Olygodendrocite progenitor cell

PSENEN is the minimal subunit of the multiprotein complex γ-secretase, which promotes the differentiation of oligodendrocyte progenitor cells into astrocytes in the central nervous system.

Khazaei et al. describes protocols for the efficient generation of oligodendrogenic neural progenitor cells (o-NPCs) from human induced pluripotent stem cells (hiPSCs). Specifically, detailed methods are provided for the maintenance and differentiation of hiPSCs, human induced pluripotent stem cell-derived neural progenitor cells (hiPS-NPCs), and human induced pluripotent stem cell-oligodendrogenic neural progenitor cells (hiPSC-o-NPCs) with the final products being suitable for in vitro experimentation or in vivo transplantation. Throughout, cell exposure to growth factors and patterning morphogens has been optimized for both concentration and timing, based on the literature and empirical experience, resulting in a robust and highly efficient protocol. Using this derivation procedure, it is possible to obtain millions of oligodendrogenic-NPCs within 40 days of initial cell plating which is substantially shorter than other protocols for similar cell types. This protocol has also been optimized to use translationally relevant human iPSCs as the parent cell line. The resultant cells have been extensively characterized both in vitro and in vivo and express key markers of an oligodendrogenic lineage [1].

Oligodendrocyte progenitor cells (OPC) in the CNS are characterised by expression of Nerve-glial antigen 2 protein (NG2, also termed chondroitin sulfate proteoglycan 4 (CSPG4)), a type 1-transmembrane protein and chondroitin sulfate proteoglycan [2] [3].

Adult rat olfactory sphere cells express oligodendrocyte progenitor cell (OPC) markers and differentiate into mature oligodendrocytes. Although OSCs also express nestin, a marker of neural stem cells (NSCs), it remains unclear whether adult rat OSCs are multipotent and capable of giving rise to neurons as well as oligodendrocytes.

Synaptic signaling to NG2-expressing oligodendrocyte precursor cells (NG2 cells) could be key to rendering myelination of axons dependent on neuronal activity, but it has remained unclear whether NG2 glial cells integrate and respond to synaptic input.

NG2-expressing oligodendrocyte precursor cells (OPCs) are ubiquitous and generate oligodendrocytes throughout the young and adult brain. Previous work has shown that virtually every NG2 cell receives synaptic input from many axons, but the meaning of this signaling is not understood. In particular, it is unclear whether neurons specifically synapse onto OPCs or whether OPCs merely trace adjacent neurotransmitter release sites and are not recognized by the presynaptic neuron. Here, we show with whole-cell recordings from distinct developmental stages of oligodendroglial cells in brain slices that synaptic input essentially disappears as soon as OPCs differentiate into premyelinating oligodendrocytes (NG2(-), DM20/PLP(+), O1(+)). Uncaging experiments and tracer loading revealed that premyelinating oligodendrocytes still express a substantial number of AMPA/kainate receptors and many processes, but spontaneous and stimulated synaptic currents are mostly absent. Nevertheless, in a minority of premyelinating cells, electrical stimulation evoked small synaptic currents with an unusual behavior: their amplitude compared well with the quantal amplitude in OPCs

but they occurred asynchronously and with the remarkable latency of 40-100 ms, indicating that the presynaptic release machinery has become ineffective. Mature myelinating oligodendrocytes completely lack AMPA/kainate receptors and respond to uncaging and synaptic stimulation with glutamate transporter currents. Our data show that neurons selectively synapse onto only one of several coexisting developmental stages of glial cells and thereby indicate that neurons indeed specifically signal to OPCs and are able to modulate transmitter output by regulating the local release machinery in a manner specific to the developmental stage of the postsynaptic glial cell [4)].

NG2 expressing oligodendrocyte precursor cells stand out from other types of glial cells by receiving classical synaptic contacts from many neurons. This unconventional form of signaling between neurons and glial cells enables NG2 cells to receive information about the activity of presynaptic neurons with high temporal and spatial precision and has been postulated to be involved in activity-dependent myelination. While this still unproven concept is generally compelling, how NG2 cells may integrate synaptic input has hardly been addressed to date.

Sun et al., review the biophysical characteristics of synaptic currents and membrane properties of NG2 cells and discuss their capabilities to perform complex temporal and spatial signal integration and how this may be important for activity-dependent myelination [5)].

He show that NG2 cells perform linear integration of glutamatergic synaptic inputs and respond with increasing dendritic calcium elevations. Synaptic activity induces rapid Ca2+ signals mediated by low-voltage activated Ca2+ channels under strict inhibitory control of voltage-gated A-type K+ channels. Ca2+ signals can be global and originate throughout the cell. However, voltage-gated channels are also found in thin dendrites which act as compartmentalized processing units and generate local calcium transients. Taken together, the activity-dependent control of Ca2+ signals by A-type channels and the global versus local signaling domains make intracellular Ca2+ in NG2 cells a prime signaling molecule to transform neurotransmitter release into activity-dependent myelination [6)].

1)
Khazaei M, Ahuja CS, Fehlings MG. Generation of Oligodendrogenic Spinal Neural Progenitor Cells From Human Induced Pluripotent Stem Cells. Curr Protoc Stem Cell Biol. 2017 Aug 14;42:2D.20.1-2D.20.14. doi: 10.1002/cpsc.31. PubMed PMID: 28806852.
2)
Trotter J, Karram K, Nishiyama A (2010) NG2 cells: Properties, progeny and origin. Brain Res Rev 63: 72–82. doi: 10.1016/j.brainresrev.2009.12.006
3)
Nishiyama A, Komitova M, Suzuki R, Zhu X (2009) Polydendrocytes (NG2 cells): multifunctional cells with lineage plasticity. Nat Rev Neurosci 10: 9–22. doi: 10.1038/nrn2495
4)
Kukley M, Nishiyama A, Dietrich D. The fate of synaptic input to NG2 glial cells: neurons specifically downregulate transmitter release onto differentiating oligodendroglial cells. J Neurosci. 2010 Jun 16;30(24):8320-31. doi: 10.1523/JNEUROSCI.0854-10.2010. PubMed PMID: 20554883.
5)
Sun W, Dietrich D. Synaptic integration by NG2 cells. Front Cell Neurosci. 2013 Dec 20;7:255. doi: 10.3389/fncel.2013.00255. eCollection 2013. PubMed PMID: 24391539; PubMed Central PMCID: PMC3868909.
6)
Sun W, Matthews EA, Nicolas V, Schoch S, Dietrich D. NG2 glial cells integrate synaptic input in global and dendritic calcium signals. Elife. 2016 Sep 19;5. pii: e16262. doi: 10.7554/eLife.16262. [Epub ahead of print] PubMed PMID: 27644104.