Institutionen för Klinisk Neurovetenskap, Karolinska Institutet, Stockholm

Features of Adult Neural Progenitor Cells

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ABSTRACT

The adult Central Nervous System (CNS) harbors neural progenitor cells (NPCs) in three areas: the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone in the hippocampus and around the central canal in the spinal cord. The NPCs can be isolated and cultured *in vitro*. To improve recovery after a CNS trauma by using endogenous NPCs as well as by NPC transplantation, it is important to understand the features and localization of the NPC populations. It is crucial to understand the effects of inflammatory mediators on NPCs since neuroinflammation is involved in many CNS conditions such as trauma, neurodegenerative disorders, stroke and infections. The aim of this thesis was to study different NPC features: 1. How the NPCs transcriptionally and functionally differ throughout the neuroaxis, 2. If and how inflammation effects NPCs and 3. If human Filum Terminale harbors NPCs.

I. NPCs express TLR receptors and can following activation of the receptors produce TNFα.
Toll like receptors (TLR) are involved in the innate immune system which constitutes the first line of defense against pathogens. TLR2 and TLR4 were detected in NPC cultures and *in vivo* in the SVZ. Stimulation by macrophage supernatant and the cytokines IFNγ and TNFα resulted in a differentially regulated expression of these receptors on the NPCs. Moreover, TLR2 and TLR4 agonists induced expression of both mRNA and the TNFα protein which was released from NPC.

II. NPCs change fate after exposure to chronic inflammation
We used the experimental autoimmune encephalomyelitis (EAE) model to study NPCs after chronic inflammation. NPCs were isolated and cultured from SVZ, cervical, thoracic and caudal part of the spinal cord. Thereafter a global transcriptome analysis (Affymetricx Gene Chip®) was preformed paralleled by functional analysis where the NPC capacity to differentiate was determined using immunhistochemistry and western blot. In healthy situations significant changes was found between SVZ and spinal cord- derived NPCs. SVZ NPCs had a more neurogenic fate and NPC from spinal cord was more prone to astroglial differentiation. After inflammation spinal cord NPCs transcriptional profile was altered in functions such as myelination and survival of oligodendrocytes, several canonical pathways involved in gliogenesis was downregulated. This was translated into functional fate of the spinal cord NPCs with decreased oligo-and astrogliogenesis and increased neurogenesis. SVZ NPCs after inflammation fate was skewed towards astroglia.

III. NPCs are affected by a distant on-going inflammation
In this paper we focus on NPCs from levels within the EAE-affected spinal cord which did not show signs of high level of inflammation. NPCs from spinal cord revealed an altered transcription and differentiation pattern *in vitro*. which were independent of the level of active inflammation. We also detected an increased proliferative capacity of the NPCs after inflammation in the thoracic part.

IV. Human Filum Terminale harbors NPC which can be isolated and propagated
We here characterize and describe the existence of NPCs and their distribution in Filum Terminale immunohistochmically. NPCs were also isolated and differentiated *in vitro*. After addition of growth factor NPCs displayed increased neurogenesis. We also detected an age-related difference in growth and proliferation capacity which were higher in NPCs derived from young individuals.

In conclusion, we demonstrated that NPCs differ in neurogenic and gliogenic potential depending on their origin in the healthy situation. After chronic inflammation we found that NPCs fate is altered. We also present that NPC in the SVZ express TLR receptors and can produce cytokines after inflammatory stimuli. These findings may increase the knowledge how inflammation alters the NPC fate and their regenerative potential. In human Filum Terminale harbors NPCs ressembling NPC from other CNS locations. Hypothetically Filum Terminale could be a potential cell replacement source.

Key words: adult neural progenitor cell, filum terminale, neuroinflammation, gliogenesis, neurogenesis, gene expression, spinal cord, ependymal layer, subventricular zone

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