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Review

Glia–neuron interactions in the mammalian retina

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ABSTRACT

The mammalian retina provides an excellent opportunity to study glia–neuron interactions and the interactions of glia with blood vessels. Three main types of glial cells are found in the mammalian retina that serve to maintain retinal homeostasis: astrocytes, Müller cells and resident microglia. Müller cells, astrocytes and microglia not only provide structural support but they are also involved in metabolism, the phagocytosis of neuronal debris, the release of certain transmitters and trophic factors and K^+ uptake. Astrocytes are mostly located in the nerve fibre layer and they accompany the blood vessels in the inner nuclear layer. Indeed, like Müller cells, astrocytic processes cover the blood vessels forming the retinal blood barrier and they fulfil a significant role in ion homeostasis. Among other activities, microglia can be stimulated to fulfil a macrophage function, as well as to interact with other glial cells and neurons by secreting growth factors. This review summarizes the main functional relationships between retinal

List of abbreviations: AAV, adeno-associated virus; Ach, acetylcholine; AGA, amadori-glycated albumin; AGE, advanced glycation end-products; AhR, aryl hydrocarbon receptor; AKT, protein kinase B; AMD, age-related macular degeneration; AP-1, activating protein-1; APC, antigen-presenting cells; Apo, apolipoprotein; AQP, aquaporin; ASCL1, achaete-scute family bHLH transcription factor 1; Atoh7, atonal homolog 7; ATP, adenosine triphosphate; BBB, blood–brain barrier; Bcl-2, B-cell lymphoma 2; BDNF, brain-derived neurotrophic factor; bFGF, basic fibroblast growth factor; BMP, bone morphogenetic protein; BV, blood vessel; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase; Car2, carbonic anhydrase II; CCL2, monocyte Chemotactic Protein-1; CCR2, C–C chemokine receptor type 2; CD45, cluster of differentiation 45; Cdc14A, cell division cycle 14A; Cdk10, cyclin-dependent kinase 10; Ch, choroid; ChAT, choline acetyltransferase; CHX10, Ceh-10 homeodomain-containing homolog; CNS, central nervous system; CNTF, ciliary neurotrophic factor; CNV, choroidal neovascularisation; CRALBP, cellular retinaldehyde-binding protein C; CREB, cAMP response element-binding protein; CSF1R, colony stimulating factor 1 receptor; CSPG, chondroitin sulphate proteoglycans; CTGF, connective tissue growth factor; CX3CL1, chemokine (C-X3-C Motif) Ligand 1; CX3CR1, CX3C chemokine receptor 1; DAPI, 4′,6-diamidino-2-phenylindole; DAPT, γ-Secretase inhibitor; DHA, docosahexaenoic acid; DKK3, Dickkopf-related protein 3; DR, diabetic retinopathy; EAAT, excitatory amino acid transporter; ECM, extracellular matrix; ED-1, monoclonal antibody against glycoprotein CD68; EGF, epidermal growth factor; EMV, extracellular membrane microvesicles; ESMV, embryonic stem cells microvesicles; FG, fluorogold; FGF, fibroblast growth factor; FKN, fraktalkine; G6P, Glucose-6-Phosphate; GABA, γ-aminobutyric acid; gadd45b, growth Arrest And DNA-Damage-Inducible Beta; GCL, ganglion cell layer; GDNF, glia-derived neurotrophic factor; GFAP, glial fibrillary acidic protein; GFP, green fluorescent protein; GK, Goto Kakizaki; GLAST, glutamate-aspartate transporter; GLT1, glial Glutamate Transporter 1; Gpc, glypican; GS, glutamine synthetase; hMGSC, human Müller glia stem cells; HSPG, heparin sulphate proteoglycan; IBA1, ionized calcium-binding adapter molecule 1; IF, intermediate filaments; IFN, interferon; IGF, insulin-like growth factor; IL, interleukin; ILM, inner limiting membrane; INL, inner nuclear layer; IOP, intraocular pressure; IP3R2, IP3 receptor type 2; IPL, inner plexiform layer; JNK, C-Jun N-terminal kinase; Kir, inwardly rectifying potassium channels; LCA, Leber congenital amaurosis; LDL, low-density lipoproteins; LGN, lateral geniculate nucleus; LIF, leukaemia inhibitory factor; MAPK, mitogen-activated protein kinases; Mash1, mammalian achaete-scute homolog-1; MCP1, monocyte chemoattractant protein-1; Megf10, multiple epidermal growth factor-like domains protein 10; Mertk, tyrosine-protein kinase Mer; MHC, major histocompatibility complex; MMP, matrix metalloproteinases; mTOR, mechanistic target of rapamycin; NAD, nicotine adenine dinucleotide; NADPH, nicotinamide adenine dinucleotide phosphate; NF, neurofilaments; NFL, nerve fibre layer; NFκ&Bgr, uclear factor kappa-light-chain-enhancer of activated B cells; NGF, nerve growth factor; NMDA, N-Methyl-D-aspartate; NO, nitric oxide; NPD1, neuroprotectin D1; NPPB, 5-nitro-2-[(3-phenylpropyl)amino]benzoic acid; NV, neovascularisation; OIR, oxygen-induced retinopathy; OLM, outer limiting membrane; ON, optic nerve; ONL, outer nuclear layer; OPC, oligodendrocyte precursor cells; OPL, outer plexiform layer; OPN, osteopontin; OS, outer segment layer; P2Y, metabotropic purinergic; Pax6, paired box 6; PCAG, primary closed-angle glaucoma; PCG, primary congenital glaucoma; PE, pigment epithelium; PEDF, pigment epithelium-derived factor; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; PKB, protein kinase B; PLC, phospholipase C; POAG, primary open angle glaucoma; PSD95, postsynaptic density protein 95; rd10, retinal degeneration 10; RFP, red fluorescent protein; RGC, retinal ganglion cells; RGCL, retinal ganglion cells layer; RNA, ribonucleic acid; ROS, reactive oxygen species; RP, retinitis pigmentosa; RPE, retinal pigment epithelium; RT-PCR, reverse transcription polymerase chain reaction; RVD, regulatory Volume Decrease; SELDI-TOF, surface-enhanced laser desorption ionization-time of flight; SNAP25, synaptosomal-associated protein 25; SP-A, surfactant protein A; Spbc25, spindle pole body component 25; STAT, signal transducers and activators of transcription transient; STZ, streptozotozin; TAK1, transforming growth factor β-activated kinase 1; TCA, tricarboxylic acid cycle; TGF&Bgr, transforming growth factor beta; Thy-1, thymocyte antigen 1; TN-C, tenascin C; TNF, tumour necrosis factor; TRK&Bgr, tropomyosin receptor kinase B; uPA, urinary-type plasminogen activator; VEGF, vascular endothelial growth factor; Vim, vimentin; WNT, Wingless-Type MMTV integration site family.

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Astrocytes
Müller glia
Microglia
Macrophages
Retinal ganglion cells
Photoreceptors
Glaucoma
Retinitis pigmentosa
Neuroprotection
Neurotrophins
Plasticity
Integrins
Extracellular matrix

glial cells and neurons, presenting a general picture of the retina recently modified based on experimental observations. The preferential involvement of the distinct glia cells in terms of the activity in the retina is discussed, for example, while Müller cells may serve as progenitors of retinal neurons, astrocytes and microglia are responsible for synaptic pruning. Since different types of glia participate together in certain activities in the retina, it is imperative to explore the order of redundancy and to explore the heterogeneity among these cells. Recent studies revealed the association of glia cell heterogeneity with specific functions. Finally, the neuroprotective effects of glia on photoreceptors and ganglion cells under normal and adverse conditions will also be explored.

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