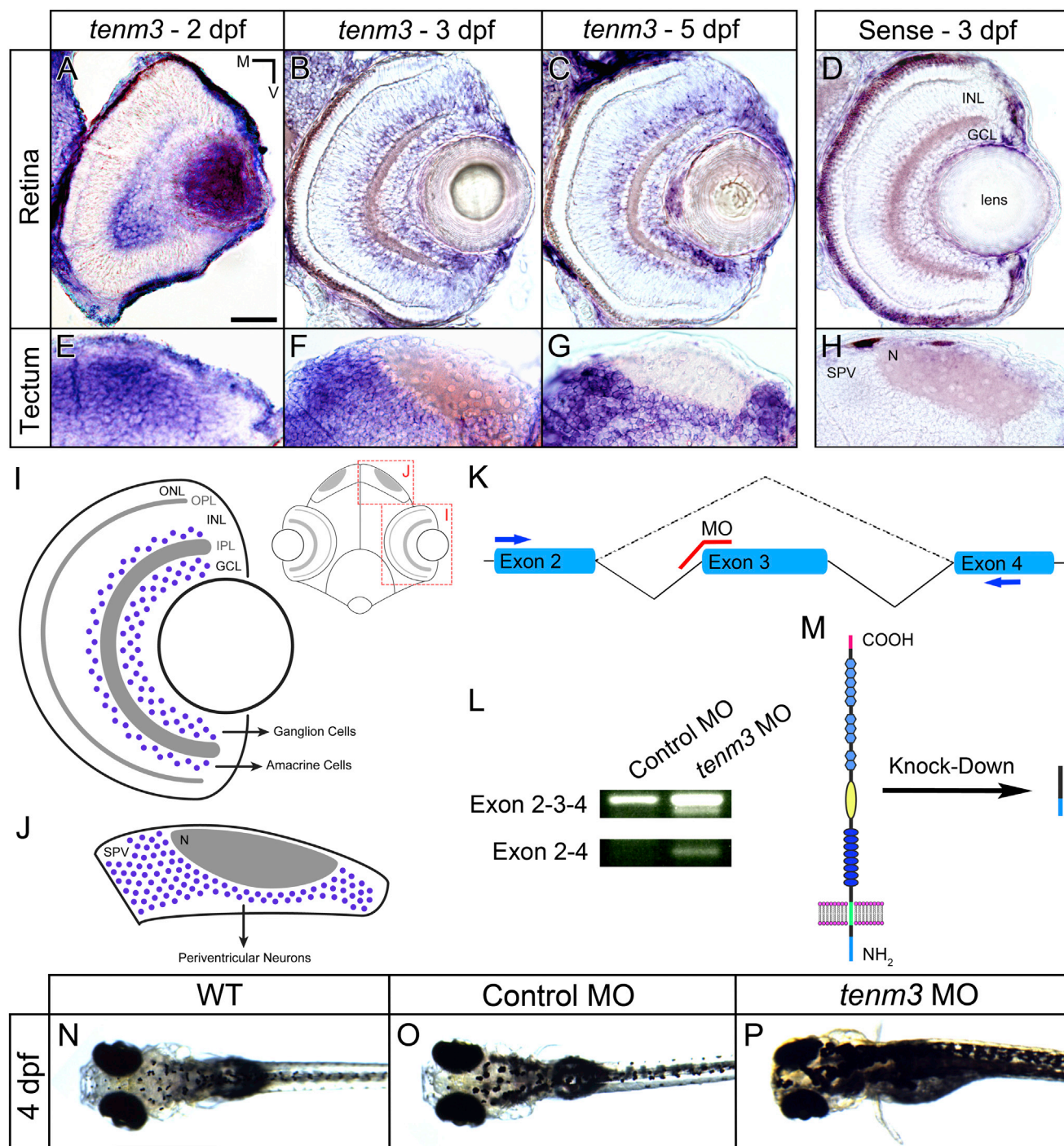
2011). Similarly, such attractive and repulsive cues are also crucial in establishing specific connectivity between RGC axons and their targets in the brain (Osterhout et al., 2011; Xiao et al., 2011). Our understanding of the molecular mechanisms that specify connections within the retina and between the retina and retinorecipient nuclei in the brain, however, is still far from complete.

Teneurins (Ten-m/Odz) are a phylogenetically conserved family of type II transmembrane proteins (Tucker et al., 2012; Tucker and Chiquet-Ehrismann, 2006). Their large extracellular domain contains eight epidermal growth factor (EGF)-like repeats, multiple tyrosine and aspartate (YD) repeats and five NHL (NCL-1, HT2A, and Lin-41) repeats, which mediate homophilic recognition and adhesion (Beckmann et al., 2013). In vertebrates, these proteins are encoded by four genes, *teneurin 1–4* (also called *odz1–4*), expressed in distinct and often interconnected regions of the nervous system (Tucker and Chiquet-Ehrismann, 2006). In *Drosophila*, the role of teneurins in synaptic partner matching and target choice has been elegantly shown in the olfactory system (Hong et al., 2012) and at the neuromuscular junction (Mosca et al., 2012). In mice, teneurins regulate the generation of binocular visual circuits by controlling the development of ipsilaterally projecting RGCs (Dharmaratne et al., 2012; Leamey et al., 2007; Young et al., 2013). However, a role for teneurins in mediating synapse-specific functional wiring in the vertebrate visual system has yet to be demonstrated.

Here, we investigate the role of *teneurin-3* (hereafter referred to as *tenm3*) in shaping the morphological and functional connectivity of RGCs in vivo using zebrafish. We report that *tenm3* is expressed in RGCs, amacrine cells, and the main retinorecipient target in the brain, the optic tectum. We show that *tenm3* knockdown induces stratification and targeting errors of both dendrites and axons in a subset of RGCs. In support of this, we provide evidence showing that orientation-selective, but not direction-selective, responses are impaired in *tenm3* morphants, suggesting that *tenm3* is involved in wiring subsets of functionally defined visual circuits.

RESULTS

Our study focused on time points between 2 days postfertilization (dpf) and 5 dpf, a period during which RGCs undergo a rapid



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