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Review

The immunomodulatory oligodendrocyte

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ABSTRACT

Oligodendrocytes, the myelinating glial cells of the central nervous system (CNS), are due to their high specialization and metabolic needs highly vulnerable to various insults. This led to a general view that oligodendrocytes are defenseless victims during brain damage such as occurs in acute and chronic CNS inflammation. However, this view is challenged by increasing evidence that oligodendrocytes are capable of expressing a wide range of immunomodulatory molecules. They express various cytokines and chemokines (e.g. Il-1β, Il17A, 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. Their potential immunomodulatory properties can, at specific times and locations, influence ongoing immune processes as shown by numerous publications. Therefore, oligodendrocytes are well capable of immunomodulation, especially during the initiation or resolution of immune processes in which subtle signaling might tip the scale. A better understanding of the immunomodulatory oligodendrocyte can help to invent new, innovative therapeutic interventions in various diseases such as Multiple Sclerosis.

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Contents

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1. General introduction

Oligodendrocytes are the myelinating cells of the central nervous system. Their main function is to insulate axons to enable saltatory conduction. They further support neurons by providing continuous metabolic and trophic support (Nave and Trapp, 2008). To fulfill these tasks, oligodendrocytes maintain up to 50 single myelin sheaths supporting many axons at a time.

Oligodendrocytes derive from the neuroectoderm and are the last neural cells differentiating during development. Oligodendrocyte precursor cells (OPCs) proliferate, migrate and finally contact axons which they ultimately myelinate. This process is tightly controlled not only by a complex intrinsic oligodendrocyte differentiation program (Brinkmann et al., 2008), but also by external reciprocal signaling processes such as the degree of neuronal differentiation (Bradl and Lassmann, 2010). Due to their complex architecture and high metabolic demands, oligodendrocyte function can be easily disturbed; because of that they are often referred to as “the most vulnerable cells of the CNS” (Bradl and Lassmann, 2010). This is especially unfortunate in the case of disturbances of brain homeostasis. Many events can lead to such disturbances; among them inflammatory pathomechanisms of the CNS. In the context of inflammation, oligodendrocytes are generally believed to be simply victims of the inflammatory reaction, being lucky they survive (Zeis and Schaeren-Wiemers, 2008). However, this view is probably too simple, and an increasing body of evidence demonstrates that oligodendrocytes can react and/or act if challenged by immune reactions (Peferoen et al., 2014; Steinman, 1993; Zeis and Schaeren-Wiemers, 2008). These potential immunomodulatory features of oligodendrocytes are the topic of this review.

2. Oligodendrocytes as victims

The high specialization of oligodendrocytes is key to their general vulnerability. First of all, oligodendrocytes have to ensure myelin synthesis in order to enable saltatory conduction. To do so, vast amounts of lipids have to be produced and maintained which demands a very high metabolic rate and consumes large amounts of oxygen and ATP (McTigue and Tripathi, 2008). The various metabolic processes lead to the generation of hydrogen peroxide and reactive oxygen species (ROS) (McTigue and Tripathi, 2008), which have to be taken properly care of. Additionally, oligodendrocytes are reported to store large amounts of iron (Cheepsunthorn et al., 1998; Connor and Menzies, 1996), but have low concentrations of glutathione (Thorburne and Juurlink, 1996). This combination makes oligodendrocyte potentially vulnerable to oxidative damage (Cheepsunthorn et al., 1998; McTigue and Tripathi, 2008; Thorburne and Juurlink, 1996). A disturbance of the clearance of toxic molecules might therefore lead to oligodendrocyte dysfunction or death (Dewar et al., 2003; Ott et al., 2007; Uberti et al., 1999).

Hydrogen peroxide and ROS are used by the immune system as cytotoxic mediators in inflammatory reactions (Martinvalet et al., 2005). Due to the already intensively used capacity to metabolize these harmful molecules, oligodendrocytes might not be capable of handling their increased abundance during an inflammatory reaction.

In earlier reviews we and others have summarized the many possibilities leading to oligodendrocyte injury or death (Bradl and Lassmann, 2010; McTigue and Tripathi, 2008; Peferoen et al., 2014; Zeis and Schaeren-Wiemers, 2008). Basically, many different immune cells possess mechanisms by which they can harm oligodendrocytes. Additionally, brain resident cells such as astrocytes and microglia can trigger oligodendrocyte injuries or induce oligodendrocyte apoptosis.

However, a growing body of evidence suggests that oligodendrocytes are not just victims but can well be capable of defending themselves and even shaping ongoing inflammatory processes in their vicinity.

3. The immunomodulatory oligodendrocyte

In several publications, oligodendrocytes are reported to express a range of factors known to be involved in immunological processes (Table 1). By the expression of these molecules oligodendrocytes are potentially able to act upon immunological processes and modify them.

3.1. *Cytokines*

Oligodendrocytes were reported to express different cytokines involved in the control of the immune system and its reactions. In 2008, Tzartos et al. reported that not only T cells are capable of expressing IL-17A but also astrocytes and, surprisingly, oligodendrocytes (Tzartos et al., 2008). IL-17A is reported to be a pro-inflammatory cytokine playing a critical role against extracellular microorganisms and in the pathogenesis of autoimmune diseases (Isailovic et al., 2015). IL-17A signaling leads to the expression of chemokines and other cytokines which are known to promote neutrophil and