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Lipids and lipid-reactive antibodies as biomarkers for multiple sclerosis

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Abstract

Multiple sclerosis (MS) is an autoimmune disease that targets the central nervous system (CNS). MS initially follows a relapsing–remitting course (RRMS) in which acute attacks are followed by a complete recovery. Eventually, 65% of the RRMS patients go on to develop secondary progressive MS (SPMS), characterized by the progressive and irreversible accumulation of neurological disability. It has been proposed that the transition from RRMS to SPMS results from changes in the nature of the inflammatory response and the progressive accumulation of neurodegeneration. To date, however, there is no reliable method to monitor the activity of the different immune and neurodegenerative processes that contribute to MS pathology. Thus, there is a need for biomarkers useful for the diagnosis, treatment and monitoring of MS patients. In this review, we discuss the potential use of lipids and the immune response against them as biomarkers of inflammation and neuro-degeneration for MS.

Keywords

Multiple sclerosis; Biomarkers; Lipids; Anti-lipid antibodies

1. Introduction

Multiple sclerosis (MS) is the leading cause of neurological disability in young adults (Noseworthy et al. 2000; Sospedra and Martin, 2005). In 85% of the patients, MS initially follows a relapsing–remitting course (RRMS) in which acute attacks are followed by a complete recovery (Compston and Coles, 2008). An adaptive immune response against the central nervous system (CNS) is linked to the pathogenesis of RRMS.

Eventually, 65% of the RRMS patients go on to develop secondary progressive MS (SPMS), characterized by the progressive and irreversible accumulation of neurological disability (Compston and Coles, 2008). The progressive disease course observed in SPMS generally occurs in the absence of new inflammatory lesions, and therapies that target the adaptive immune response on SPMS show limited efficacy, suggesting that other mechanisms play a role in this stage of MS (Rovaris et al., 2006). Based on these observations, it has been proposed that while both adaptive and innate immune responses contribute to RRMS, sustained activation of CNS innate immunity drives SPMS (Weiner, 2008). Thus, it is important to quantify the activity of the different pathogenic processes that contribute to the development and progression of MS, to design therapeutic interventions suited to the individual needs of each patient.

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A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (Biomarkers Definitions Working Group, 2001). In the context of MS, biomarkers are being actively sought for the early diagnosis and the identification of individuals at risk of developing MS, the prediction of disease course, the monitoring of disease progression, the staging of MS patients, the selection of specific treatments and the monitoring of response to therapy and the evaluation of novel therapeutics (Bielekova and Martin, 2004; Berger and Reindl, 2006; Martin et al., 2006).

Several biomarkers are currently under investigation for MS. Lipids are important components of myelin and they are targeted by B cells and T cells during the course of MS (Podbielska and Hogan, 2009). Thus, the study of both myelin lipids and the immune response against them has the potential to identify biomarkers of inflammation and neurodegeneration. In this review, we will focus on the use of lipids and the antibody response against them as biomarkers for MS.

2. Lipids as biomarkers for MS

2.1. Cholesterol

Approximately 25% of the cholesterol in the body is located in the brain (Dietschy and Turley, 2004). Most of the cholesterol in the CNS is incorporated in myelin sheaths, and a minor fraction is associated with the membranes of astrocytes and neurons (Dietschy and Turley, 2004). Notably, low levels of metabolites derived from cholesterol in the CNS are released to the circulation and excreted in the urine (Ramsey and Nicholas, 1982). Thus, it is conceivable that myelin damage would be reflected in the levels of cholesterol in the circulation. Indeed, Shore et al. (1987) found increased levels of cholesterol and low and high-density lipoproteins (LDL and HDL) in the plasma of rats following experimental autoimmune encephalomyelitis (EAE) induction. Those findings were corroborated by Harold and Nicholas using ^{14}C-labeled CNS cholesterol to examine the effect of demyelination on the release of CNS cholesterol metabolites (Nicholas and Taylor, 1994). They found that experimental demyelination induced with chemical agents or during the course of experimental autoimmune encephalomyelitis (EAE) was reflected as a significant increase in cholesterol metabolites in urine.

Giubilei et al. (2002) investigated the correlation between plasma cholesterol levels and MS activity, finding a correlation between the number of gadolinium (Gd)-enhancing MRI lesions and the plasma levels of both total and low density lipoprotein. Indeed, they estimated an increase in total plasma cholesterol levels of about 4.4 mg/dl for each gadolinium enhancing lesion. Moreover, a follow up study found an association between clinical worsening of MS and higher levels of LDL, total cholesterol and triglycerides (Weinstock-Guttman et al., 2011). Taken together, these studies suggest that the analysis of cholesterol levels might be useful for the evaluation of MS patients, however in the clinical practice its use might be limited by the use of statins and the confounding effects of the patients' diet.

2.2. Oxidized lipids

Reactive oxygen species and nitric oxide intermediates are produced by activated macrophages and microglia, and are thought to promote the neurodegeneration that leads to the irreversible accumulation of neurological disability in SPMS patients (Basso et al., 2008). The analysis of myelin and other samples from MS patients shows a decrease in the content of phospholipids containing polyun-saturated fatty acids, consistent with increased lipid peroxidation (Yu et al., 1982; Neu, 1983; Cherayil, 1984). Indeed, oxidized lipids and DNA are found in active MS lesions (Haider et al., 2011). Thus it has been hypothesized

that oxidized lipids can be exploited as biomarkers to monitor pathogenic mechanisms in MS. Naidoo and Knapp (1992) measured lipid peroxides in cerebrospinal fluid (CSF) and serum samples from MS patients or control subjects. They found increased lipid peroxidation in serum of MS patients. Other studies have found similar results, however a clear association between the circulating levels of oxidized lipids and specific stages of MS has not been reliably found yet. Koch et al. (2007), for example, measured the levels of plasma fluorescent lipid peroxidation products (PFLPP). They found a significant upregulation of PFLPP levels in MS, but no differences were found between RRMS, SPMS and primary progressive (PP) MS patients. Thus the analysis of lipid peroxidation might help in the early diagnosis of MS, but does not seem to be useful for the staging of MS patients.

Isoprostanes are prostaglandin-like compounds which are formed by free radical catalyzed peroxidation of arachidonic acid esterified in membrane phospholipids (Greco et al., 2000). Isoprostanes are increased in the CSF of RRMS patients, and correlate with disability in RRMS patients (Greco et al., 2000). However their levels do not seem to correlate with the presence of Gd-enhancing MRI lesions (Greco et al., 2004). Thus, it has been suggested that isoprostanes are not useful as surrogate inflammatory markers in MS, but might be biomarkers of the neurodegenerative phenomena that drive disease progression in SPMS. The use of isoprostanes as biomarkers for SPMS is supported by a recent study in which urine isoprostane levels in 26 SPMS were found to be significantly higher than those present in 12 healthy controls (Miller et al., 2011). However, this study is limited by the lack of RRMS and PPMS samples, needed to evaluate the utility of isoprostanes as stage-specific biomarkers for MS. Future studies should evaluate isoprostane levels in different categories of MS patients.

2.3. Oxysterols

The control of neuronal cholesterol levels requires its conversion into the more polar metabolite 24S-hydroxycholesterol, which can cross the blood brain barrier to be released into the circulation (Leoni, 2009). Since 24S-hydroxycholesterol is produced as part of physiological processes that control cholesterol levels in neurons, plasma concentrations of 24S-hydroxycholesterol are thought to reflect the mass of metabolically active neurons (Leoni, 2009). Thus, it has been proposed that 24S-hydroxycholesterol can be used as a marker of brain atrophy in patients with MS and other CNS disorders (Leoni, 2009). Indeed, plasma concentrations of 24S-hydroxycholesterol are significantly reduced in RRMS and PPMS patients (Leoni et al., 2002; Teunissen et al., 2003; Karrenbauer et al., 2006). However, although a trend towards reduced levels of 24S-hydroxycholesterols seems to be associated with the SP form of the disease, it does not reach statistical significance (Teunissen et al., 2003). Since SPMS is characterized by the accumulation of axonal loss (Rovaris et al., 2006), future studies should investigate the accuracy of 24S-hydroxycholesterol as a biomarker of neurodegeneration for MS staging.

Oxidized derivatives of cholesterol different from 24S-hydroxycholesterol have also been studied in MS. During the course of the immune-mediated destruction of the myelin sheaths, cholesterol molecules in myelin are exposed to oxygen radicals resulting in the generation of oxidized derivatives of cholesterol, some of which are neurotoxic (Chang and Liu, 1998; Chang et al., 1998a, 1998b). The study of a small number of samples suggested that increased levels of oxidized derivatives of cholesterol are found in the CSF (Diestel et al., 2003) and the serum (Farez et al., 2009) of MS patients. These oxysterols were found to activate macrophages, microglia and astrocytes to trigger the release of neurotoxic and chemotactic molecules, suggesting that they might play an important role in MS pathology (Diestel et al., 2003; Farez et al., 2009). The analysis of oxysterols in biological samples, however, is challenging because of the presence of cholesterol and other more abundant

lipids (Griffiths and Wang, 2011). Thus these findings await further validation in independent cohorts of MS patients.

2.4. Lipidomics

Lipidomics is defined as the large-scale study of pathways and networks of cellular lipids in biological systems (Watson, 2006; Wenk, 2010). In the context of biomarker research, the aim of lipidomics is to identify molecular signatures linked to specific disease conditions (Adibhatla and Hatcher, 2007). The application of lipidomics to search for disease biomarkers has been boosted by the development of new mass spectroscopic techniques, particularly electrospray ionization and matrix-assisted laser desorption/ionization. Recently, Del Boccio et al. (2011) reported the use of a highly optimized capillary-liquid chromatography-time method of flight mass spectrometry to profile serum lipids in MS samples. Their studies, identified altered levels of lysoglycerophosphatidylcholine (lysoPC) and glycerophosphatidylcholine (PC) species in MS samples. The total lysoPC/PC ratio showed a significant decrease in MS (Del Boccio et al., 2011), suggesting that a large-scale lipidomics approach may be successful in the identification of serum lipid signatures that can be potentially used as biomarkers, and which might also provide new information about pathologic mechanisms operating in MS.

3. Antibody response to lipids as a biomarker for MS

MS is an autoimmune disease caused by a dysregulated immune response against the CNS. Accordingly, T cells and antibodies to myelin basic protein (MBP), proteolipid *protein* (PLP) and myelin oligodendrocyte protein (MOG) have been detected in MS patients (Noseworthy et al., 2000; Sospedra and Martin, 2005). However, lipids constitute up to 70% of myelin (Podbielska and Hogan, 2009). Thus it is not surprising that T cells and B cells reacting with lipids have been identified in MS patients. Accordingly, antibodies to lipids are considered potential biomarkers for MS, particularly with regard to their linkage to specific pathogenic process.

3.1. Lipid reactive antibodies in CSF

Clonally expanded B cells are found in the lesions and the CSF of MS patients (Qin et al., 1998). These CNS-resident B cells have been linked to the production of intrathecal antibodies of restricted specificity, detectable as oligoclonal bands (OCBs) (Obermeier et al., 2008; Holmøy, 2009). Although it is clear that myelin-reactive antibodies are present in the CSF of MS patients (von Büdingen et al., 2008) and CSF antibodies have been reported to react with MOG (O'Connor et al., 2005), MBP (O'Connor et al., 2003) and PLP (Warren and Catz, 1994), the specificity of these OCBs is a matter of discussion (von Büdingen et al., 2008; Owens et al., 2009).

Lipids have also been identified as targets of CSF antibodies. For example, IgG antibodies to sulfatide, ganglioside GM4 and galactocerebroside have been found in the CSF of MS patients (Kasai et al., 1986; Ilyas et al., 2003). In a recent study, Brennan et al. (2011) used lipid arrays to analyze the reactivity of CSF antibodies. They detected lipid-reactive antibodies in 60% of the CSF samples of MS patients and 25% of control samples taken from other neurologic diseases. Moreover, they found that recombinant IgG1 antibodies derived from clonally expanded CSF B cells isolated from MS patients reacted with sulfatide, sulfatide-containing complexes or cholesterol. CSF clonally expanded B cells are considered a source of OCBs (Obermeier et al., 2008), thus these data suggest that OCBs are highly reactive with lipids such as sulfatide and cholesterol.

Villar et al. (2005) reported an association between the intrathecal synthesis of lipid-reactive oligoclonal IgM and disease course in MS. These authors found that increased levels of IgM

OCBs reactive with lipids, mostly phosphatidylcholine, were associated with increased numbers of CD19+ CD5+ B cells in the CNS, and a more aggressive disease course (Villar et al., 2005; Thangarajh et al., 2008). Recently, the same group has reported that the production of lipid-reactive IgM OCBs correlates with the recruitment of CD19+ CD5+ B cells to the CNS by a CXCL13-dependent mechanism triggered by TNFα (Villar et al., 2010). The pathogenic processes controlling the activation and recruitment of CD19+ CD5+ B cells to the CNS in MS seem to be heterogeneous, as lipid reactive IgM OCBs are associated to RRMS and SPMS, but not to PPMS (Villar et al., 2009). All in all, these data suggests that the antibody response to lipids in the CSF might have prognostic value in MS.

3.2. Lipid reactive antibodies in serum

Because of their proximity to the target of the pathogenic autoimmune attack, CSF antibodies are more likely to reflect the status of the immune response in MS. However, serum biomarkers are considered more useful from a practical standpoint, because blood is relatively simple to collect and thus allow repetitive sampling for the continued monitoring of disease status. Thus, a considerable effort has been given to the identification of serum antibodies to lipids that might have potential as biomarkers in MS.

Menge et al. (2005) described low affinity IgG antibodies to galactocerebroside detectable in MS patients but not in healthy subjects. These anti-galactocerebroside antibodies were associated to the RRMS form of the disease, suggesting that they are indicators of ongoing disease activity. Conversely, serum antibodies directed against ganglioside GM3 were reported to be upregulated in 56% and 43% of PPMS and SPMS patients, respectively (Sadatipour et al., 1998). These findings suggest that anti-lipid antibodies of varied specificities might provide information about the pathogenic processes that operate during the course of MS.

3.3. Antigen arrays for the study of lipid antibodies

Antigen microarrays allow the high-throughput characterization of the antibody response using limited amounts of sample (Robinson et al., 2002; Quintana et al., 2004), with greater sensitivity than ELISA (Robinson et al., 2002; Quintana et al., 2008b). We and others have used antigen arrays to characterize the immune response in MS (Kanter et al., 2006; Garren et al., 2008; Quintana et al., 2008b) and EAE (Robinson et al., 2003; Kanter et al., 2006; Quintana et al., 2008a), other autoimmune conditions (Quintana and Cohen, 2001; Quintana et al., 2004; Li et al., 2005; Wu et al., 2008; Espinosa et al., 2009), tumors (Merbl et al., 2009) and healthy individuals (Merbl et al., 2007; Ilan et al., 2010).

Antigen arrays have been recently used to investigate the antibody response to lipids in the CSF of MS patients (Kanter et al., 2006). Robinson et al. (2002, 2003) used microarrays containing a collection of lipids present in the myelin sheath, including ganglioside, sulfatide, cerebroside, sphingomyelin and total brain lipid fractions, to study CSF antibodies to lipids in MS patients. They found increased levels of specific antibodies against sulfatide, oxidized phosphocholine, oxidized cholesterol, sphingomyelin and asialo-GM1 both in MS patients and EAE mice.

To investigate the potential pathogenic role of some of these antibodies Kanter et al. (2006) used the mouse model of EAE. They found that sulfatide administration led to the induction of antibodies against sulfatide and other lipids, concomitant with a significant worsening of EAE. Interestingly, the administration of a sulfatide-specific monoclonal antibody also led to a significant worsening of EAE, suggesting that antibodies to sulfatides play a pathogenic role in MS.

Based on their analysis of biopsies taken from MS patients, Lucchinetti et al. (2000) defined specific immunopathologic patterns in MS lesions. As part of our efforts to characterize the antibody response in MS, we used antigen arrays to analyze serum samples corresponding to patients that presented immunopathologic Pattern I or II (Quintana et al., 2008b). Pattern I is characterized by T-cell/macrophage-mediated demyelination, while Pattern II is characterized by antibody/complement-associated demyelination (Lucchinetti et al., 2000). Both Pattern I and II lesions show the typical perivenous distribution and sharp borders that are the pathological hallmarks of MS lesions and are thought to result from classical autoimmune mechanisms (Lucchinetti et al., 2000). We found that Pattern I subjects showed increased IgG reactivity to 7 lipids; 3 of these lipids were oxidized derivatives of cholesterol (15-ketocholestene, 15-ketocholestane and 15a-hydroxycholestene). Notably, antibodies to some of these oxysterols were also found by Kanter et al. (2006) when they studied CSF antibodies to lipids in SPMS using antigen arrays.

We investigated the potential pathogenic role of some of these antibodies and lipids using the mouse model of EAE. We found that administration of these lipids at the time of EAE induction worsened EAE symptoms and augmented demyelination and axonal loss (Quintana et al., 2008b; Farez et al., 2009). This worsening did not result from the activation of lipid-specific T cells or B cells. Indeed, oxidized derivatives of cholesterol have been found to activate microglia and macrophages by a mechanism mediated by the activation of poly (ADP-ribose)-polymerase-1 (PARP-1) (Diestel et al., 2003; Farez et al., 2009). Together with the data of Robinson et al. (2002, 2003), our data illustrate the use of antigen arrays for the investigation of lipid-specific antibodies in CSF and serum. Moreover, these studies demonstrate how the use of techniques for the high throughput characterization of lipid-specific antibodies might lead to the identification of antibody dependent and independent mechanisms by which lipids contribute to disease pathogenesis in MS.

4. Conclusion

The study of lipids and antibodies to lipids has the potential to identify biomarkers linked to the different pathogenic processes involved in MS. Practical considerations suggest that it is preferable that these biomarkers are detectable in blood, to facilitate the collection of serial samples during the monitoring of disease progression and response to therapy over time. It is likely that not one, but several biomarkers will be required to capture the activity of the diverse pathological processes that participate in MS. The measurement of multiple biomarkers will therefore require platforms compatible with the high throughput analysis of hundreds of analytes, like the lipidomics and antigen array approaches described in this review. Ultimately, the integration of the data generated with different platforms (genomics, transcriptomics, lipidomics, antigen arrays) has the potential to generate a complete view of the pathogenic process operating in each patient (Quintana et al., 2008c). In combination with advanced bioinformatics tools, these platforms will lead to a personalized and more effective approach for the management of MS.

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