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Macromolecular markers in normal human retina and applications to human retinal disease

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ABSTRACT

Macromolecular cell markers are essential for the classification and characterization of the highly complex and cellularly diverse vertebrate retina. Although a plethora of markers are described in the current literature, the immunoreactivity of these markers in normal human tissue has not been fully determined. This is problematic as they are quintessential to the characterization of morphological changes associated with human retinal disease. This review provides an overview of the macromolecular markers currently available to assess human retinal cell types. We draw on immunohistochemical studies conducted in our laboratories to describe marker immunoreactivity in human retina alongside comparative descriptions in non-human tissues. Considering the growing number of eye banks services offering healthy and diseased human retinal tissue, this review provides a point of reference for future human retina studies and highlights key species specific disease applications of some macromolecular markers.

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1. Introduction

Historically, our understanding of the anatomy of the human retina has been possible through the study of post-mortem eyes and extrapolation of information from animal eyes including rodents, rabbit, cat, dog, pig and monkey. Mammalian tissues have been useful in providing insights into the anatomical and functional features of the human retina in health and disease. Studies using human retina are increasing due to a growing number of eye banks supplying tissues for research to industries and academics (Eye Bank Association of America statistical report, 2014) or collaboration with ophthalmologists to obtain biopsy tissues during ocular surgery (de Souza et al., 2013; de Souza et al., 2012a, b, c). In addition, through advances in post-mortem OCT imaging (Brown et al., 2009; Curcio, 2005) fundus imaging correlation with histopathology has been possible (Chen et al., 2006). This growing availability of human tissue for research allows for morphological and functional investigations of the human retina.

Retinal tissue is commonly characterised using cell markers that label specific neurons or glia. These markers are also used to assess retinal disease changes such as loss or migration of retinal cell bodies, sprouting or pruning of neuronal processes and activation of specific disease pathways such as gliosis (Bringmann et al., 2006; Cuenca et al., 2014; Marc et al., 2003; Strettoi et al., 2002). Despite similarities in retinal anatomy between human and other animal species, cell marker immunoreactivity appears to be more varied. For example, parvalbumin, a robust marker for the *AII* amacrine cell in the rodent and rabbit retina (Casini et al., 1995; Wässle et al., 1993), mostly labels horizontal cells in monkey (*Cercopithecus*

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aethiops) and human retina (Nag and Wadhwa, 1996; Rohrenbeck et al., 1987). Descriptions of cell markers for the human retina are scattered through the literature (e.g. Chiquet et al., 2002; Crooks and Kolb, 1992; Curcio et al., 1991; de Souza et al., 2012a, b, c; Haverkamp et al., 2003; Lee et al., 2015; Nag and Wadhwa, 1996). Thus, a complete description of cell markers for the normal human retina is needed for more efficient assessment of human retina and correct identification of anatomical and functional changes which may occur secondary to retinal disease.

This review provides an overview of macromolecular markers currently available for cell types of the human retina. We collate descriptions from current literature and results from our own laboratories using normal human mid-peripheral retina tissue (de Souza et al., 2012a; de Souza et al., 2012b, c) to provide a succinct overview of cell markers available for the normal, non-complicated human retina. We also provide examples of the use of these markers in assessing retinal remodelling in human rhegmatogenous retinal detachment. Overall, this review serves as a point of reference for future studies on healthy and pathological human retinal tissue.

2. Macromolecular markers for the through pathway

The mammalian retina contains more than 60 types of neurons organized into 5 major classes: photoreceptors (3–4 types), bipolar cells (~12 types), ganglion cells (~18 types), horizontal cells (2–3 types), amacrine cells (~30 types; Kolb et al., 1992; Masland, 2001). These cells function as the neural pre-processing element of the visual system and signal via two pathways. The vertical signalling pathway, composed of photoreceptors, bipolar cells and ganglion cells is termed the "through" pathway and employs the fast excitatory neurotransmitter glutamate (Marc, 2011; Massey and Redburn, 1987). Horizontal cells and amacrine cells comprise the "lateral" pathway and modulate vertical signal flow using fast inhibitory neurotransmitters γ-aminobutyric acid (GABA) and glycine (Massey and Redburn, 1987). These pathways can be further divided based on the two major photoreceptor types into the rod and cone pathways (Fig. 1). The rod and cone pathways are associated with specific bipolar cell, amacrine cell and ganglion cell subtypes which process different aspects of visual stimuli (Fig. 1). Glia of the retina include Müller cells, microglia and astrocytes; the former playing a vital role in the neuronal function (Bringmann et al., 2006).

2.1. Photoreceptors

Photoreceptors function as the first point of the through pathway, converting incoming light into an electrical signal that can ultimately be transmitted to the visual cortex. Upon light activation, visual photopigments within the photoreceptor outer segment trigger a signalling cascade called phototransduction, leading to photoreceptor hyperpolarization (Baylor et al., 1979; Dacheux and Miller, 1976; Lamb and Pugh, 2004). Hyperpolarisation reduces the release of glutamate neurotransmitter at the photoreceptor synaptic terminal and leads to signal transduction to second order neurons.

Photoreceptors can be identified using markers against the opsin proteins found within photopigments (Curcio et al., 1991; de Souza et al., 2012a; Fariss et al., 2000; Lerea et al., 1989; Li et al., 1995; Shelley et al., 2009). Specifically, rods can be labelled with antibodies against rhodopsin, 'red' and 'green' or long-wavelength-sensitive (L) and medium-wavelength-sensitive (M) cones can be labelled with L/M opsin and 'blue' or short-wavelength-sensitive (S) cones, cones can be labelled with S opsin. Fig. 2A shows examples of these cell makers in human mid-peripheral retina. Retinal samples were obtained from enucleated donor eyes we have previously characterised as normal human retina (de Souza et al., 2012a, b, c). For all opsin markers, immunoreactivity is most obvious in the photoreceptor outer segments where the majority of the photopigment is localized. Alterations to opsin location can be an indicator of retinal remodelling and dysfunction (see section 7).

Other proteins in the phototransduction pathway such as transducin (Lerea et al., 1989), arrestin (John et al., 2000), guanylyl cylase-activating proteins (Cuenca et al., 1998) and recoverin (Haverkamp et al., 2003) can also be effective markers for photoreceptors (Fig. 2B). Calbindin, a calcium binding protein, can specifically label L/M cone photoreceptors (Chiquet et al., 2002) although Haley et al. (1995) showed an eccentricity related calbindin D-28K immunoreactivity of cones in the peripheral retina and reduced or absent labelling in fovea and perifovea. In addition, unlike L/M cone opsin, calbindin immunoreactivity is more prominent in the inner segment and cell body of L/M cones than the outer segment (Fig. 2B). Co-localisation of cell markers for rod and cones also highlights the differences in cell body location for each photoreceptor - cones located along a single layer in the distal ONL whilst rods are found throughout the ONL.

2.2. Bipolar cells

Bipolar cells conduct the visual signal from photoreceptors to cells of the through and lateral pathways in the inner retina

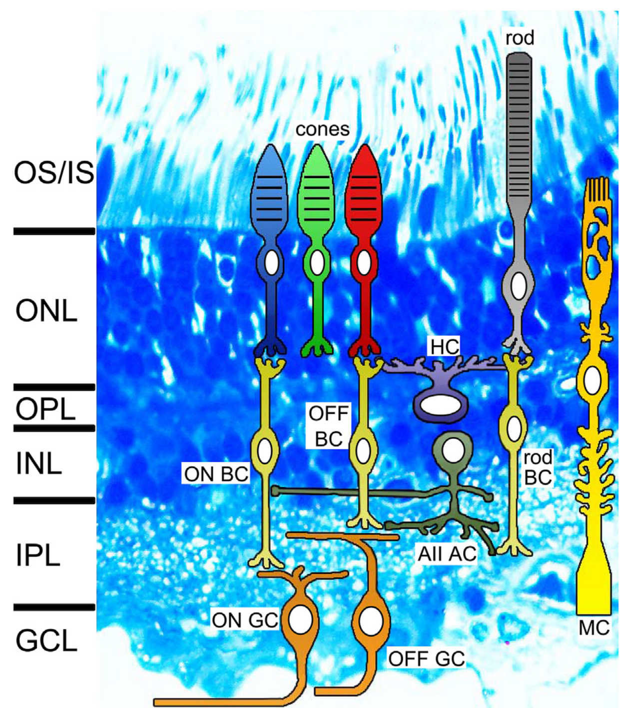

Fig. 1. Schematic diagram of the human retina. Five types of neurons compose the mammalian retina: photoreceptors (rods and three cone types), horizontal cells (HCs), bipolar cells (BCs), amacrine cells (ACs) and ganglion cells (GCs). These cells form the cone pathway where cone photoreceptors signal both ON and OFF cone bipolar cells which connect with ON and OFF ganglion cells respectively. The rod pathway is formed by rod photoreceptors connecting with rod bipolar cells. Rod BCs in turn connect with *AII* amacrine cells which connect with ON and OFF ganglion cells. Horizontal cells and amacrine cells allow for information modulation in both pathways. Müller cells (MCs), the main glia of the retina, span the whole retina. Abbreviations: OS/IS, outer and inner segments of rods and cones; ONL, outer nuclear layer; OPL, outer plexiform layer; INL, inner nuclear layer; IPL, inner plexiform layer; GCL, ganglion cell layer; NFL, nerve fibre layer.

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