Oligodendrocyte

Oligodendrocytes are a type of glial cell found in the central nervous system (CNS) that provide support and insulation to axons.

Function

Their main function is to produce myelin, a fatty substance that forms a sheath around axons and helps to speed up nerve impulses. Each oligodendrocyte can myelinate multiple axons, unlike Schwann cells in the peripheral nervous system, which can only myelinate one axon.

Oligodendrocytes also play a role in maintaining the health and stability of the nervous system. They are involved in the regulation of ion and neurotransmitter concentrations, and they can also respond to injury or disease by releasing growth factors and cytokines.

Dysfunction of oligodendrocytes has been linked to several neurological disorders, such as multiple sclerosis, leukodystrophies, and cerebral palsy. Research on oligodendrocytes is ongoing and is important for understanding the mechanisms underlying these disorders and developing new treatments.

Diffuse glioma is a term used to encompass a variety of poorly marginated infiltrating central nervous system tumor, which histologically appear similar to Glial cells, specifically astrocytes and oligodendrocytes. These range in biological behavior from very indolent to extremely aggressive and this is reflected in grading that ranges from grade 1 to grade 4.

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see also Oligodendrocyte progenitor cell.

Oligodendrocyte transcriptional factor-2 (Olig2) is an essential marker for oligodendrocytes expression. Olig2 marker cannot be used as an alternative diagnostic method for 1p 19q co-deletion to distinguish oligodendrogliomas from other glial neoplasms. Although some glial tumors showed diffuse Olig2 expression, 1p19q co-deletion testing is the best diagnostic method [1].

A single oligodendrocyte can extend its processes to 50 axons, wrapping approximately 1 µm of myelin sheath around each axon; Schwann cells, on the other hand, can wrap around only 1 axon. Each oligodendrocyte forms one segment of myelin for several adjacent axons.

While myelinating oligodendrocytes are attractive candidates for cell-based regenerative therapies, producing them in adequate quantities and regulation of progenitor differentiation pathways has proven limiting. Hubler et al. (2018) and Madhavan et al. (2018) generated cerebral organoids with myelinating oligodendrocytes and manipulated sterol pathway small molecules to promote myelin synthesis [2].

Oligodendrocytes (OLs) in the adult spinal cord express EphB3 as well as other members of the Eph receptor family. Spinal cord injury (SCI) is associated with tissue damage, cellular loss and disturbances in EphB3-ephrinB3 protein balance acutely (days) after the initial impact creating an environment for a dependence receptor-mediated cell death to occur. Genetic ablation of EphB3 promotes OL survival associated with increased expression of myelin basic protein and improved locomotor function in mice after SCI. Moreover, administration of its ephrinB3 ligand to the spinal cord after injury also promotes OL survival. Our in vivo findings are supported by in vitro studies showing that ephrinB3 administration promotes the survival of both oligodendroglial progenitor cells and mature OLs cultured under pro-apoptotic conditions. In conclusion, the present study demonstrates a novel dependence receptor role of EphB3 in OL cell death after SCI, and supports further development of ephrinB3-based therapies to promote recovery [3)].

Oligodendrocytes, the presumed cell of origin of oligodendrogliomas, highly express the genes encoding myelin basic protein (MBP) and proteolipid protein (PLP).

Within the microenvironment of multiple sclerosis lesions, oligodendrocytes are subject to metabolic stress reflecting effects of focal ischemia and inflammation. Previous studies have shown that under optimal conditions in vitro, the respiratory activity of human adult brain-derived oligodendrocytes is lower and more predominantly glycolytic compared to oligodendrocytes differentiated in vitro from post natal rat brain oligodendrocyte progenitor cells. In response to sub-lethal metabolic stress, adult human oligodendrocytes reduce overall energy production rate impacting the capacity to maintain myelination. Here, we directly compare the metabolic profiles of oligodendrocytes derived from adult rat brain with oligodendrocytes newly differentiated in vitro from oligodendrocyte progenitor cells obtained from the post natal rat brain, under both optimal culture and metabolic stress (low/no glucose) conditions. Oxygen consumption and extracellular acidification rates were measured using a Seahorse extracellular flux analyzer. Our findings indicate that under optimal conditions, adult rat oligodendrocytes preferentially use glycolysis whereas newly differentiated post natal rat oligodendrocytes, and the oligodendrocyte progenitor cells from which they are derived, mainly utilize oxidative phosphorylation to produce ATP. Metabolic stress increases the rate of ATP production via oxidative phosphorylation and significantly reduces glycolysis in adult oligodendrocytes. The rate of ATP production was relatively unchanged in newly differentiated post natal oligodendrocytes under these stress conditions, while it was significantly reduced in oligodendrocyte progenitor cells. Our study indicates that both age and maturation influence the metabolic profile under optimal and stressed conditions, emphasizing the need to consider these variables for in vitro studies that aim to model adult human disease [4)].

Stalled oligodendrocyte differentiation

When oligodendrocyte differentiation stalls, myelination is impaired, and this can have severe consequences on CNS function. Some of the factors that can lead to stalled oligodendrocyte differentiation include genetic mutations, environmental factors, and injuries to the CNS.

One of the most common causes of stalled oligodendrocyte differentiation is multiple sclerosis (MS),

an autoimmune disease in which the immune system attacks myelin in the CNS, leading to demyelination and neurodegeneration. In MS, oligodendrocytes fail to differentiate properly, leading to a reduction in myelin production and impaired neuronal function.

Other factors that can lead to stalled oligodendrocyte differentiation include exposure to toxins or environmental pollutants, viral infections, and traumatic brain injuries. Research is currently underway to better understand the mechanisms underlying stalled oligodendrocyte differentiation and to develop new therapies to promote myelin repair and improve CNS function.

Roughly 50% of Adult-type diffuse gliomas harbor isocitrate dehydrogenase mutations. According to the 2021 WHO classification guideline, these gliomas are diagnosed as astrocytomas, harboring no 1p/19q co-deletion, or oligodendrogliomas, harboring 1p19q co-deletion. Recent studies report that IDH-mutant gliomas share a common developmental hierarchy. However, the neural lineages and differentiation stages in IDH-mutant gliomas remain inadequately characterized.

Using bulk transcriptomes and single-cell transcriptomes, Wei et al. identified genes enriched in IDH-mutant gliomas with or without 1p19q co-deletion, they also assessed the expression pattern of stage-specific signatures and key regulators of oligodendrocyte lineage differentiation. They compared the expression of oligodendrocyte lineage stage-specific markers between quiescent and proliferating malignant single cells. The gene expression profiles were validated using RNAscope analysis and myelin staining and were further substantiated using data of DNA methylation and single-cell ATAC-seq. As a control, they assessed the expression pattern of astrocyte lineage markers.

Genes concordantly enriched in both subtypes of IDH-mutant gliomas are upregulated in oligodendrocyte progenitor cells (OPC). Signatures of early stages of oligodendrocyte lineage and key regulators of OPC specification and maintenance are enriched in all IDH-mutant gliomas. In contrast, signature of myelin-forming oligodendrocytes, myelination regulators, and myelin components are significantly down-regulated or absent in IDH-mutant gliomas. Further, single-cell transcriptomes of IDH-mutant gliomas are similar to OPC and differentiation-committed oligodendrocyte progenitors, but not to myelinating oligodendrocyte. Most IDH-mutant glioma cells are quiescent; quiescent cells and proliferating cells resemble the same differentiation stage of oligodendrocyte lineage. Mirroring the gene expression profiles along the oligodendrocyte lineage, analyses of DNA methylation and single-cell ATAC-seq data demonstrate that genes of myelination regulators and myelin components are hypermethylated and show inaccessible chromatin status, whereas regulators of OPC specification and maintenance are hypomethylated and show open chromatin status. Markers of astrocyte precursors are not enriched in IDH-mutant gliomas.

The studies show that despite differences in clinical manifestation and genomic alterations, all IDH-mutant gliomas resemble early stages of oligodendrocyte lineage and are stalled in oligodendrocyte differentiation due to blocked myelination program. These findings provide a framework to accommodate biological features and therapy development for IDH-mutant gliomas [5].

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