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Review

Astrocyte structural reactivity and plasticity in models of retinal detachment

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ABSTRACT

Although retinal neurodegenerative conditions such as age-related macular degeneration, glaucoma, diabetic retinopathy, retinitis pigmentosa, and retinal detachment have different etiologies and pathological characteristics, they also have many responses in common at the cellular level, including neural and glial remodeling. Structural changes in Müller cells, the large radial glia of the retina in retinal disease and injury have been well described, that of the retinal astrocytes remains less so. Using modern imaging technology to describe the structural remodeling of retinal astrocytes after retinal detachment is the focus of this paper. We present both a review of critical literature as well as novel work focusing on the responses of astrocytes following rhegmatogenous and serous retinal detachment. The mouse presents a convenient model system in which to study astrocyte reactivity since the Müller cell response is muted in comparison to other species thereby allowing better visualization of the astrocytes. We also show data from rat, cat, squirrel, and human retina demonstrating similarities and differences across species. Our data from immunolabeling and dye-filling experiments demonstrate previously undescribed morphological characteristics of normal astrocytes and changes induced by detachment. Astrocytes not only upregulate GFAP, but structurally remodel, becoming increasingly irregular in appearance, and often penetrating deep into neural retina. Understanding these responses, their consequences, and what drives them may prove to be an important component in improving visual outcome in a variety of therapeutic situations. Our data further supports the concept that astrocytes are important players in the retina's overall response to injury and disease.

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1. Introduction

Retinal astrocytes, are generally not considered particularly reactive cells when compared to the large radial Müller glia (Fisher and Lewis, 2003; Fisher et al., 2005; Reichenbach and Bringmann, 2013; Smith et al., 1997; Vogler et al., 2014). Indeed, since their first descriptions by neuroanatomists such as Ramón y Cajal, Golgi, Virchow, and Deiters in the mid-19th century, the exact functionality of astrocytes in the central nervous system (CNS) has been controversial. These cells were initially referred to as "connective tissue" or as their name implies, "nerve glue" (Kettenmann and Verkhratsky, 2008; Somjen, 1988). However, as technology has improved, more precise descriptions of their roles have emerged: i.e., their functional roles in development, synaptic function and plasticity, the blood-brain/retina barrier, injury responses, learning, memory, and even the regulation of breathing (Chung et al., 2013; Fields et al., 2014; Gourine et al., 2010; Pearson-Leary et al., 2015). However, fundamental questions remain such as whether astrocytes within a defined region of the CNS comprise a homogenous population (Zhang and Barres, 2010). One of the best-studied features of brain and spinal cord astrocytes is their "reactivity" following injury or in neurodegenerative disease or injury, including the prominent formation of "glial scars" (Buffo et al., 2010; Pekny and Pekna, 2014; Sofroniew, 2009). However questions remain about the exact roles and mechanisms of action in this well-described situation. Reactivity by retinal astrocytes has received less attention because of the more obvious responsiveness of the larger Müller cells (Charteris et al., 2002; Eibl et al., 2007; Erickson et al., 1983; Sethi et al., 2005). Simple PubMed searches with key phrases "astrocytes, brain and/or spinal cord injury" or "astrocytes and retinal injury" return 641 references for the former and 245 for the latter between 1975 and 2016. Comparatively, the much smaller retinal astrocytes with their very fine processes, have proven more difficult to study. There is, however, recent data indicating that optic nerve head (ONH) astrocytes undergo important structural remodeling in glaucoma and optic nerve crush (Lye-Barthel et al., 2013; Sun and Jakobs, 2012; Sun et al., 2010). Here we provide a study of the normal structure of astrocytes in a variety of species and show that they undergo significant remodeling after retinal detachment, thus providing further evidence that the reactivity of these cells is worthy of additional study.

Studies in the uninjured cerebral cortex and hippocampus demonstrate that protoplasmic astrocytes anatomically tile, each occupying distinct spatial domains that do not change size in

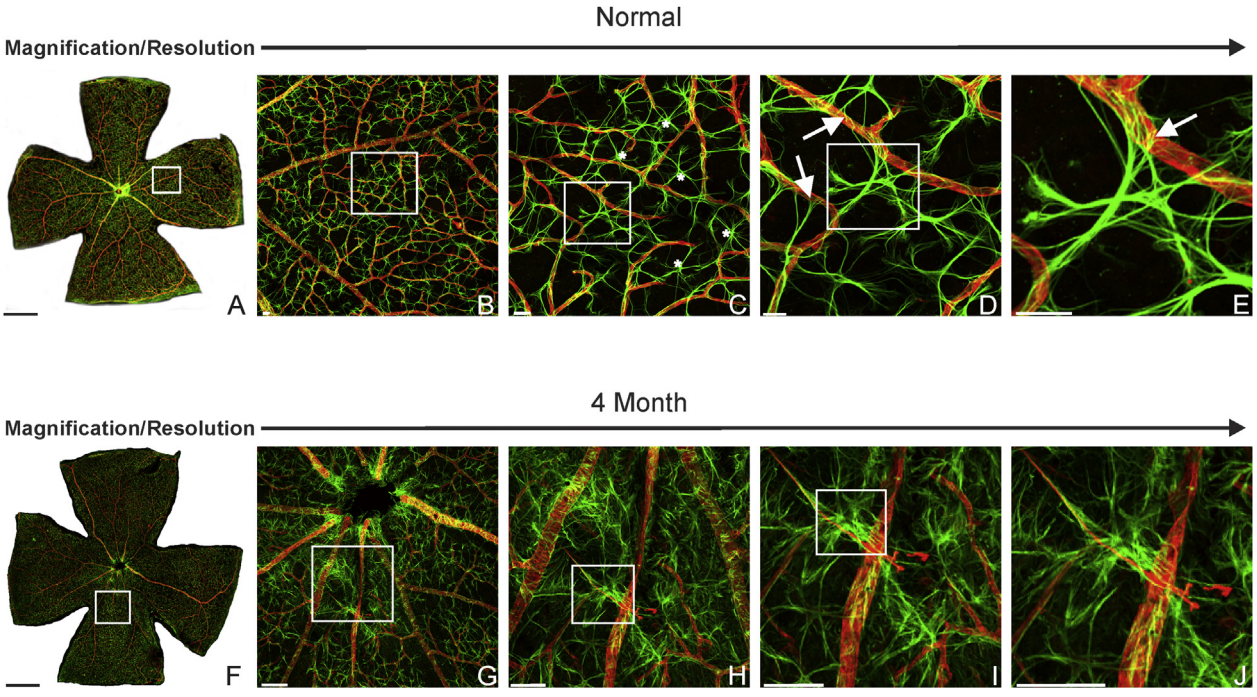

Fig. 1. Images from high-resolution montages using wholemounts of mouse retina stained with anti-GFAP (green, astrocytes), and anti-collagen type IV (red, blood vessels). **A**–**E**. Examples from a wholemount of normal retina. In the normal retina, processes of the smooth. Well-defined stellate-shaped (intravascular) astrocytes (examples marked by asterisks in A3) make discrete contacts (arrows, **D**, **E**) on blood vessels. **F**–**J**. Examples from a wholemount of a retina detached for 4 months. Sequential images in A–E and F–J show selected areas (white boxes) from the wholemounts in increasing magnification. After four months of retinal detachment astrocytes show dramatic changes in the GFAP staining. These cells lose their smooth stellate shape with their processes appearing "frayed" and making more branched and diffuse contacts with blood vessels. Scale bars = 200 μm (A1, B1), 20 μm (A2-5, B2-5).