ImmunoTools *special* Award 2015

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The immunomodulatory oligodendrocyte: implications for innovative therapeutic strategies in inflammatory demyelinating diseases

Oligodendrocytes, the myelinating glial cells of the central nervous system have recently emerged to play an active role in modulating immune response. Indeed, at specific times and locations, they influence ongoing immune processes. They seem capable of expressing a wide range of immunomodulatory molecules that might not be constitutively expressed but rather under certain circumstances or only upon a specific stimulation.

In this way, in the right place at the right time, by a proper signaling event, oligodendrocytes might become immunologically active and be able of skewing an inflammatory reaction towards a certain outcome.

They express various cytokines and chemokines (e.g. IL-1β, IL-17A, CCL2, CXCL10), antigen presenting molecules (MHC class I and II) and co-stimulatory molecules (e.g. CD9, CD81), complement and complement receptor molecules (e.g. C1s, C2 and C3, C1R), complement regulatory molecules (e.g. CD46, CD55, CD59), tetraspanins (e.g. TSPAN2), neuroimmune regulatory proteins (e.g. CD200, CD47) as well as extracellular matrix proteins (e.g. VCAN) and many others.

Therefore, oligodendrocytes are well capable of immunomodulation, especially during the initiation or resolution of immune processes and modify them. A better understanding of the immunomodulatory oligodendrocyte can help us to develop novel therapeutic strategies in various diseases such as Multiple Sclerosis (MS) (*Zeis et al., 2015).*

On the basis, the aim of my project is to understand which are i) the triggers that induce oligodendrocytes to acquire an “active” phenotype; ii) the immunomodulatory

molecules released in this conditions; iii) the effect of these phenotypic changes on the differentiation process and on their myelinating properties.

In order to trigger the “active” phenotype, we will expose primary oligodendrocyte precursor cells (OPCs), isolated from brains of P2 rats, to different cocktails of recombinant cytokines (e.g. IL-12, IL-18) for 30 minutes. Then, the medium will be changed and supernatants collected after a 24-hour incubation in order to perform ELISA assay for IL-1β, TNFα, TGF-β, IL-17A, CCL2, CXCL-10, CXCL-12.

Then, adult OPCs (aOPCs) in demyelinating conditions (thus activated aOPCs) will be isolated from brains of cuprizone-fed transgenic mice (where OPCs are GFP-positive) by fluorescent-activated cell sorting and cultured in vitro. The ELISA assay will be repeated on the supernatants collected from cultured adult OPCs.

To evaluate the effect of the phenotypic changes on the differentiation process, we will trigger primary OPCs isolated from brains of P2 rats, as described above, and sorted by CD9 or CD81. These sorted cells will be cultured and the differentiation process will be analysed by immunocytochemistry.

A better knowledge of new oligodendroglial functions might enable us to understand the molecular basis of lesion formation, repair and clearance in diseases like MS.

Indeed, the immunomodulatory potential of oligodendrocytes might be an important factor in the initiation of inflammation or its resolution, especially in oligodendrocyte-directed or inflammatory demyelinating diseases.

These insights will be crucial to identify and develop new therapeutic approaches for disorders in which myelin damage is inextricably associated with innate immune activation in the CNS.