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Modelling of Autoimmune Encephalomyelitis in a Non-Human Primate

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1. Introduction

Multiple sclerosis (MS) is a chronic disabling disease characterized by inflammation, demyelination, and axonal damage in the central nervous system (CNS), affecting both white and grey matter. Commonly observed symptoms are visual and balance disturbances, spasticity, bladder dysfunction, pain, and fatigue. At a later disease stage, paralysis may occur (Compston & Coles 2008; Sospedra & Martin 2005).

For both exploratory and applied research into MS the use of a valid animal model is indispensable. The most widely used animal model for MS is experimental autoimmune encephalomyelitis (EAE), which is induced by active immunization with myelin derivatives formulated in adjuvant. EAE has been induced in a wide variety of species, including rabbits, guinea pigs, rats, mice, and non-human primates (Brok et al 2000; Genain et al 1995; Gold et al 2006; Massacesi et al 1995; Wekerle 2006).

The EAE model in the common marmoset (*Callithrix jacchus*), a small-sized New World monkey, is exquisitely suitable for translational research into pathogenic mechanisms and therapy development for MS. A feature that distinguishes the model from classical rodent EAE models is that marmosets are exposed to the same environmental cues as humans, including those associated with MS susceptibility, i.e. viral pathogens. In this chapter, we will summarize our investigations into the core pathogenic autoimmune mechanisms underlying the development of pathology and clinical symptoms. In addition, we will discuss the separate and combined role of B cells and T cells, in this model. Finally, we will briefly discuss how the model can be used for testing new therapies.

1.1 Immunology and genetics of the common marmoset

The marmoset is immunologically, anatomically, and neurologically more closely related to humans than rodents. In contrast to laboratory rodent strains, the marmoset is an outbred species, and the clinical and pathologically heterogeneity of the EAE model resembles the heterogeneous situation in MS.

A particularly interesting aspect of marmosets is the stable bone marrow chimerism between twin siblings that is caused by the sharing of the placental blood stream. Consequently, the immune systems of twins are educated in the same thymic environment, making fraternal siblings immunologically more similar than siblings from different births

(Niblack et al 1977). This principle can be used in therapy trials where one twin sibling is treated with an experimental agent and the other sibling with placebo.

The strongest genetic influence on MS susceptibility in the human population is exerted by the major histocompatibility complex (MHC). The MHC is a highly polymorphic genetic region that encodes for antigen presentation molecules, which according to international consensus nomenclature are indicated with the acronym *Caja*, being derived from *Callithrix jacchus*. MHC class II molecules are constitutively expressed on B cells and antigen presenting cells (APC) and are involved in the activation of CD4⁺ T cell responses. MHC class I molecules are expressed on all nucleated cells and are involved in the activation of CD8⁺ T cells. In the marmoset, MHC class I diversity is more limited than in humans. The classical *A*, *B*, and *C* molecules could not be identified in marmosets, but non-classical *E* (oligomorphic) and *G* genes (polymorphic) have been described (Cadavid et al 1997; Knapp et al 1998). The marmoset MHC class II region contains *DQA1*, *DQB1*, and *DQB2* genes, but *DQA2* and *DP* genes could not be identified. Marmosets contain one *DRB* region configuration, containing the three lineages *DRB1*03*, *DRB*W12*, and *DRB*W16*. *Caja-DRB1*03* and *-DRB*W16* are polymorphic with 13 and 20 alleles, respectively. *Caja-DRB*W12* appears to be monomorphic with two alleles, which differ only at two codons. All marmosets express *DRB*W1201* or *DRB*W1202* (Antunes et al 1998; Doxiadis et al 2006; Prasad et al 2006; Wu et al 2000).

Despite the limited polymorphism of the MHC, marmosets contain a diverse and evolutionary stable T cell receptor α - and β -chain repertoire (Fujii et al 2010; Uccelli et al 1997).

1.2 Myelin oligodendrocyte glycoprotein

Demyelination is the pathological hallmark of MS and is caused by a combined cellular and humoral autoimmune attack on myelin. The myelin sheath is produced by oligodendrocytes and is wrapped around axons to ensure fast saltatory pulse conduction. Myelin is composed of 80% lipids and 20% proteins, such as myelin basic protein (MBP), proteolipid protein (PLP), and myelin oligodendrocyte glycoprotein (MOG).

MOG is a type I membrane glycoprotein and a member of the Ig superfamily produced by oligodendrocytes. MOG is located on the outer myelin sheath with the N-terminal amino acids 1 to 125 exposed to the extracellular environment where it is accessible for immune cells (Kroepfl et al 1996; Ohler et al 2004). MOG probably forms homodimers (Clements et al 2003) and is highly conserved among species (Delarasse et al 2006; Mesleh et al 2002).

The function of MOG in the CNS is unknown, as MOG-deficient mice do not present clinical or histological abnormalities (Delarasse et al 2003). However, MOG is an important target of the autoimmune attack in EAE. Autoimmunity against MOG is crucial for the progression of EAE in Biozzi ABH mice (Smith et al 2005) and marmosets (Jagessar et al 2008). Immunization with recombinant human MOG (rhMOG) protein or MOG peptides induces pathogenic antibody and T cell responses (Iglesias et al 2001; von Büdingen et al 2001). Antibodies against MOG facilitate demyelination and phagocytosis *in vitro* (Kerlero de Rosbo et al 1990; Van der Goes et al 1999) and enhance demyelination *in vivo* in mice (Morris-Downes et al 2002), rats (Linington et al 1988; Schluesener et al 1987), and marmosets (Genain et al 1995; McFarland et al 1999). T cell responses against MOG are found in EAE models in mice (Mendel et al 1995), rats (Stefflerl et al 2000), marmosets (Brok et al 2000), and rhesus macaques (Kerlero de Rosbo et al 2000).

2. Modelling of MS in the common marmoset

The marmoset EAE model was first developed by Genain and co-workers (Massacesi et al 1995). Since then, the model has been continuously refined to improve the similarity with MS (t Hart et al 2009). All EAE models that have been developed in the past years vary in their clinical and pathological features, see Table 1.

The first documented EAE model in the marmoset was induced with human myelin emulsified in complete Freund's adjuvant (CFA) supplemented with *Bordetella pertussis* particles. The disease was very acute and gave an acute disseminated encephalomyelitis (ADEM) like disease (Massacesi et al 1995). Several large seriously destructive lesions in the white matter of the brain and spinal cord were detected in this model.

EAE induction with human or mouse myelin in CFA, but without *Bordetella pertussis*, gave essentially the same pathology but had a slower disease progression. We observed in these models high T and B cell responses against various myelin proteins, i.e. MOG, MBP and PLP; we chose to study the role of MOG in more detail. To confirm the pathogenic significance of MOG, one sibling of a marmoset twin was sensitized against myelin derived from wild type C57BL/6 mice and the other sibling with myelin derived from MOG deficient mice of the same strain (Jagessar et al 2008). Animals immunized with MOG deficient myelin showed only mild clinical EAE symptoms, inflammation and small demyelinated areas in the white matter. We assume that these are caused by autoimmune reactions against other myelin proteins, such as MBP and PLP.

The addition of a physiological dose of recombinant MOG to mice immunized with MOG-deficient myelin restored the induction of chronic relapsing EAE in Biozzi ABH mice (Smith et al 2005). This observation emphasizes the immunodominance of MOG, which was investigated in further detail in marmosets immunized with recombinant human MOG (rhMOG) in CFA. This formulation induced a more chronic disease and a typical MS like pathology, characterized by active lesions in the CNS with macrophages containing myelin degraded products (Kap et al 2008). Moreover antibody formation against the whole MOG protein and specific MOG peptides were observed, such as MOG₁₄₋₃₆, MOG₃₄₋₅₆ and MOG₅₄₋₇₆. Interestingly, animals that developed clinical EAE signs showed specific T cell proliferation against MOG₃₄₋₅₆ and MOG₇₄₋₉₆.

To test the immunogenicity of the peptides, marmosets were immunized with some of the peptides separately in CFA. It was observed that MOG₁₄₋₃₆ is only moderately encephalitogenic inducing only small-sized inflammatory lesions (Brok et al 2000). MOG₇₄₋₉₆ was not encephalitogenic, whereas marmosets immunized with MOG₃₄₋₅₆ displayed essentially similar pathology and disease course as the EAE model with rhMOG in CFA (Kap et al 2008). Antibodies against rhMOG, MOG₃₄₋₅₆ and the overlapping peptide MOG₂₄₋₄₆ were formed in the MOG₃₄₋₅₆/CFA EAE model.

The absence of antibodies binding MOG protein directs the attention to the MOG₃₄₋₅₆ specific cytotoxic T cells as a cause of the widespread demyelination that was observed in the MOG₃₄₋₅₆/CFA model. T cell lines raised against MOG₃₄₋₅₆ were phenotypically characterized as CD4⁺, CD8⁺ or CD4/8 double positive, expressing also CD56⁺ but not CD16 (Kap et al 2008). Interestingly, T cells with a similar phenotype have been associated with demyelination in MS (Vergelli et al 1996; Antel et al 1998). Further phenotypical characterization in humans showed that the T cells were CD45RO⁻, CD27⁺CD28⁻CCR7⁻, being a phenotype reminiscent to the NK-CTL effector memory subpopulation (Mazzarino et al 2005).

CFA is a major cause of the serious discomfort experienced by animals engaged in the EAE model. This prompted us to test if EAE could be induced without usage of CFA. Hence, animals were subjected to a challenge-boost protocol with MOG₃₄₋₅₆ in incomplete Freund's adjuvant (IFA) (Jagessar et al 2010). It is of note that the inoculum lacked microbial antigens for innate immune activation. Nevertheless, all animals developed clinically evident EAE, which was characterized by marked inflammation and demyelination in the grey and white matter of the brain and spinal cord. Freshly isolated T cells also showed the NK-CTL phenotype, with cytolytic capacities and a Th17 cytokine profile as immunological hallmark. The replacement of CFA by IFA makes this model more useful for the study of subtle regulatory networks that keep T and B cells in check and maintain homeostasis within the CNS.

Antigen	Adjuvant	Disease type	Demyelination		T cells	IgG to rhMOG
			Grey matter	White matter		
Human myelin	CFA+ <i>B. pertussis</i>	Acute	N/A	+	N/A	N/A
Human myelin	CFA	Acute	N/A	+	N/A	N/A
Mouse myelin	CFA	Acute	N/A	+	N/A	N/A
MBP	CFA	Mild	N/A	+/-	N/A	N/A
MOG ^{-/-} mouse myelin	CFA	Mild	N/A	+/-	N/A	-
rhMOG	CFA	Chronic	+	+	Th1/Th17	+
MOG ₁₄₋₃₆	CFA	Chronic	N/A	+	N/A	+
MOG ₃₄₋₅₆	CFA	Chronic	+	+	Th1/Th17	+
MOG ₃₄₋₅₆	IFA	Chronic	+	+	Th17	-

CFA, complete Freund's adjuvant; IFA, incomplete Freund's adjuvant; MOG, myelin oligodendrocyte glycoprotein; N/A, not available

Table 1. All marmosets EAE models with their characteristics.

3. Role of B cells in the marmoset EAE models

We observed no relation between the diversity of the antibody response and the rate of EAE progression in marmosets (Kap et al 2008). In addition, EAE can be induced in the absence of anti-rhMOG antibodies (Jagessar et al 2010). This was not entirely unexpected. Although a role of anti-MOG antibodies in the induction of CNS demyelination has been proven (Genain et al 1995; Genain et al 1999), the main pathogenic antibody reactivity is thought to be mainly directed against non-linear/conformational epitopes (von Büdingen et al 2004).

Recently, treatment with Rituximab, an anti-CD20 antibody, in MS patients showed clear beneficial effect. The amount of lesions and relapses reduced significantly in the anti-CD20 treated group compared to the placebo group, although antibody levels did not reduce significantly (Hauser et al 2008; Bar-Or et al 2008). These data suggest that Rituximab does not deplete plasma cells, which lack CD20 expression, and that the antigen presentation or a regulatory role by B cells may play a key role in disease development.

A similar study in marmoset monkeys was performed to understand the role of B cells in further detail (Kap et al 2010b). This study showed a profound effect of anti-CD20 treatment in animals with EAE, see also section 6.4. In addition to the study in MS patients, impaired activation of autoreactive T cells in lymphoid organs was observed and reduced mRNA levels of IL-7 and pro-inflammatory cytokines, e.g. IL-6, IFN γ and TNF α . Also less inflammation and demyelination was detected in the white as well as the grey matter.

It is assumed that there is a relation between MS and EBV infected B cells, see section 5.2. To investigate the role of EBV transformed B cells, we are creating an *in vivo* model for EBV infection in marmosets. Marmoset monkeys will be infused with autologous B lymphoblastoid cell (B-LCL) induced with the marmoset EBV B95-8 virus. By *ex vivo* pulsing of the B-LCL with the dominant MOG peptide 34 to 56, and injecting them back, the B-LCL will acquire the capacity to activate encephalitogenic T cells. As control, the sibling will be infused with B-LCL, but these cells will not be pulsed with the MOG peptide.

4. Role of T cells in the marmoset EAE models

T cells reactive against MOG are present in the natural T cell repertoire of healthy human individuals (Diaz-Villoslada et al 1999; Koehler et al 2002) as well as in healthy marmosets (Villoslada et al 2001). These autoreactive T cells are not depleted during development of the immune system because MOG is absent outside the CNS (Bruno et al 2002) and is likely expressed within the CNS relatively late during fetal development (Allamargot & Gardinier 2007). A significant increase in the number of MOG-specific T cells was reported in blood and cerebrospinal fluid (CSF) of MS patients (Kerlero de Rosbo et al 1993; Sun et al 1991).

T cells play a central role in the marmoset EAE model, as EAE can be induced by the activity of MOG-specific T cells without support of autoantibodies. Below, the specificity, phenotype, and function of the T cells that are activated in the EAE model will be discussed.

4.1 Specificity

Immunization of marmosets with rhMOG in CFA leads to a 100% disease incidence that maps to the MHC class II allele *Caja-DRB*W1201*, which is ubiquitously expressed in marmosets (Antunes et al 1998; Brok et al 2000; Doxiadis et al 2006). In marmosets immunized with rhMOG, *Caja-DRB*W1201* presentation of MOG₂₄₋₃₆ leads to the activation of MOG₂₄₋₃₆ specific Th1-cells in all animals (Brok et al 2000). However, T cells against this peptide alone are not sufficient to induce the full aspect of the disease as shown by immunization (Brok et al 2000) or adoptive transfer (Villoslada et al 2001). This suggests an important pathogenic role of T cells directed against other MOG epitopes.

In a meta-analysis of T cell response profiles from about 30 rhMOG-immunized marmosets, we observed that T cells from monkeys developing clinically evident EAE early after immunization (fast progressors) proliferate against a wider range of MOG peptides than T cells from monkeys developing overt disease at a later time point (slow progressors) (Kap et al 2008). T cell responses against the peptide MOG₃₄₋₅₆ were confined to fast progressor monkeys. As discussed above, immunization with MOG₃₄₋₅₆ in either CFA or IFA leads to EAE (Jagessar et al 2010; Kap et al 2008). This shows that MOG₃₄₋₅₆ contains crucial T cell epitopes for the activation of T cells that can induce neurological disease.

The T cell response in marmosets against MOG is similar to MS, being mainly directed against three domains in the extracellular part of MOG, i.e. 1-22, 34-56, and 64-96 (Bielekova & Martin 2004; Kerlero de Rosbo et al 1997; Van der Aa et al 2003).

4.2 Phenotype and function

It has long been thought that CD4⁺/Th1 cells were the main pathogenic T cells in MS, but more recent literature highlights an important pathogenic contribution of Th17 cells and CD8⁺ T cells as well (Brucklacher-Waldert et al 2009; Ifergan et al 2008; Kebir et al 2007; Serafini et al 2007; Tzartos et al 2008). We have investigated the role of the different T cells subsets in more detail in the marmoset EAE model.

Immunization of marmosets with rhMOG or MOG₃₄₋₅₆ leads to the proliferation of CD4⁺CD8⁻, CD4⁻CD8⁺, and CD4⁺CD8⁺ MOG₃₄₋₅₆-specific T cells. In addition, a large population of these T cells expresses CD56, which is a marker for natural killer-cytotoxic T lymphocytes (NK-CTL).

MOG₃₄₋₅₆-specific T cells have also other characteristics of NK-CTLs, as they are able to lyse MOG₃₄₋₅₆ pulsed cells (Jagessar et al 2010; Kap et al 2008). This is similar to MS patients, in which cytotoxic MOG-specific T cells have also been observed (Koehler et al 2002; Van der Aa et al 2003). This suggests that MOG₃₄₋₅₆ specific T cells can induce cytolysis of oligodendrocytes leading to demyelination.

The contribution of IFN- γ producing Th1 and IL-17A producing Th17 cells is an ongoing debate in MS, but also in the EAE models (Haak et al 2009; Komiyama et al 2006; Kroenke et al 2008; Langrish et al 2005; O'Connor et al 2008). Immunization of marmosets with rhMOG in CFA leads to the activation of both Th1 and Th17 cells (Kap et al 2010a). Inhibition of IL-17A in this model has only a marginal effect on the disease course, suggesting that Th1 cells or the cytotoxicity of these T cells are more crucial than the single cytokine (Kap et al 2010a). Immunization of marmosets with MOG₃₄₋₅₆ in IFA leads to the production of IL-17A, but not to IFN- γ , suggesting that Th17 and cytotoxic T cells dominate in this model.

5. Role of viruses

It is believed that the origin of autoimmune diseases, i.e. MS, has multiplex backgrounds. The role of genetic predisposition and environmental factors are much less defined, although viral infections have long been associated with MS development. Viral infections are known as the most critical environmental factors. Herpesviruses, such as human herpesvirus type 6 (HHV-6) (Fotheringham & Jacobson 2005; Lunemann et al 2007), Epstein-Barr virus (EBV) and to a lesser extent cytomegalovirus (CMV) (Kanzaki & Yabuki 1994) are suspects.

5.1 CMV

CMV is a beta herpes virus and a leading cause of opportunistic infection in the human population. CMV infection is estimated at a range from 50% to 80% in humans, and remains asymptomatic in the vast majority of infected individuals (Staras et al 2006). The prevalence is quite variable as it varies in different geographic areas, different social economic population and ethnic origin. CMV has been associated with several autoimmune diseases, i.e. Systemic Lupus Erythematosus (Sekigawa et al 2002), diabetes mellitus type 1 and 2 (Filippi & von Herrath 2005; Roberts & Cech 2005) and with the Guillain-Barré Syndrome, a demyelinating disorder of peripheral nervous system (Yuki et al 2001), but there is no obvious association with MS. However, the virus has been involved in acute CNS inflammatory disorders, causing meningo-encephalitis in immunocompromised and immunocompetent individuals (Devetag & Boscaruolo 2000). Moreover, recently it was observed that MS patients sufficient for Vitamin D were associated with an increased CMV

antibody level, while such an association was absent or in the opposite direction in controls (Mowry et al 2010). Furthermore, CD8⁺ T cells specific against CMV could be isolated from brain lesions of MS patients (Scotet et al 1999). In support of a role of CMV in MS is the observation that CD8⁺ T cells from rhesus EAE monkeys immunized with MOG₃₄₋₅₆ in CFA display high proliferation against a 9-mer peptide derived from the immunodominant UL86 antigen of human CMV, encoding the major capsid protein (Sylwester et al 2005). Interestingly, the amino acid sequence 986 to 993 (WLRSPFSR) of the major capsid protein showed striking similarity with the MOG sequence 39 to 46 (WYRPPFSR). T cells from rhesus monkeys sensitized against the mimicry motif proliferated against MOG₃₄₋₅₆, whereas CD3⁺ T cells infiltrates were detected within the CNS white matter and meninges (Brok et al 2007). This data suggests that anti-CMV memory T cells can be activated by APC that present MOG₃₄₋₅₆. We hypothesise that CMV does not provoke MS, but those individuals that are predisposed with CMV generate a repertoire of memory T cells. These memory T cells might exacerbate CNS inflammation and demyelination upon activation with MOG₃₄₋₅₆ presenting APC as in the marmoset EAE model (Kap et al 2008).

5.2 EBV

EBV is a gamma herpes virus, which causes lymphoproliferative diseases, such as Hodgkins lymphoma, nasopharyngeal carcinoma and acute infectious mononucleosis (Levin et al 2003). The prevalence of EBV infection in Western countries is very high; in adulthood more than 90% of the population are infected with EBV. Half of this population becomes EBV positive after the age of ten. Individuals (30-50%) who experience a primary EBV infection in adolescence will develop infectious mononucleosis. A CD8⁺ T cell response develops against an impressive expansion of EBV infected B cells, where 10 to 30% of the B cells carry the virus (Cohen et al 2000).

In developing countries most of the children become in contact with EBV, before the age of ten; all children are EBV infected and mostly without symptoms. This indicates an age-related association between a primary EBV infection and infectious mononucleosis.

Over the years many studies have found an association between EBV infection and the development of MS. MS patients showed a significant increase of anti-EBV antibody levels, i.e. anti-EBNA-1, compared to controls (Sumaya et al 1980). It was also found that the antibody levels increased before the onset of MS (Levin et al 2005). Meta-analysis of thirteen studies has found an odd ratio of 0.06 for the risk to develop MS, when EBV seronegative individuals were compared with seropositive individuals. Of all MS patients, 99.5% were seropositive for EBV related to 94% of the controls. In children with MS 99% were positive for EBV, while 72% of the age-matched controls were negative (Ascherio & Munger 2007; Pohl et al 2006). In MS patients also increased CD4⁺ T cell responses to EBNA-1 were observed compared to controls (Lunemann et al 2006; Lunemann et al 2008).

6. Immunotherapies tested in the marmoset EAE model

The immunological proximity to humans and the clinico-pathological similarity with MS makes the EAE model in marmosets an exquisite test system for the preclinical evaluation of novel immunotherapies. This is especially the case for biological agents, which due to high species-specificity are inactive in lower species. A particularly attractive aspect of the marmoset model is the possibility to visualize the large-sized lesions in the brain with clinically relevant magnetic resonance techniques (Blezer et al 2007; 't Hart & van Kooyk

2004). This has enabled determination of the direct effect of new immunotherapies on lesions independent of the effects on neurological signs ('t Hart & Heije 2005).

In the past years a variety of biological agents was tested mainly aiming at modulating APC-T cell interactions.

6.1 Anti-human CD40 mAb

CD40 is a costimulatory molecule that is constitutively expressed on B cells and induced on myeloid antigen presenting cells, e.g. dendritic cells and macrophages. The interaction of CD40 with its ligand CD154 induced on activated T cells plays an important role in the activation of T and B cells as well as of myeloid antigen presenting cells and macrophage effector functions. The pleiotropic effects of CD40-CD154 interaction on immune functions create an attractive target of immunotherapy in autoimmune diseases, such as MS. Indeed, it was found that a chimeric antagonist anti-CD40 antibody administered during the onset of EAE in marmosets had a strong inhibitory effect on the disease (Boon et al 2001).

6.2 Anti-human IL-12p40 mAb

One of the factors produced by activated APC of the myeloid lineage is IL-12, which is a critical cytokine in the induction of Th1 responses. The notion that Th1 cells have a key pathogenic role in relapsing-remitting MS warranted efficacy evaluation of ustekinumab, a novel human-anti-human IL-12p40 antibody, in the marmoset EAE model. A prophylactic study-design in marmoset EAE induced with human myelin in CFA, showed complete protection against EAE (Brok et al 2002). Next, the same antibody was tested in a therapeutic setting, i.e. starting treatment when brain white matter lesions could be detected on T2-weighted MR images. This experiment showed complete suppression of the inflammatory activity in lesions as well as of lesion enlargement, but only delayed the onset of neurological deficit ('t Hart et al 2005).

6.3 Anti-human IL17A mAb

Many of the immunopathogenic mechanisms driving EAE that were previously assigned to the IL-12-Th1 pathway are actually mediated via the IL-23-induced activation of Th17 cells (Cua et al 2003; Langrish et al 2005), which exerts its pro-inflammatory effects via IL-17A/F, IL-6 and TNF- α . Therefore, we tested the effect of a neutralizing human antibody against human IL-17A in the rhMOG/CFA-induced EAE model. It was observed that the antibody did not protect against EAE, but caused only a moderate delayed onset of neurological signs (Kap et al 2010a). Our interpretation of this experiment is that it supports a role of IL-17A in late stage disease, rather than in the disease onset. This is in agreement with the observation that the MOG₃₄₋₅₆ specific T cells that are associated with onset of neurological signs display IL-17A production as immunological hallmark.

6.4 Anti-human CD20 mAb

MS has for a long time been regarded as a T cell-driven disease, with a less important contribution of B cells, i.e. only the amplification of demyelination via the secretion of anti-myelin antibodies that elicit complement- (CDC) or macrophage-dependent (ADCC) cytotoxicity reactions. In this light it was rather unexpected that antibody-mediated depletion of CD20⁺ B cells with rituximab had an almost immediate and longlasting beneficial effect on relapsing-remitting MS (Hauser et al 2008). As serum antibody levels

remained essentially unaltered the mechanism underlying this remarkable clinical effect is poorly understood. Recent work in rheumatoid arthritis shows a reduction of Th17 responses in patients treated with rituximab, an effect that could be highly relevant for MS as well.

We have tested another human-anti-human CD20 antibody related to ofatumumab in the rhMOG/CFA induced marmoset EAE model. It was observed that weekly administration of the CD20⁺ B cell depleting antibody, which was started at day 21 post-immunization, had a similar profound clinical effect as rituximab in relapsing-remitting MS (Kap et al 2010b). Remarkably, at the pathological level we observed the complete absence of lesions in the white as well as the grey matter. Mechanistically, suppressed autoantibody levels and profoundly altered cytokine profiles, especially of IL-7 and IL-17A, were detected.

7. Conclusion

The data discussed above clearly demonstrated that the outcome of a preclinical efficacy test with a new candidate therapeutic is strongly influenced by the chosen animal model. It is not surprising that reagents targeting Th1 cells are effective in EAE models induced with CFA, as CFA skews cellular immune reactions into the direction of Th1, with a less prominent pathogenic role of Th17 cells. By contrast, our data show that the marmoset EAE model induced with antigen in IFA is more dominated by Th17 cells; thus would thus be the elected model for testing reagents targeting Th17 cells. Obviously, the most important question is which model is the best representation of MS. Much could be learned from mechanistic analysis of successful and failed trials in MS. There is a marked discrepancy between the positive effect of the anti-human IL-12p40 antibody, ustekinumab, in the rhMOG/CFA-induced marmoset EAE model (Brok et al 2002; 't Hart et al 2005) and the inefficacy in relapsing-remitting MS. This may suggest that Th1 cells have a less prominent role in relapsing MS than in the EAE model, being consistent with the notion that Th17 cells may be pathogenetically more relevant in MS (Langrish et al 2005). On the other hand, depletion of CD20⁺ B cells has a similar beneficial effect in the rhMOG/CFA-induced marmoset EAE model and relapsing MS (Hauser et al 2008; Kap et al 2010b). Intriguingly, the depletion of B cells also diminishes IL-7 mRNA levels in the lymphoid organs (Kap et al 2010b), which could impair the activation of Th17 effector memory cells (Liu et al 2011). The MOG₃₄₋₅₆/IFA EAE model shows that the T cells that mediate CNS inflammation and demyelination in marmosets can be *in vivo* activated without the need of APC activating innate receptor ligands, suggesting that they may be effector memory cells (Jagessar et al 2010). Data obtained from MS patients suggests that this may also be the case in MS (Bielekova et al 2004).

As discussed, the marmoset EAE model resembles MS closely and is a valid model for exploratory and applied research. Future work should make clear which model resembles MS most and should be used for preclinical testing.

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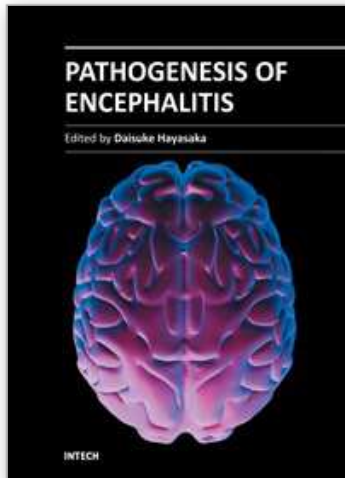
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Pathogenesis of Encephalitis

Edited by Dr. Daisuke Hayasaka

ISBN 978-953-307-741-3

Hard cover, 344 pages

Publisher InTech

Published online 09, December, 2011

Published in print edition December, 2011

Many infectious agents, such as viruses, bacteria, and parasites, can cause inflammation of the central nervous system (CNS). Encephalitis is an inflammation of the brain parenchyma, which may result in a more advanced and serious disease meningoencephalitis. To establish accurate diagnosis and develop effective vaccines and drugs to overcome this disease, it is important to understand and elucidate the mechanism of its pathogenesis. This book, which is divided into four sections, provides comprehensive commentaries on encephalitis. The first section (6 chapters) covers diagnosis and clinical symptoms of encephalitis with some neurological disorders. The second section (5 chapters) reviews some virus infections with the outlines of inflammatory and chemokine responses. The third section (7 chapters) deals with the non-viral causative agents of encephalitis. The last section (4 chapters) discusses the experimental model of encephalitis. The different chapters of this book provide valuable and important information not only to the researchers, but also to the physician and health care workers.

How to reference

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S. Anwar Jagessar, Nicole Heijmans, Nikki van Driel, Bert A. 't Hart and Yolanda S. Kap (2011). Modelling of Autoimmune Encephalomyelitis in a Non-Human Primate, Pathogenesis of Encephalitis, Dr. Daisuke Hayasaka (Ed.), ISBN: 978-953-307-741-3, InTech, Available from: <http://www.intechopen.com/books/pathogenesis-of-encephalitis/modelling-of-autoimmune-encephalomyelitis-in-a-non-human-primate>

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