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Oligodendroglial heterogeneity in time and space (NG2 glia in the CNS)

Introduction

Oligodendrocytes are an important cell type in the central nervous system (CNS). They generate myelin, which is responsible for the fast, saltatory nerve conduction. Until a few years ago it was believed that myelination takes place only during development and is completed at young adolescence. However, the progenitor cells that generate oligodendrocytes during development are also present in the adult brain and spinal cord. These oligodendrocyte progenitor cells are also known as polydendrocytes or NG2 glia, because of their appearance and the expression of the proteoglycan NG2. They generate not only oligodendrocytes but also astrocytes in a region-dependant manner during development [12]. Further, they are the only proliferating cell population outside the neurogenic niches in the adult brain and are able not only to renew themselves, but also to differentiate into mature, myelin-producing oligodendrocytes [4]. During the last years it became obvious that NG2 glia have even more functions in the brain. Thus, NG2 glia express a variety of ion channels and can form excitatory as well as inhibitory synapses with neurons (see article by C. Steinhäuser and D. Dieterich in this issue). Despite the high number of NG2 glia in the adult brain (5–10% of all cells) und their fundamental ability to generate oligodendrocytes, this maturation process is not sufficient to ensure efficient myelin repair after disease or injury. A targeted increase in the maturation of NG2 glia under pathological conditions like Multiple Sclerosis or injury would be beneficial, but first more detailed information about their differentiation, the signalling processes during development and the differences between NG2 glia in young and aged individuals are required. Another heavily discussed question of the last years with relevance for repair processes in the brain concerns the heterogeneity of the NG2 glia population. This aspect will be investigated as part of the SPP 1757 (Glial heterogeneity).

A complete list of literature can be requested from the authors.

NG2 glia in the developing CNS

NG2 glia are first detected rather late during ontogenesis. In the murine spinal cord NG2 glia develop after several neuronal subpopulations have already been generated. As cells of neuroectodermal origin, NG2 glia develop from the neuroepithelial progenitor cells of the ventricular zone [8]. In the spinal cord NG2 glia originate in the ventral area from precursor cells that express the transcription factor Olig2 and have generated motor neurons before. The Olig2 expression is sustained in NG2 glia. Remarkably additional NG2 glia are formed later in the dorsal region of the ventricular zone. Also in other regions of the CNS NG2 glia develop in different areas of the ventricular zone in a distinct temporal order. In the forebrain the medial ganglionic eminence is the earliest origin for NG2 glia, followed by the lateral ganglionic eminence and finally the dorsal telencephalon. As a consequence NG2 glia have various origins along the dorso-ventral and anterior-posterior axes. As the cells leave the ventricular zone, the growth factor receptor Pdgfra and the transcription factor Sox10 are induced. The expression of the proteoglycan NG2 follows with a slight delay. Despite their heterogeneity in origin most NG2 glia are characterised by the joint expression of Olig2, Sox10, Pdgfra and the eponymic NG2 marker protein. NG2 glia retain their ability to undergo cell division also in the parenchyma and are able to efficiently populate the whole CNS from their defined site of origin, due to their high migratory activity. As a consequence, many CNS areas are already populated by “ventral” NG2 glia, before “dorsal” NG2 glia are even generated. In line with this, NG2 glia with dorsal origin only represent a small proportion of the total population in the spinal cord. However, in the forebrain many of the early NG2 glia with ventral origin are later replaced by NG2 glia with dorsal origin. These observations argue that “ventral” and “dorsal” NG2 glia may have functional differences. However, an argument against this hypothesis is that so far no differences in the properties of "ventral" and "dorsal" NG2 glia or mature oligodendrocytes could be demonstrated and that the selective ablation of NG2 glia of a certain origin can be compensated in the mouse brain by remaining NG2 glia without phenotypical consequences. However, it needs to be stated, that the missing proof of a phenotype does not necessarily mean that this phenotype does not exist. It cannot be excluded that NG2 glia from different origins are heterogeneous under normal conditions, but show a high rate of plasticity in case of dis-

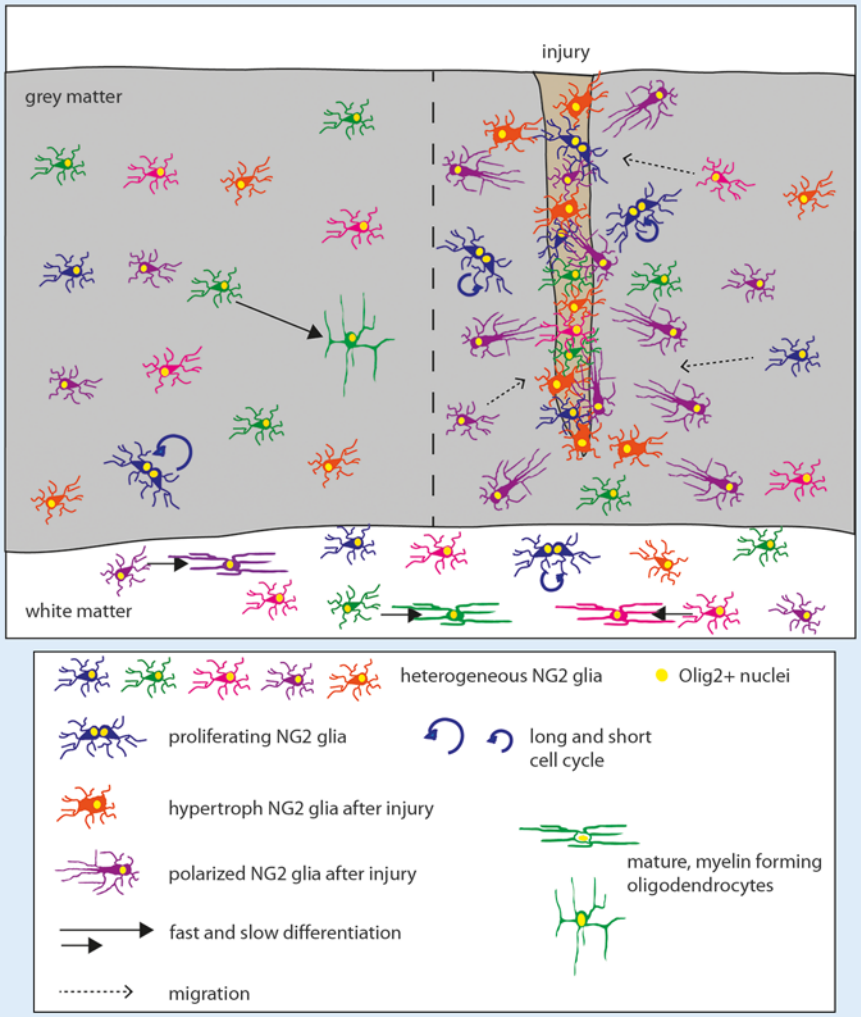

Fig. 1 ▲ NG2 glia are a heterogeneous population under physiological (*left*) and pathological (*right*) conditions: NG2 glia in the *grey* matter have a long cell cycle, differentiate slowly and only partially to mature oligodendrocytes with most cells remaining as NG2 glia. In contrast, NG2 glia located in the *white* matter have a shorter cell cycle and differentiate faster and in a higher amount into oligodendrocytes. After injury (**Fig. 1**, *right*) NG2 glia in the *grey* matter show a very fast and heterogeneous reaction. They become hypertrophic, polarize, migrate and proliferate more strongly with a shorter cell cycle

turbances in CNS development or injury so they are able to compensate for each other.

Relation of NG2 glia in the developing and adult CNS

During CNS development most NG2 glia differentiate to oligodendrocytes. Due to this, NG2 glia are usually referred to as oligodendrocyte progenitor cells (OPCs) in developmental studies. Disturbances in development and differentiation of NG2 glia are related to demyelinating diseases and leukodystrophies. Part of the NG2 glia population does not differentiate, but remains as an autonomous cell population in the adult CNS. At the moment it is unclear, which signals and mechanisms decide, whether a NG2 glia cell differentiates further or stays at a progenitor state. Further, NG2 glia have to adapt to the modified situation in the adult brain in various characteristics and abilities. How this is achieved on mechanistic and molecular levels is currently unclear and part of our research in the SPP 1757 (Glial heterogeneity).

NG2 glia in the adult brain

In the adult brain NG2 glia are able to proliferate and to renew themselves, but in contrast to developmental states, the cell cycle is rather slow. In the last years it has been shown, that NG2 glia generate mature, myelin-generating oligodendrocytes also in adulthood and hence at a time point, when myelination has already been completed. The role of these newly generated oligodendrocytes is not known. Recent studies lead to the assumption, that these oligodendrocytes could be important for complex, motor learning tasks [7]. Interestingly, for adult NG2 glia the ability to proliferate and divide is strongly region-dependent. While the majority of NG2 glia in the white matter of the cerebral cortex (e.g. in the corpus callosum) generates mature, myelin-producing oligodendrocytes, most of the NG2 glia in the grey matter keep their identity as progenitor cells. Homo- and heterotopic transplantations in the brain of adult mice point to a substantial heterogeneity of NG2 glia in different brain regions, which can either be explained by different intrinsic determinants or by divergent environmental stimuli [9]. Further, the proportion of proliferating NG2 glia is smaller in the grey matter and cell cycle length is increased, compared to NG2 glia residing in the white matter (**Fig. 1**). Proliferation and differentiation can also be influenced by neuronal modulation. This can be explained by the fact that NG2 glia interact closely with synapses and nodes of Ranvier and some NG2 glia are also in contact with neurons via synapses. All of these observations underline, that under physiological conditions NG2 glia act as a heterogeneous population, which can react differently to a variety of stimuli. This heterogeneity needs to be understood, before therapeutics based on NG2 glia can be developed and applied to remyelination and repair (for a review article see [2]).

Also within the same region heterogeneity of NG2 glia was observed. The transcription factor Mash1/Ascl1 was only detected in a subpopulation of NG2 glia in the cerebral cortex. It remains unclear, whether Ascl1-positive and –negative NG2 glia show differences in proliferation- and differentiation behaviour. Also the G-protein coupled membrane receptor 17 (GPR17) is only expressed in a subpopulation of NG2 glia in the brain. Sur-

prisingly, NG2 glia expressing GPR17 do not develop to mature oligodendrocytes in an investigated period of 3 months. As part of SPP1757, the molecular differences between GPR17-positive and GPR17-negative NG2 glia will be analysed to identify molecules and signalling pathways that are important and necessary for the differentiation of NG2 glia.

Regulatory mechanisms of NG2 glia

Different properties of NG2 glia in the developing and in the adult brain are caused by alterations of the gene regulatory network. For NG2 glia in the developing CNS the main components of the network are known [5]. Among those are the two transcription factors and marker proteins for NG2 glia Olig2 and Sox10. Both are supported in their function by closely related proteins (Olig1 for Olig2; and Sox8, Sox9 support Sox10), but are functionally dominant compared to the corresponding paralogous proteins. Their effect is further modulated by additional transcription factors. The helix-loop-helix proteins Id2 and Id4 inhibit Olig2 and the transcription factor Sox10 is regulated in its activity by the related proteins Sox5 and Sox6. Additional crucial regulators are the helix-loop-helix protein Mash1/Ascl1, the zinc finger protein Sip1 and the homeodomain protein Nkx2.2. New studies give first insights into the complex interactions of these transcription factors inside the gene-regulatory network that involves antagonistic as well as synergistic and inductive relations and establish a variety of control circuits, which additionally are influenced by the exact amount of the corresponding transcription factor, post-translational modifications and epigenetic factors [10, 11]. Currently, there is insufficient knowledge how the gene regulatory network in NG2 glia during development differs from the adult CNS. However, current research hints at some functionally relevant differences. The influence of Olig2 and Olig1 on the differentiation of NG2 glia appears to be interchanged between developing and adult CNS. Whereas Olig2 is responsible for many developmental aspects und properties of NG2 glia in the developing CNS and can not be substituted by Olig1, regeneration and differentiation of adult NG2 glia depends on Olig1 and is drastically reduced if only Olig2 is present [1]. By using comparative genomics to investigate the regulatory network we hope to receive important information about the causes for differences and similarities between NG2 glia in the developing and in the adult brain. Further, we will tackle the question, how the modulation of the network influences the heterogeneity of NG2 glia during adulthood.

Response of NG2 glia after injury

NG2 glia react towards injurý or other pathological conditions with a change in their morphology and proliferation rate. The type and time course of this reaction is dependent on the nature of the insult. After demyelination NG2 glia become hypertrophic, more cells proliferate with a shortened cell cycle and differentiate finally to mature oligodendrocytes to repair myelin. NG2 glia react similarly in neurodegenerative diseases such as Morbus Alzheimer or Amyotrophic Lateral Sclerosis (ALS), but no hypertrophy can be detected in these cases. It remains unclear, whether the reaction of NG2 glia also differs between different kinds of injury and other pathological states. Using repetitive *in vivo* 2-photon microscopy, first evidences for a heterogeneous reaction of NG2 glia towards acute injury (e.g. focal laser lesion and stab wound) was detected ([6]; von Streitberg, Dimou et al., unpublished data). Some NG2 glia polarize and migrate towards the site of injury, while others proliferate and/or become hypertrophic (**Fig. 1**). All these events lead to an accumulation of NG2 glia at the lesion site. The relevance of this behaviour remains unclear (for a review see [3]). Speed and strength of the reaction lead to the assumption that NG2 glia are responsible for wound closure and scar formation.

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Abstract

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Abstract

NG2 glia represent a neural cell population that expresses the proteoglycan NG2 and is distinct from other cell types of the central nervous system. While they generate oligodendrocytes and a subset of astrocytes during development, their progeny in the adult brain solely consists of oligodendrocytes and further NG2 glia. In the last years, it has become clear that NG2 glia represent a heterogeneous population of cells with different properties and potential. In this review we will first discuss the similarities and differences between NG2 glia of the developing and adult CNS, before we will describe the regulatory mechanisms in these cells to finally concentrate on the heterogeneity of NG2 glia under physiological and pathological conditions.

Keywords

Heterogeneity · Differentiation · Proliferation · Transcription factors · Injury

Leda Dimou studied biology at the Ruprecht-Karls-University Heidelberg and did her PhD at the Center for Molecular Biology (ZMBH) in Heidelberg and at the Max-Planck-Institute for Experimental Medicine in Göttingen focussing on the homologs of the main myelin protein PLP in the brain. After a postdoctoral fellowship at the Institute for Brain Research in Zurich she moved to the Department of Physiological Genomics at the Biomedical Center of the Medical Faculty (LMU) in Munich, where she leads her own research group since 2012. Her research group investigates the role of NG2 glia in the adult brain under physiological and pathological conditions using molecular and cell biological- as well as imaging methods.

Michael Wegner studied biology at the universities of Münster and Würzburg and did his PhD from 1987 to 1990 at the Institute of Biochemistry in Würzburg. After postdoctoral work at the University of California at San Diego (UCSD) he took over a position as leader of a junior research group at the Center for Molecular Neurobiology at Hamburg University (ZMNH) in 1994 and was appointed to the chair of Biochemistry and Pathobiochemisty at the Institute of Biochemistry of the Medical Faculty at the Friedrich-Alexander-University Erlangen-Nürnberg in 2000. His research is dealing with the transcriptional and epigenetic control of glial cells and myelin formation.

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