NG2-glia proliferation and differentiation following CNS injuries

Abstract

NG2 glia display wide proliferation and differentiation potential under physiological and pathological conditions. They are very well known as precursors of oligodendrocytes, however, following central nervous system (CNS) injury they play an important role in regeneration. For this reason, we examined these features following different types of brain disorders such as focal cerebral ischemia (FCI), cortical stab wound (SW), and demyelination (DEMY) in young (3-months-old) mice, in which NG2 glia are labeled by tdTomato under the Cspg4 promoter. In the case of FCI, the factor of age was also studied using 18-months-old mice. To address these issues, we employed many techniques on tissue/cellular levels, such as single-cell RT-qPCR, single-cell/bulk RNA-sequencing, immunohistochemistry, and the patch-clamp technique in situ. First, such approach enabled us to distinguish two main populations (NG2 glia, oligodendrocytes), each of them comprising four distinct subpopulations. Next, the expression profiling revealed that a subpopulation of NG2 glia expressing GFAP, a marker of reactive astrocytes, appears transiently after FCI. However, following less severe injury, namely the cortical SW and DEMY, subpopulations mirroring different stages of oligodendrocyte maturation markedly prevail. Additionally, differential gene expression across ischemia and age uncovered downregulation of axonal and synaptic maintenance genetic program and increased activation of type I interferon (IFN-I) in aged mice. These results paint a picture of the complex heterogeneity of NG2 glia-their multipotent phenotype following CNS injuries and point to ischemia as a complex age-related disease.

Keywords

aging, astrocytes, demyelination, focal cerebral ischemia, oligodendrocytes, stab wound