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Müller Cell Molecular Heterogeneity: Facts and Predictions

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Abstract

The retina was historically considered as an "approachable part of the brain"; advantageous, for its simplicity, to use as a model organ for deciphering cellular and molecular mechanisms underlying physiology and pathology of the nervous system. However, the most relevant discoveries arise precisely from unveiling the complexity of the retina. A complexity that partially relies on the layered organization of an extended variety of specialized neuronal and glial cellular types and subtypes. Based on functional, morphological or transcriptome data, over 40 subtypes of retinal ganglion cells or 60 subtypes of retinal amacrine cells have been described. A high degree of specialization, that may lead to segregation into functionally diverse subtypes, is also conceivable for Müller cells, a pleiotropic glial component of all vertebrate retinas. The essential role of Müller glia in retinal homeostasis maintenance involves participation in structural, metabolic and intercellular communication processes. Additionally, they are the only retinal cells that possess regenerative potential in response to injury or disease, and thus may be considered as therapeutic tools. In the assumption that functional heterogeneity might be driven by molecular heterogeneity this review aims to compile emerging evidence that could broaden our understanding of Müller cell biology and retinal physiology.

Summary statement

Müller glial cells exert multiple essential functions in retinal physiology and retinopathies reflecting perhaps the existence of distinct Müller cellular subpopulations. Harnessing Müller cell heterogeneity may serve to enhance new therapeutic approaches for retinal disease.

Keywords

molecular heterogeneity, retina, stem cell, transcriptome

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Introduction

Müller cells are the main glial component of the retina and account for approximately 16% of the total number of retinal cells (Jeon et al., 1998). Both from anatomical and functional perspectives, the retina is considered to be built up by columnar units consisting of one Müller cell and a species-specific number of neurons (Reichenbach et al., 1993). Müller cells expand all the thickness of the retina and interact with retinal neurons to fulfill multiple functions that include neuronal support and nutrition, blood retinal barrier maintenance, and modulation of retinal synaptic activity by release and recycling of glio- and neuro- transmitters (excellently reviewed in Reichenbach & Bringmann, 2020; Vecino et al., 2016). While most of these functions are highly conserved from invertebrates to humans, an outstanding full regenerative capacity of Müller cells seems to be restricted to some teleost fish and amphibians such as zebrafish (*Danio rerio*) *or Xenopus laevis* (Langhe et al., 2017; Wan & Goldman, 2016). Although mammalian Müller glia appears to be able express the same molecular machinery involved in retinal regeneration in other species, so that they can awake a certain potential to reprogram and regenerate (reviewed in Salman et al., 2021), their efficiency is very limited.

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Notorious inter-species differences have since long been attributed to morphology (Ramón y Cajal, 1892), location in the peripheral or central retina (Boije et al., 2010), vascularization versus avascularization (Chidlow et al., 2019), adaptation to dim or intense light conditions (Karl et al., 2018), presence or absence of classical glial Kir 4.1 channels (Zayas-Santiago et al., 2014), or existence of a fovea (Reichenbach & Bringmann, 2020).

More subtle, but equally crucial differences, between individual cells in a single species suggest that Müller glia represent a heterogeneous group of cells. Heterogeneity may underly distinct functional capacities such as the activation of specific signal transduction pathways in response to a certain signal or the ability to mount a regenerative reaction.

To the best of our knowledge, at present human Müller cells are formally subdivided in only two categories associated to their presence in the central foveola or in the surrounding foveal walls (Reichenbach & Bringmann, 2020). Apart from regionalization, both subtypes differ in macular pigment content; Glial Fibrillary Acidic Protein (GFAP), Glutamine synthetase (GS) and glutamate transporter (GLAST) expression; neuronal support and capacity to improve light transmission (Reichenbach & Bringmann, 2020). In zebrafish, three populations of Müller glia may be distinguished by the combined expression of Stat3-Ascl1 in response to damage (Nelson et al., 2012).

However, Müller cell heterogeneity regarding many other aspects, including a differential genetic and epigenetic regulation of gene expression is revealed constantly in the specialized literature. Nonetheless, the scattered information has not allowed a proper understanding of the functional implication of these observations or the pertinence of a further subclassification of this cell type. In this review, we will compile reported data regarding Müller cell molecular differences and their associated functional features. We will also dare to advance some predictions regarding the application of a more profound knowledge of Müller glia complexity.

Müller Cell Molecular Heterogeneity: Facts

Authors of the earliest detailed profile of the Müller glia transcriptome at the single cell level (Roesch et al., 2008), already highlighted a certain degree of heterogeneity regarding the expression of house-keeping genes, Chx10 or Rlbp1. However, at the same time, these authors pointed out the limited knowledge about the significance and extent of this heterogeneity. Since then, accumulating reports reinforce the notion that Müller glia subpopulations may exist; and molecular discrepancies within these subpopulations may be contemplated from a functional perspective regarding well-known specific roles of Müller glia in the retina (Table 1).

Positional Considerations

As mentioned before, a large allowance in gene expression disparities relates to positional differences both through development and adulthood (Nelson et al., 2012; Reichenbach & Bringmann, 2020; Yamagata et al., 2021). Indeed, a complete atlas of the E18 chick retina based on single cell RNA sequencing has been recently reported that demonstrates the existence of distinct clusters of specific gene expression that reveal a positional foundation for the transcriptomic heterogeneity of Müller glia (Yamagata et al., 2021).

In vivo studies had previously demonstrated that Pax2, a paired homeobox family member involved in retinal morphogenesis, develops a restricted pattern of expression in the chicken retina that is maintained through adulthood and distinguishes central Pax2 + and peripheral Pax2- populations (Boije et al., 2010). The authors suggested possible functional consequences related to the existence of these two subclasses, but they ruled out a direct effect on the Müller cell proliferative or damage response. In human retinas, the differential expression of the PHGDH gene in Müller cells from the highly specialized macula served to reveal a higher susceptibility of macular cells to oxidative stress with respect to peripheral cells (Zhang et al., 2019). In addition, polyamines like the gliotransmitters spermine and spermidine, which maintain a predominant role of Müller cells such as potassium homeostasis, also display a significant retinal center versus periphery heterogeneity (Skatchkov et al., 2000).

Metabolic Considerations and Response to Light

Seminal articles described years ago that, in the chick retina at specific age points, only a subpopulation of Müller cells were able to respond to extracellular ATP with an increase of intracellular calcium concentration, and associated this observation with the developmentally regulated pattern of expression of the purinergic receptors P2Y (Uckermann et al., 2002).

In an excellent recent review, Pfeiffer et al. highlight an important fact: while the healthy Müller cells show a remarkably precise metabolic homogeneity, upon degeneration, stress or disease Müller cells diverge into numerous separable subclasses of metabolic phenotypes (Pfeiffer et al., 2020). Variable metabolites, enzymes and related proteins include polyamines, taurine, glutamate, glutamine, GS and CRALBP, all essential to normal Müller cell performance (Biedermann et al., 1998; Pfeiffer et al., 2016; Skatchkov et al., 2000). Many questions remain unanswered as to the mechanisms driving metabolic heterogeneity in disease and the observations point more to the appearance of individual metabolic profiles than to the existence of distinct Müller cell populations. Further studies are required to explore this crucial aspect of Müller cell physiology.

An exciting novel role for Müller glia in retinal physiology comes from the description of light-driven responses in chicken cultures that are sustained by the expression of specific opsins (Marchese et al., 2022; Rios et al., 2019). Interestingly, three subpopulations may be distinguished with respect to the intensity of the response to this stimulus.

Table 1. Müller Cell Molecular Heterogeneity.

Gene/protein	Biological process	Heterogeneity	Species	Reference
Bing4/Prss2/Ube1C/ GNB1l	Müller-specific transcripts Progenitor marker	Detected in 3 out of 5 cells analyzed[1] 4 out of 5 cells[1]	Mice	Roesch et al., 2008 Roesch et al., 2008
Pax6	Functional component of visual cycle	70% of the cells[2]		Rowan & Cepko, 2004
Rlbp1		4 out of 5 cells[1]		
CHx10	Cell differentiation	Subpopulation in vivo[3]		
Pax2	Development	Restricted to centrally located cells	Chicken Zebrafish	Boije et al., 2010
Notch	Embryonic develop. Retinal regeneration	Higher expression in peripheral cells	Chicken	Ghai et al., 2010
CD44	Cell-Matrix interaction	Restricted to peripherally located cells[4]	Human	Too et al., 2017
PHGDH	de novo serine metabolism	Higher expression in macular Müller cells[5]	Human	Zhang et al., 2019
Clusters	Various	Positional restriction[5]	Chicken	Yamagata et al., 2021
P2Y	Neuron-glia communication ATP response	Only a percentage (*in vivo* and in culture)	Chicken	Uckermann et al., 2002
Taurine	Metabolism	Variable express. in neighboring Müller glia during retinal deg.	Rabbit	Pfeiffer et al., 2016
Glutamate Glutamine GS /CRALBP Endogenous Polyamines	Potassium homeostasis	Center vs periphery[4]	Frog	Pfeiffer et al., 2020 Skatchkov et al., 2000
Opsins	Response to light	Three distinct subpopulations in culture	Chicken	Rios et al., 2019 Marchese et al., 2022
Genes associated to AMD FTH1 FTL	Pathology Iron homeostasis	Subpopulation 1 Subpopulation 2	Human	Menon et al., 2019
Stat 3 / Ascl1	Response to damage	Subpopulation *in vivo*[3]	Zebrafish	Nelson et al., 2012
GS/ GFAP	Müller cell marker Response to damage	Subpopulation in primary culture[3]	Rat Pig	Vecino et al., 2016
Nestin Synemin	Cytoskeleton reorganization in response to damage	Increased expression in a subpopulation in culture[3]	Rat	Luna et al., 2010
Fyn kinase	Cell adhesion, proliferation	Expressed by a subpopulation in vivo and in culture[3]	Mice	Chavez-Solano et al., 2016

[1] Single cell microarray; [2]in situ hybridization; [3]immunofluorescence; [4]immunohistochemistry; [5]RNA sequencing. Abreviations: Ascl1,Achaete-scute homolog 1; Bing4, WD repeat containing protein (also known as WDR46); CD44, Cluster of differentiation 44; Chx10, CEH10 homeodomain-containing homolog (also known as VSX2); CRALBP, Cellular retinaldehyde–binding protein; FTH1/FTL, Ferritin heavy/light chain; GFAP, Glial fibrillary acidic protein; GLAST, Glutamate aspartate transporter; GNB1l, G protein subunit beta 1 like; GS, Glutamine synthetase.

Pathology and Aging: Regenerative and non-Regenerative Response to Damage

The evaluation of the behavior of Müller cells through disease has also yield an insight into molecular heterogeneity. Initial studies in two different mouse models of retinitis pigmentosa revealed differential expression of multiple transcripts among individual cells although a functional correlation between diverse subpopulations could not be provided (Roesch et al., 2012). A recent seminal study aiming to test the association between heterogeneous Müller subpopulations and the progression of age-related macular degeneration (AMD) features what we consider to be the most daring functional hypothesis based on the observed molecular differences (Menon et al., 2019). Thus, it has been proposed that the subpopulation-restricted expression of proteins with a central role in iron homeostasis or of regulators of the inflammatory response may attribute a crucial role for these subpopulations in AMD pathophysiology (Menon et al., 2019).

The fact that Müller glia presents an heterogenous response to damage has attracted considerable attention since understanding these responses may be instrumental to decipher the reason behind the impairment of the regenerative capacity of mammalian Müller glia or even the tool to awake a dormant neurogenic capacity in these same cells. Consecutive processes follow retinal injury. Initial steps, common to regenerative and non-regenerative species, encompass a rapid modification of Müller cell morphology sustained by

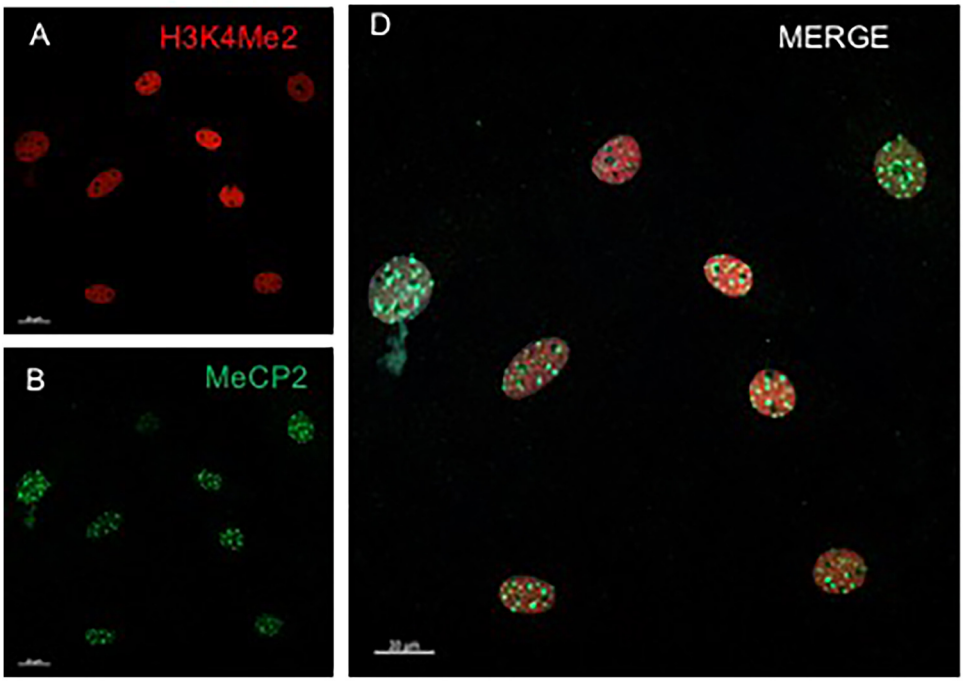

Figure 1. Immunofluorescence revealing the epigenetic diversity in müller glial cells. Immunoreactivity to H3K4Me3 (Millipore Cat# 07-473, RRID:AB_1977252) and MeCP2 (Sigma-Aldrich Cat# M6818, RRID:AB_262075) was evaluated in mouse Müller glia primary cultures at third passage following the standardized protocol from manufacturers.

an increased expression of intermediate filaments such as nestin, synemin or GFAP. A great variability among individual Müller cells with respect to the expression of these proteins have been demonstrated in rat and pig cell cultures (Luna et al., 2010; Vecino et al., 2016). Subsequently, specific changes in gene expression sustain the occurrence of molecular mechanisms that lead either to a regenerative dedifferentiation, acquisition of a stem cell-like phenotype, proliferation, migration and neuronal differentiation programs or to a non-regenerative gliotic response (García-García et al., 2020; Graca et al., 2018). In the gold-standard animal model for retinal regeneration, the zebrafish, the induction of the expression of transcription factor Stat3 in subsets of Müller glia define the existence of populations with different proliferative and regenerative capacities (Nelson et al., 2012). In human and chicken Müller cells the restricted peripheral expression of CD44, a cell surface glycoprotein, and the increased expression of Notch pathway-associated genes have been associated to a potential stem-cell favoring environment and a greater transdifferentiation capacity (Ghai et al., 2010; Too et al., 2017).

Furthermore, after dedifferentiation achievement of efficient retinal regeneration in the zebrafish requires Müller glia nuclei migration. The relevance of cell to cell adhesion in this process has been demonstrated (Nagashima et al., 2013). In this sense, the differential expression of Fyn kinase and its effect on the processes on cell adhesion and proliferation has been demonstrated in subpopulations of mice Müller cells in vivo and in culture although its effect on the regenerative capacity of Müller glia has not been explored (Chavez-Solano et al., 2016).

Epigenetic Considerations

The research effort towards unveiling the critical mechanisms that drive retinal regeneration in some species but impair this end in mammalian cells is rapidly turning to the evaluation of epigenetic landscapes in Müller cells. From early and seminal works in zebrafish the notion that DNA methylation, histone acetylation or microRNAs modulate the regenerative capacity of Müller glia arose (Mitra et al., 2018; Powell et al., 2012, 2013; Ramachandran et al., 2010; Thummel et al., 2006). These observations have been confirmed and enriched in other experimental models including rodent and human cells (Georgi & Reh, 2010; Jorstad et al., 2017; Reyes-Aguirre & Lamas, 2016). To our knowledge, the heterogeneity in the epigenetic responses in Müller cells has received scant attention, but our own preliminary unpublished observations using mice Müller cell primary cultures reveal epigenetic diversity translated into different degrees of immunoreactivity of histone and DNA methylation marks (H3K4Me3: Histone H3 trimethylated at lysine 4; and MeCP2: Methyl-CpG binding protein 2) within individual cells (Figure 1). If this is indeed the case, a further characterization of this feature will perphaps shed a light upon the need for a potential molecular-based functional subclassification of Müller cells.

Müller Cell Molecular Heterogeneity: Predictions

Heterogeneity among, what up-to-now are considered as, specific cell types is becoming a commonplace. Development of high-throughput single-cell transcriptomic profiling techniques has allowed comprehensive and high-resolution descriptions of retinal cell diversity in mouse, chicken and human (Lukowski et al., 2019; Macosko et al., 2015; Shekhar et al., 2016; Voigt et al., 2019; Yamagata et al., 2021). Multiplicity has been demonstrated for the neuronal population: photoreceptors, amacrine cells, ganglion cells, amacrine cells, they all have been subclassified in number that account for more than 150 classes in average (Macosko et al., 2015; Peng et al., 2019; Rheaume et al., 2018; Shekhar et al., 2016; Tran et al., 2019; Yamagata et al., 2021; Yan et al., 2020). As for the macroglial populations of the retina, astrocytes reveal an extensive molecular heterogeneity in health and disease (Miller, 2018), and Müller cells are in the same pathway.

A pressing endeavor at this time must be establishing a proof of concept for distinct functional contributions of putative Müller cellular subsets. This should be facilitated by the development of roadmaps in the form of single-cell transcriptomic atlases that allow for the specific determination of biomarkers able to distinguish major cell subtypes, isolation of subpopulations and functional assessments. This knowledge should boost and enrich the, already in use, approach of stimulation of Müller glia potential through the manipulation of gene expression (Jorstad et al., 2017; reviewed in Lahne et al., 2020 and Martin & Poché, 2019). Subpopulation-specific targeted approaches could translate into more refined data and a higher efficiency of the procedures.

A special focus should be directed towards the evaluation of single-cell epigenomes as it has been repeatedly shown that epigenetic mechanisms such as DNA methylation or Histone modification may impair, for example, the regenerative capacity of Müller cells (Mitra et al., 2018; Reyes-Aguirre & Lamas, 2016; VandenBosch et al., 2020) or the role of these cells in pathology (Zorrilla-Zubilete et al., 2018).

This more complex vision of Muller glia leads to many outstanding questions, and some "required-to-be-tested" hypothesis. Would this heterogeneity extend to less explored, but nevertheless exciting, new functional traits of Müller glia such as light transmission (Franze et al., 2007), photoreceptor-to-glia electrical and signaling coupling (Zayas-Santiago et al., 2014) or neuron-Müller communication through retinal development (Rosa et al., 2015)? Would it be possible that the regenerative or healing capacity of Müller cells, or even their normal function in the healthy retina could depend on the interaction of multiple Müller cell types? If so, could it be possible to refine current cell-based therapeutic approaches in ocular disease? Could we envision the existence of subtype specific mechanisms of Müller-to-Müller intercellular communication that could induce the enrichment of a distinct subclass that could be either more susceptible or more resistant to a certain damage? All these questions indeed augur very exciting research avenues to come in the next future.

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