Title: The immunomodulatory oligodendrocyte

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Number of words in the manuscript: 3635

Keywords: Oligodendrocyte, Immunomodulation, Immune process, Inflammation, Cytokine, Chemokine, Multiple Sclerosis, N1Regs, Tetraspanins

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-1 β , 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.

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.

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.

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.

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 monocyte chemotaxis (Gaffen et al., 2014; Isailovic et al., 2015; Shen et al., 2005). Further, dysregulated IL-17 production and signaling is associated with the development of autoimmune diseases such as Multiple sclerosis (MS) (Gaffen et al., 2014). Although Tzartos et al. reported only a subpopulation of oligodendrocytes in active MS lesions to be IL-17 positive, they might play their part in shaping the inflammatory reaction in active lesions of this demyelinating disease.

Another cytokine reported to be expressed by oligodendrocytes is IL-1 β (Moyon et al., 2015). In this study, the authors performed a differential gene expression analysis between adult oligodendrocyte progenitor cells (aOPCs) upon cuprizone treatment (termed activated aOPCs) and normal aOPCs from control brain. They found that the activated aOPCs have an increased expression of IL-1 β , a cytokine involved in innate immune system functions (Moyon et al., 2015). IL-1 β is an effector molecule of the so-called inflammasomes and an important proinflammatory mediator coordinating among others cellular recruitment (Schroder and Tschopp, 2010).

In line with the finding of IL-1 β expression by activated aOPCs, we have found oligodendrocytes to express components of the inflammasome complex (Figure 1, own data). By in-situ hybridization analysis we could detect the inflammasome sensor molecules NLRP1, NLRP3 and NLRC4, the inflammasome adapter molecule ASC as well as the caspase effector CASP4 in oligodendrocytes of the MS normal appearing grey matter (NAGM). The expression of inflammasomes in oligodendrocytes is further supported by (Kummer et al., 2007) who showed by immunohistochemistry that oligodendrocytes express NLRP1. These findings suggest that oligodendrocytes have the potential to express functional inflammasomes, and thus be able to act in an immunomodulatory way. In 2004, Cannella and Raine reported that oligodendrocytes in control and MS brain are able to express IL-18 (Cannella and Raine, 2004). In the presence of IL-12, IL-18 is reported to induce the production of IFN- γ from T, B and NK cells and is a co-stimulant of Th1 cells. Alternatively, in the absence of IL-12, IL-18 can also induce the production of Th2-related cytokines from T and NK cells (Nakanishi et al., 2001).

Another cytokine which oligodendrocytes were shown to express is IL-6 (Ramesh et al., 2012). IL-6 is thought to play a role during the transition from innate to acquired immunity (Scheller et al., 2011). It is necessary for neutrophil, monocyte and T cell chemotaxis and plays a crucial role in B and T cell differentiation (Scheller et al., 2011).

Chemokines

Oligodendrocytes were also reported to express CCL2 (Balabanov et al., 2007; Moyon et al., 2015). Like IL-1 β , CCL2 is also known to regulate immune cell migration. It has been shown that CCL2 enhances microglia (Moyon et al., 2015), macrophage and monocyte migration (Hinojosa et al., 2011), and that it is a potent factor in the polarization of Th0 cells toward a Th2 phenotype (Deshmane et al., 2009; Gu et al., 2000). Balabanov et al. further reported the expression of CXCL10, CCL3 and CCL5 in oligodendrocytes upon IFN- γ stimulation (Balabanov et al., 2007). CXCL10 was reported to regulate immune responses by activation and recruitment of leukocytes (Farber, 1997; Lee et al., 2009). CCL3 has many functions, of which the most important seems to be chemotaxis of various immune cells (Menten et al., 2002). CCL5 also shows chemotactic properties, as it induces migration and recruitment of e.g. T cells, dendritic cells and NK cells (Marques et al., 2013).

In 2012, Ramesh et al. showed that human oligodendrocyte cell lines can be stimulated to express IL-8 upon incubation with *B. Burgdorferi*, the causal agent of Lyme disease (Ramesh et al., 2012). IL-8 is a proinflammatory chemokine reported to activate neutrophils and inducing chemotaxis and exocytosis (Baggiolini and Clark-Lewis, 1992). Another regulator of neutrophil chemotaxis and activation is CXCL5 (Walz et al., 1997), which was found to be expressed in the rat CG4 oligodendrocyte cell line (Merabova et al., 2012).

Antigen presentation molecules

In the realm of antigen presentation, oligodendrocytes in MS were shown to be able to express MHC class I molecules and therefore are potential targets of Class I MHC restricted cytotoxic T cells (Hoftberger et al., 2004). Expression of MHC class I molecules was further shown in hESC-derived OPCs (Okamura et al., 2007). Additionally, Okamura et al. demonstrated that upon treatment with either IFN- γ or TNF- α hESC-derived OPCs are capable of expressing PD1LG2 (CD273) as well as CD274. Both are costimulatory molecules which are crucial in shaping the activation of T lymphocytes (Wang and Chen, 2004) by either inhibiting or activating T cell proliferation (Greenwald et al., 2005). In 1992, Bergsteindottir et al. reported that cultured oligodendrocytes from rat optic nerves can be stimulated to express MHC class II molecules in the presence of dexamethasone (Bergsteindottir et al., 1992). The capability of oligodendrocytes to express MHC class I and II molecules as well as costimulatory molecules under certain circumstances suggests that these cells are capable of shaping an inflammatory reaction in their vicinity.

Tetraspanins

Tetraspanins are a superfamily of integral membrane proteins which are involved in microdomain organization and were reported to be involved in both innate and adaptive immunity (Jones et al., 2011). Oligodendrocytes were shown to express several tetraspanins such as CD9 (Ishibashi et al., 2004), CD81 (Sullivan and Geisert, 1998), CD82 (Mela and Goldman, 2009; Mela and Goldman, 2013), TSPAN2 (Birling et al., 1999). Of these, CD81 and CD82 were shown to interact with MHC class I (Szollosi et al., 1996) and together with CD9 also with MHC class II molecules (Engering and Pieters, 2001; Hammond et al., 1998; Jones et al., 2011; Rubinstein et al., 1996; Szollosi et al., 1996). They are thought to be involved in the clustering of MHC molecules and thereby to modulate T or B cell activation (Jones et al., 2011). Further, TSPAN2 as well as PLP, the major myelin tetraspan protein expressed in oligodendrocyte, were shown to be involved in the suppression of astrocyte and microglia activity (de Monasterio-Schrader et al., 2013).

Neuroimmune regulatory proteins (NIRegs)

Another class of molecules involved mainly in the regulation of the innate immune responses are the NIRegs. Of those CD200 was reported to be expressed by oligodendrocytes (Chitnis et al., 2007; Koning et al., 2009a). CD200 plays a critical role in suppressing macrophage and microglia activity (Koning et al., 2009b). A protein with similar function is CD47 which is also expressed by oligodendrocytes. CD47 was reported to downregulate myelin phagocytosis by macrophages and microglia (Gitik et al., 2011). Both CD200 and CD47 might be expressed by oligodendrocytes also in order to control microglial activity and thereby prevent immunological reaction in the brain (Griffiths et al., 2010).

In addition, SEMA3A, known to induce activated microglia apoptosis (Majed et al., 2006), was shown to be expressed by oligodendrocytes (Williams et al., 2007).

Oligodendrocytes were also shown to express FasL (Dowling et al., 1996; Li et al., 2000), a cytokine belonging to the tumor necrosis factor superfamily. FasL can potentially trigger apoptosis on FAS expressing activated NK and T cells (Choi and Benveniste, 2004) and thus limit inflammatory processes in the brain (Griffiths et al., 2010). Besides that, the expression of FasL by oligodendrocytes is potentially playing a role in the immune privilege of the brain as suggested in other privileged sites such as the eye (Green and Ferguson, 2001). The expression of NIREgs by oligodendrocytes therefore enables them to affect immune responses in the brain.

Complement and complement receptors

It has been demonstrated that oligodendrocytes express many of the complement proteins such as C1s, C2, C3 and others (Hosokawa et al., 2003). Besides their role in innate immunity, complement proteins are also involved in the regulation of the adaptive immunity where they were reported to affect, for example, T cell activation and T and B cell responses (Dunkelberger and Song, 2010; Kemper and Atkinson, 2007; Sarma and Ward, 2011). By their expression, oligodendrocytes might have another set of proteins to modulate immune processes.

Complement regulatory proteins

CD55, found to be expressed by adult human oligodendrocytes *in vitro*, is involved in the regulation of the complement cascade (Gasque and Morgan, 1996; Scolding et al., 1998). CD55 accelerates complement protein decay, preventing damage to host cells. It was further reported that CD55 can suppress T cell immunity *in vivo* (Liu et al., 2005). Further, oligodendrocytes of the oligodendrocyte cell line HOG were shown to be capable to express the complement regulatory proteins CD59 (Scolding et al., 1998) and CD46 (Gasque and Morgan, 1996), both reported to influence T cell proliferation and their ability to produce cytokines (Longhi et al., 2006). Studies of CD59 knock-out mice suggest that CD59 down-modulates CD4+ T cell activation (Longhi et al., 2005; Longhi et al., 2007), however this effect was reported to be complement independent (Longhi et al., 2006).

Extracellular matrix proteins

VCAN, an extracellular matrix proteoglycan, was also reported to be expressed by oligodendrocytes (Gu et al., 2007). Interestingly, VCAN was reported to have various functions in the control of the inflammatory response such as influencing immune and inflammatory cell types as well as playing a role in leukocyte adhesion and activation (Wight et al., 2014).

Further genes potentially involved in immunological processes

In 2008, Cahoy et al. generated a transcriptome database of astrocytes, neurons and oligodendrocytes in order to identify genes expressed by these brain resident cells (Cahoy et al., 2008). To investigate the possible immunological properties of oligodendrocytes we have analyzed their 3'-Array MAS 5.0 master data table (Supplemental Table 3 in (Cahoy et al., 2008)) with 20'932 probe sets showing

significant expression in the CNS. From these data, we generated a list of probe sets that are expressed at significant levels in OPCs, OLs or myelinating OLs. We then searched these genes for genes tagged with the GO:0002376 (Immune system process) GO term. From the total of 2'186 classified genes/proteins tagged with the GO:0002376 GO term (QuickGO, EMBL-EBI, <http://www.ebi.ac.uk/QuickGO/>, Filters: Taxon: 9606 and 10090, Evidence = Manual All, Aspect = Biological process), 847 genes are expressed in OPCs (about 39%), 771 are expressed in OLs (about 35%) and 696 are expressed in myelinating OLs (about 32%; Table 2). Many of these genes code for probably pleiotropic proteins, possibly fulfilling different roles in oligodendrocytes than in, for example, microglia or T or B cells. However, this demonstrates that among the genes known to be expressed by oligodendrocytes are a wide array of genes which bear the potential to influence immune processes. This is without even considering the large set of genes whose expression in oligodendrocytes is yet to be characterized.

The immune responding oligodendrocyte

Besides the capacity of oligodendrocytes to express several immunomodulatory molecules, there are numerous reports showing that oligodendrocytes express various receptors for immune related molecules (Balabanov et al., 2007; Cannella and Raine, 2004; Zeis et al., 2008). This enables them to sense inflammatory reactions and to react within the range of their functional capacities. As this review focus on the immunomodulatory capacity and possible actions of oligodendrocytes, the precise expression of these molecules is not discussed in detail.

Oligodendrocytes in disease

Various diseases that are caused by, or affect oligodendrocytes are known, of which probably the most prominent is MS, a primary demyelinating autoimmune disease of the CNS. Further, allergic or inflammatory and infectious demyelinating diseases such as e.g. ADEM (acute disseminated encephalomyelitis) are known. Other oligodendrocyte diseases are the hereditary metabolic diseases of myelin (e.g. Metachromatic leukodystrophy and Krabbe's leukodystrophy), nutritional diseases of myelin (e.g. Vitamin B12 deficiency) and the acquired toxic-metabolic diseases of myelin (e.g. hexachlorophene encephalopathy in earlier times). Finally, oligodendrocytes were reported to play a part in chronic pain as well as in neurodegenerative diseases. In many of the mentioned diseases, immune processes are taking place, which, as described before, could be modulated by oligodendrocytes. As an example, we take a closer look within the research field of MS.

Multiple Sclerosis: a meta-analysis

The pathological hallmarks of MS are the so-called lesions or plaques, regions of demyelination and inflammatory infiltrates in the white matter tissue. In addition, grey matter lesions have been identified in which demyelination takes place but lacking the extensive inflammatory component seen in white matter lesions. The hallmark of

lesions in both tissue types is the loss of myelin. This makes MS an interesting disease to investigate immunomodulatory capacities of oligodendrocytes in the context of an inflammatory demyelinating disease.

The most widely accepted and promoted hypothesis is that MS is originated by immune dysregulation. For example, in 2011, a large GWAS study was published by the International Multiple Sclerosis Genetics Consortium & the Wellcome Trust Case Control Consortium 2 (International Multiple Sclerosis Genetics et al., 2011). In this study, it was stated that “the overrepresentation of genes that influence T-cell maturation provides independent and compelling evidence that the critical disease mechanisms primarily involve immune dysregulation.” However, one should not forget that this inference is based on the yet incomplete databases. Especially gene enrichment analyses have to be interpreted cautiously as our knowledge of the function as well as the occurrence and expression pattern of most genes is largely incomplete. For this reason, the databases based on this knowledge are themselves incomplete and biased. To illustrate this point of view in the context of MS, we have compared the findings of the GWAS study by the International Multiple Sclerosis Genetics Consortium (International Multiple Sclerosis Genetics et al., 2011) to the literature and to the gene expression study by Cahoy et al, 2008 in which the gene expression of oligodendrocyte precursor cells (OPCs), oligodendrocytes and myelinating oligodendrocytes was analyzed. All genes with proximity to a single nucleotide polymorphism (SNP) with evidence of association to MS published by the International Multiple Sclerosis Genetics Consortium have been evaluated for their expression in oligodendrocytes (Table 3). An expression in oligodendrocytes assumes that these genes are functional in these cells. In a next step, the BP (biological process) GO term annotations of those genes were searched for an oligodendrocyte related GO term. However, most genes which are expressed in oligodendrocytes do not have a single GO term relating them to oligodendrocytes in one way or another (Table 3). Due to this lack of information, a possible enrichment of genes involved in oligodendrocyte functions (be it immunomodulatory or not) is significantly less likely. Hence, gene enrichment analyses are biased towards well-investigated research fields whereas other fields are like “blind spots”, influencing the interpretation of the results.

In contrast to the popular view, Barnett and Prineas have shown extensive oligodendrocyte apoptosis and microglial activation in myelinated tissue containing few or no lymphocytes or myelin phagocytes (Barnett and Prineas, 2004). This finding suggests that apoptotic oligodendrocyte death could also be the primary cause of inflammation in the MS brain (Trapp, 2004). Further, many of the above described findings of the immunomodulatory capacity of oligodendrocytes were found in MS or its animal models, emphasizing an important role of oligodendrocytes in MS pathogenesis and -physiology. Together, this suggests another hypothesis that MS is originated by brain intrinsic disturbances.

In these reviewers' opinion, several arguments and evidences are found in the literature supporting both hypotheses as described above. This was also suggested by the finding of different lesion patterns in MS pathology (Lucchinetti et al., 2000). However neither of them excludes the other. In that respect: "Nondum alea jacta est" - The die has not been cast yet. Therefore, we prompt to stay open-minded for all possible disease mechanisms and players in MS, also for unusual ones such as immunomodulatory oligodendrocytes.

Conclusion

Altogether, oligodendrocytes seem to be capable of expressing various immunomodulatory molecules. Some of these molecules are probably pleiotropic, fulfilling also different roles in oligodendrocytes than in microglia or T or B cells. Further, these immunomodulatory molecules might not be expressed at all times but rather under certain circumstances or upon a specific stimulation. However, by a proper signaling event at the right place at the right time oligodendrocytes might become immunologically active and be capable of skewing an inflammatory reaction towards a certain outcome. For example, the activation of phagocytes by oligodendrocytes and the subsequent clearance of myelin debris is a prerequisite for successful myelin regeneration. In our view, oligodendrocytes might not be able to take a significant active part during the peak of inflammation at its strongest activity. However, by making use of their immunomodulatory potential, they might be an important factor in the initiation of inflammation or its resolution, especially in oligodendrocyte directed diseases. For example in MS, a better knowledge of this mostly overlooked function of oligodendrocytes might help to understand lesion formation, repair or clearance and lead to novel therapeutic approaches.

Acknowledgements

We thank Nicolas Sanderson (Department of Biomedicine, University Hospital Basel) for critically reading the manuscript, his inputs and suggestions. This study was supported by the National Multiple Sclerosis Society of the United States of America (Grant RG 3583A1 and RG 4249A2), by the Swiss Multiple Sclerosis Society and by the Swiss National Science Foundation (31003A_159528/1).

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Figure and Table Legends

Figure 1: Oligodendrocytes express inflammasome components

In situ hybridization analysis for CASP4 (A), NLRP1 (B), NLRC4 (C), NLRP3 (D) and PYCARD (E) demonstrated their expression by grey matter oligodendrocytes in control as well as MS samples. Oligodendrocytes are identified by immunohistochemistry for Olig2 (red). In situ hybridization combined with immunohistochemistry for cellular identification was performed as described in detail in Zeis et al. (Zeis et al., 2015).

Table 1: References of documented expression of factors in oligodendrocytes which are known to be involved in immunological processes are indicated, together with the information from where the data were derived from, and with which method. Abbreviations: Array = Microarray, FC = Flow cytometry, IF = Immunofluorescence, IHC = Immunohistochemistry, ISH = In-situ hybridization, NGS = next generation sequencing.

Table 2: Genes expressed by oligodendrocytes known to be involved in immunological processes

Analysis of all genes expressed by OPCs, OLs and myelinating OLs, as published by Cahoy et al., 2008, in the context of immunological processes. The transcriptome of these cell types has been searched for genes with the GO:0002376 term (immune system process). About 40% of all genes tagged with this GO term are expressed by OPCs. In the case of oligodendrocytes and myelinating oligodendrocytes this percentage diminishes to about 35% and 32%.

Table 3: Analysis of the published risk genes for MS in the context of their expression in oligodendrocytes

All risk genes for MS - as published by (International Multiple Sclerosis Genetics et al., 2011) - have been analyzed whether they are expressed by oligodendrocytes, and whether this is reflected in the GO annotation database. Of the 55 published MS risk genes, 23 have been found to be expressed by OPCs, 21 by oligodendrocytes and 18 by myelinating oligodendrocytes as reported by (Cahoy et al., 2008), suggesting their functionality in oligodendrocytes. However, only one single gene was tagged with an oligodendrocyte related GO term showing the current lack of information in such databases, and the therefore, biased outcome of analyses based on these databases.

Table 1: Factors expressed by oligodendrocytes and know to be involved in immunological processes

Gene	Reference	PMID	<i>In vitro</i>	<i>In vivo</i>	Method
<i>Cytokines</i>					
IL-17A	Tzartos et al., 2008	18156204		X	IF, ISH
IL-1b	Moyon et al., 2015	25568099	X	X	IF, Array
NLRP1	Kummer et al., 2007	17164409		X	IHC
IL-18	Cannella and Raine, 2004	14705111		X	IHC
IL-6	Ramesh et al., 2012	22524232	X		ELISA
<i>Chemokines</i>					
CCL2	Balabanov et al., 2007	17314297	X		LiquiChip
	Moyon et al., 2015	25568099	X	X	IF, Array
CCL3	Balabanov et al., 2007	17314297	X		LiquiChip
CCL5	Balabanov et al., 2007	17314297	X		LiquiChip
CXCL10	Balabanov et al., 2007	17314297	X		LiquiChip
IL-8	Ramesh et al., 2012	22524232	X		ELISA
CXCL5	Merabova et al., 2012	22034072	X		Cytokine antibody assay, ELISA
<i>Antigen presentation molecules</i>					
MHC Class I	Hoftberger et al., 2004	14997936		X	IF
	Okamura et al., 2007	17996308	X		FC
PDCD1LG2	Okamura et al., 2007	17996308	X		FC
CD274	Okamura et al., 2007	17996308	X		FC
MHC Class II	Bergsteindottir et al., 1992	1409602	X		IHC
<i>Tetraspanins</i>					
CD9	Ishibashi et al., 2004	14715942		X	IHC
CD81	Sullivan and Geisert, 1998	9624590		X	IHC
CD82	Mela and Goldman, 2009	19741124	X		IF
	Mela and Goldman, 2013	23637186	X		IF
TSPAN2	Birling et al., 1999	10582623		X	ISH
	De Monasterio-Schrader et al., 2013	24038504		X	IHC
PLP	De Monasterio-Schrader et al., 2013	24038504		X	IHC
<i>Neuroimmune regulatory proteins</i>					
CD200	Chitnis et al., 2007	1854964		X	IF
	Koning et al., 2009a	19151626		X	IF

CD47	Gitik et al., 2011	3068094	X	IF
SEMA3A	Williams et al., 2007	17855378	X	ISH
FasL	Dowling et al., 1996	8879222	X	IHC
	Li t al., 2000	10912923	X	IHC
<i>Complement and complement receptors</i>				
C1s, C2, C3,...	Hosokawa et al., 2003	12730962	X	PCR
<i>Complement regulatory proteins</i>				
CD55	Gasque and Morgan, 1996	8958045	X	PCR
	Scolding et al., 1998	9600710	X	IHC
CD59	Scolding et al., 1998	9600710	X	IHC
CD46	Gasque and Morgan, 1996	8958045	X	PCR
<i>Extracellular matrix proteins</i>				
VCAN	Gu et al., 2007	17883936	X	IF, PCR
<i>Others</i>				
Others	Cahoy et al., 2008	18171944	X	Array
	Zhang et al., 2014	25186741	X	NGS

Table 2: Genes expressed by oligodendrocytes known to be involved in immunological processes

GO:0002376 - Immune system process		
total # of annotated proteins/genes	2186	
	#	%
Detected in OPCs*	847	39
Detected in Oligos*	771	35
Detected in myelin Oligos*	696	32

*according to Cahoy et al., 2008

Table 3: Analysis of the published risk genes for MS in the context of oligodendrocytes

Sawcer et al., 2011	Cahoy et al., 2008			QuickGo search	Literature search	
Genes in proximity to a SNP with evidence of association	Gene expression detected in			Myelin / Oligodendrocyte related GO term (BP)	Reported to be expressed by oligodendrocyte	PMID
	OPCs	Oligos	Myelin/Oligos			
HLA-DRB1	-	-	-			
HLA-A	-	-	-		Hirayama et al., 1986	3103030
MMEL1	-	-	-			
EVI5	Yes	Yes	Yes	No		
VCAM1	Yes	Yes	No	No		
CD58	-	-	-			
RGS1	Yes	Yes	Yes	No		
C1orf106	-	-	-			
PLEK	Yes	Yes	Yes	No		
MERTK	Yes	Yes	Yes	No	Prieto et al., 2000	10954847
SP140	-	-	-			
EOMES	No	No	No			
CBLB	Yes	Yes	Yes	No		
TMEM39A	Yes	Yes	Yes	No		
CD86	-	-	-			
IL12A	-	-	-			
NFKB1	Yes	Yes	Yes	No		
IL7R	-	-	-		Ashbaugh et al., 2013	23530149
PTGER4	No	No	No			
IL12B	-	-	-			
BACH2	Yes	Yes	Yes	No		
THEMIS	-	-	-			
MYB	Yes	No	No	No		
IL22RA2	-	-	-			
TAGAP	Yes	Yes	Yes	No		
ZNF746	-	-	-			
MYC	Yes	Yes	No	No	Kumar et al., 1998	9856859
PVT1	No	No	No			
IL2RA	-	-	-			
ZMIZ1	-	-	-			
HHEX	Yes	No	No	No		
CD6	-	-	-			
CXCR5	-	-	-			
TNFRSF1A	Yes	Yes	No	No	Kim et al., 2011	21044081
CLECL1	-	-	-			
CYP27B1	-	-	-			
ARL6IP4	Yes	Yes	Yes	No		
ZFP36L1	Yes	Yes	No	No		
BATF	-	-	-			
GALC	Yes	Yes	Yes	No	Mirsky et al., 1980	7358790
SOX8	Yes	Yes	Yes	Yes	Stolt et al., 2004	15102707
CLEC16A	-	-	-			
IRF8	Yes	No	Yes	No	Horiuchi et al., 2011	21261980
STAT3	Yes	Yes	Yes	No	Dell'Albani et al., 1998	9788278
RPS6KB1	Yes	Yes	Yes	No		
MALT1	-	-	-			
TNFSF14	-	-	-			
TYK2	Yes	Yes	Yes	No		
IL12RB1	No	Yes	Yes	No		
DKKL1	No	No	No			
CD40	No	No	No			
CYP24A1	-	-	-			
TNFRSF6B	-	-	-			
MAPK1	Yes	Yes	Yes	No	Bhat and Zhang, 1996	8780027
SCO2	-	-	-