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MULTIPLE SCLEROSIS IS NOT A DISEASE OF THE IMMUNE SYSTEM

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ABSTRACT

Multiple sclerosis is a complex neurodegenerative disease, thought to arise through autoimmunity against antigens of the central nervous system. The autoimmunity hypothesis fails to explain why genetic and environmental risk factors linked to the disease in one population tend to be unimportant in other populations. Despite great advances in documenting the cell and molecular mechanisms underlying MS pathophysiology, the autoimmunity framework has also been unable to develop a comprehensive explanation of the etiology of the disease. I propose a new framework for understanding MS as a dysfunction of the metabolism of lipids. Specifically, the homeostasis of lipid metabolism collapses during acute-phase inflammatory response triggered by a pathogen, trauma, or stress, starting a feedback loop of increased oxidative stress, inflammatory response, and proliferation of cytotoxic foam cells that cross the blood brain barrier and both catabolize myelin and prevent remyelination. Understanding MS as a chronic metabolic disorder illuminates four aspects of disease onset and progression: 1) its pathophysiology; 2) genetic susceptibility; 3) environmental and pathogen triggers; and 4) the skewed sex ratio of patients. It also suggests new avenues for treatment.

INTRODUCTION

MULTIPLE SCLEROSIS (MS) is an inflammatory autoimmune disease of the central nervous system (CNS) that results in the demyelination of neurons. It affects approximately 1.3 million people around the world, with high prevalence concentrated in northern latitudes. It also affects women more than men at an approximate ratio of 2:1, although men tend to have a more severe course of the disease. Several genetic and environmental factors have been as-

sociated with the risk of developing the disease, although the influence of external factors on the genetic background of patients is not currently fully understood. Definite triggers of the onset of MS, and the molecular mechanisms underlying them, have also proved elusive. MS is perceived as a disease of autoimmunity against antigens of the central nervous system (Greer and McCombe 2011). This framework, the autoimmune hypothesis, revolves around mechanisms of the immune system, such as the autoreactivity of T cells to CNS

antigens, linkage of immune-relevant genes to MS patients, and the influence of Vitamin D on immune response (Challoner et al. 1995; Kim et al. 2006; McCoy et al. 2006; Ascherio and Munger 2007; Broadley 2007; Cantorna 2008; Fensterl and Sen 2009; Ramagopalan et al. 2009; Ascherio et al. 2010; Beretich and Beretich 2010; Grant 2010; Lünemann et al. 2010; Greer and McCombe 2011).

Environmental and genetic MS risk factors have been analyzed in the context of immune system function. Dietary intake and/or UV synthesis Vitamin D3, for example, regulates the immune system and lowers the incidence of MS (Ramagopalan et al. 2009). This, however, does not explain the relatively high incidence of MS in regions where populations can obtain Vitamin D both through UV synthesis and/or diet, such as Iran or Japan (Yamasaki et al. 1996; Niino et al. 2002; Maghzi et al. 2010). Another set of proposed MS triggers is exposure to certain pathogens, such as the Epstein-Barr virus (EBV) (Lünemann et al. 2010). Again, the autoimmune framework fails to explain why genetically similar populations exposed to similar pathogens have drastically different incidence of the disease (Benoist and Mathis 2001).

Alleles associated with MS have been identified over the last two decades, but their explanatory power is partial at best. For example, a strong association of alleles of the major histocompatibility complex, such as HLA DRB1*1501, with the disease has not been confirmed for all MS patients (Yamasaki et al. 1996; Schreiber et al. 2002). Each time a genetic risk factor has shown a significant increase in MS risk in one population, it has been found to be unimportant in another. This has been the case for Vitamin D-binding protein gene polymorphisms, immune system-related polymorphisms such as CCR5-Δ32, and the HLA DRB1*1501 allele (Yamasaki et al. 1996; Niino et al. 2002; Schreiber et al. 2002; Arababadi et al. 2010; Weiner 2009; Sombekke et al. 2010).

The search for MS triggers in the context of the autoimmunity hypothesis has not yet led to unifying conclusions about the etiology of the disease. It also lacks a compelling

explanation as to why women are more at risk of developing MS than men, even though sex has been shown to affect both MS prevalence and the course of the disease (Greer and McCombe 2011). In short, the immunological framework, or autoimmune hypothesis, clarifies neither the etiology nor the relationship between environmental factors and the pathology of the disease.

I propose a new framework for understanding MS. Rather than a disease of the immune system, MS is a dysfunction of the metabolism of lipids, with mechanisms that parallel atherosclerosis, but also differ from that disease. Understanding MS as a chronic metabolic disorder illuminates four aspects of disease onset and progression: 1) its pathophysiology; 2) genetic susceptibility; 3) environmental and pathogen triggers; and 4) the skewed sex ratio of patients. It offers a unifying theoretical framework that excludes none of the well-demonstrated markers and risk factors of MS, and suggests new avenues for treatment.

This review relates the best understood genetic and environmental MS risk factors to the observed pathophysiology of the disease in the framework of a dysregulation of lipid homeostasis. To accomplish this goal, an overview of lipid metabolism is provided, along with a systematic evaluation of the links between MS risk factors and lipid metabolism. I conclude with a discussion of the predictions emerging from applying the new framework.

OVERVIEW OF LIPID METABOLISM

MAJOR PATHWAYS

There are three main pathways in the metabolism of lipids: exogenous; endogenous; and reverse cholesterol pathway. The exogenous pathway involves the synthesis of chylomicrons in the enterocytes of the small intestine, where dietary lipids are absorbed after digestion by bile salts and pancreatic lipase in the pancreas. The synthesis of chylomicrons involves the assembly of triacylglycerol (TG), cholesterol esters (CE), and the apolipoprotein B-48 by the lipid binding and transfer heterodimer, microsomal triglyceride transfer protein (MTP).

Once formed, the TG-rich VLDL molecules leave the liver to the serum and are processed by the lipoprotein lipase (LPL), which breaks down the VLDL into intermediate dense lipoprotein (IDL) and oxidized LDL (oxLDL). The LPL is then activated by the Apo CII protein, and ligates the VLDL into FFAs that go to either the production of energy or to storage cells (adipocytes). IDL breaks down into LDL molecules through the removal of TG by the hepatic lipase (HTGL). The liver absorbs most LDL molecules through binding with the scavenger receptor B1 (SR-B1). Peripheral cells and endothelial macrophages also absorb some LDL molecules via scavenger receptors, SR-B1 and CD36. The cholesterol contained in LDL is then used for the synthesis of membranes and steroids. Endothelial macrophages uptake excess LDL and CE molecules in the plasma. Lipid-laden macrophages either go through an auto-regulated apoptotic mechanism, or are emptied out of their lipid content by the reverse cholesterol pathway (Figure 1B).

In the reverse cholesterol pathway, the HDL molecule binds to the ATP-binding cassette A1 (ABCA1) receptor and removes the excess free cholesterol esters from the macrophages via the HDL cholesterol ester transport protein (CETP). The cholesterol esters are transported to the liver, where they are reused for the synthesis of VLDLs or catabolized (Figure 1C).

PEROXISOMES, FATTY ACID OXIDATION,
AND THE PEROXISOME
PROLIFERATOR-ACTIVATED RECEPTORS
(PPARS): CENTRAL NODES OF LIPID
METABOLISM

At the center of lipid metabolism are the peroxisomes, specialized organelles abundant in the liver cells. The peroxisomes regulate lipid metabolism by: a) by breaking down the long chain of fatty acids before they can be used by the mitochondria for energy production; b) by breaking down the free radical hydrogen peroxide; c) by down-regulating the LPL inhibitor Apo CIII, increasing VLDL and chylomicron lipase; d) by synthesizing cholesterol through synthesis of HMG-CoA reductase; and e) by increasing synthesis of bile acids that catabolize triacyl-

glycerols. The peroxisomes work in tandem with the mitochondria as primary site of β -oxidation of very long chain (VCLFAs) and branched chain fatty acids (BCFAs), which are essential for the synthesis of myelin (Hulshagen et al. 2008; Baes and Aubourg 2009; Chrast et al. 2011). These fatty acids, too long to be processed by the mitochondria, are transported into the peroxisome by the ABCD1 transporter and are activated by the acyl-CoA synthetase (ACS) in the outer membrane of the peroxisome. Branched chains of fatty acids, such as dietary phytanic acid, first go through α -oxidation, where they are broken down to pristanic acid. Both pristanic acid and the newly formed acyl-CoA derivatives go through β -oxidation and are catalyzed by hydrogen peroxide (H_2O_2) first, then by enoyl-CoA hydratase, hydroxyacyl-CoA dehydrogenase, and thiolase. The β -oxidation continues until short and medium chains of acyl-CoA are produced. Acetylcarnitine transferase converts the short and medium chains of acyl-CoA into carnitine derivatives, which are then transferred to the mitochondrion via the carnitine palmitoyltransferase I (CPT I) located in the outer membrane of the organelle. Carnitine palmitoyltransferase II (CPT II), located on the inner membrane of the mitochondrion, converts the short and medium chain carnitine derivatives back to acyl-CoA to be further catalyzed by β -oxidation. Unlike the β -oxidation of the peroxisomes, the mitochondrial β -oxidation produces energy (ATP) through the reoxidation of the dehydrogenase products NADH and FAD(2H). NAD^+ and FAD are produced by the oxidation of the β -carbon chain of the fatty acyl-CoA to a keto group. The first enzyme of mitochondrial β -oxidation, acyl-CoA dehydrogenase, transfers electrons from the formation of a double bond between the β and α carbons of the fatty acyl-CoA to the electron transport chain to form FAD(2H). The second step in β -oxidation is the addition of an OH group to the β -carbon chain by enoyl hydratase. The β -hydroxy acyl-CoA dehydrogenase then transfers electrons from oxidation of the hydroxyl group to NAD^+ to form NADH. Both FAD(2H) and NADH are then reoxidized into the β -oxidation cycle by the

FIGURE 2. PEROXISOMAL AND MITOCHONDRIAL OXIDATION OF LIPIDS

The boxes highlight the PPAR-regulated enzymes. The abbreviations are: very long chain of fatty acids (VLCFA); branched chain of fatty acids (BCFA); ATP-binding cassette transporter (ABC transporter); acyl-coA oxidase (ACO); enoyl-CoA hydratase 3-hydroxyacyl-CoA dehydrogenase (HD); acyl-CoA synthetase (ACS); the carnitine palmitoyl transferase I and II (CPTI and CPTII); carnitine-acylcarnitine translocase (CACT); acetyl-CoA carboxylase (ACC); fatty acid synthase (FAS).

electron chain transport, thus generating energy (ATP). Levels of NADH and ATP partially regulate β -oxidation in the mitochondria, since fatty acid oxidation cannot happen before reoxidation of NADH and FAD(2H). In the final step of β -oxidation, a thiolase cleaves the bond between the β and α carbons. A CoASH is attached to the β carbon, forming a shorter acyl-CoA. The reaction is repeated until all of the carbons of the fatty acids are converted in acyl-CoA, which can be released in the cytosol for the production of new fatty acids (see Figure 2) (Shi and Burn 2004).

The function and number of peroxisomes per cell, and many of the enzymes involved in lipid and glucose metabolism and homeostasis, are regulated by the peroxisome proliferator-activated receptors (PPARs), nuclear receptor proteins that function as transcription factors. The PPAR target genes regulate the expression of enzymes involved in mitochondrial and peroxisomal FA oxidation,

microsomal FA cytochrome P450- ω oxidation, fatty acid transports, apolipoprotein synthesis, lipogenesis and lipolysis, as well as glucose transport and utilization (see Tables 1, 2, and 3) (Braissant et al. 1996). There are three subtypes of PPAR: PPAR α (also known as the nuclear receptor subfamily 1, group C, member 1—NR1C1); PPAR β/δ (NR1C2), and PPAR γ (NR1C3) (Varga et al. 2011). To be fully functional, all three PPARs form a heterodimer with the retinoid X receptor (RXR). PPARs are coded in different regions of the genome (PPAR α on chromosome 22, PPAR β/δ on chromosome 6, and PPAR γ on chromosome 3). Although PPARs are expressed in essentially all tissue and cell types, they have higher expression in specific tissues: PPAR α is primarily expressed in the liver, heart, skeletal muscles, and kidney (see functions in Table 1); PPAR β/δ is expressed mostly in the small intestines, colon, heart, adipose tissue, skin, and the brain (see functions in Table 2); and the highest levels of PPAR γ are found in macrophages,

TABLE 1
Regulatory functions of PPARα

PPARα				
Gene		Protein/Enzyme	Effects	References
Lipid metabolism - Extracellular				
↑	Apo AI	Apolipoprotein Alpha 1	Stimulates HDL synthesis	Kota et al. 2005; Rai et al.
↑	Apo AII	Apolipoprotein Alpha 2		2008; Sladkova et al. 2011
↑	Apo E	Apolipoprotein Epsilon	Stimulates the formation of chylomicrons, binding of lipoproteins to the liver for catabolism and redirects endotoxin from macrophages to hepatocytes	Fruchart 2001; Barbier 2002; Kota et al. 2005; Brown and Plutzky 2007; Rai et al. 2008
↑ ↓	LPL	Lipoprotein Lipase	Regulates lipolysis (Up in fasting, exercising and inflammatory states;	Peters et al. 2003;
↑ ↓	Apo CII	Apolipoprotein CII	down in postprandial states)	Bighetti et al. 2009;
↑ ↓	Apo CIII	Apolipoprotein CIII		Ruby et al. 2010
↑	LCAT	Lecithin:cholesterol acyltransferase	Stimulates transformation of cholesterol and phosphatidylcholines to CE on HDL surface	Barbier 2002; Khovidhunkit et al. 2004; Fruchart 2007; Bighetti et al. 2009
↑	CETP	Cholesteryl ester transfer protein	Stimulates uptake of CE by hepatocytes and transfer of CE from HDL to other lipoproteins	Fruchart 2001; Barbier 2002; Khovidhunkit et al. 2004; Bighetti et al. 2009; Sundaram and Yao 2010
Lipid Metabolism - Intracellular - peroxisomes/mitochondrion				
↑	FATP	Fatty Acid transporter protein	Increases the uptake of long chain FA	Barbier 2002; Khovidhunkit et al. 2004; Kota et al. 2005; Ehrenborg and Krook 2009
↑	ACO	Acyl-CoA oxidase	Stimulates first step in FA β-oxidation	Kota et al. 2005; Schrader and Fahimi 2008; Baes and Aubourg 2009; Cheng et al. 2010; Wagner and Wagner 2010
↑	HD	Enoyl-CoA hydratase-3-hydroxyacyl-CoA dehydrogenase	Stimulates second and third step in FA β-oxidation	Kota et al. 2005; Varga et al. 2011
↑	ACS	Acyl-CoA synthetase	Stimulates the conversion of FA into acyl-CoA derivatives	Peters et al. 2000; Barbier 2002; Dressel et al. 2003; Khovidhunkit et al. 2004; Brown and Plutzky 2007
↑ ↓	CPTI	Carnitine palmitoyltransferase I	Regulates the transfer of long-chain FA from the cytosol to the mitochondrial (Up during fasting and inflammatory state; down during postprandial state)	Khovidhunkit et al. 2004; Davidson 2006; Wagner and Wagner 2010
↑ ↓	CPTII	Carnitine palmitoyltransferase II		
↑ ↓	CACT	carnitine-acylcarnitine translocase		
↑ ↓	MTP	Microsomal triglyceride transfer protein	Regulates the formation of chylomicrons	Stefano et al. 2007

continued

TABLE 1
Continued

PPARα				
Gene	Protein/Enzyme		Effects	References
↓	SREBP	Sterol Regulatory Element-Binding Protein	Decreases de novo lipogenesis	Yoshikawa et al. 2003
Lipid metabolism - Adipocytes - Tissue specific - Energy production				
↑	UCP	Thermogenin	Stimulate energy production	Handschin 2010
Inflammation - Pathways				
↓	NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells	Decreases transcription of inflammatory enzymes	Khovidhunkit et al. 2004; Duan et al. 2008; Varga et al. 2011
Inflammation - Cytokines - Chemokines				
↑	IL-4	Interleukin-4	Stimulates the differentiation of naive helper T cells into Th2 (CD4+) cells	Yang and Frucht 2001; Kota et al. 2005;
↓	IL-12	Interleukin-12		Collino et al. 2006;
↓	COX-1	Cyclooxygenase 1	Decreases inflammation and eicosanoid synthesis	Fruchart 2007
↓	COX-2	Cyclooxygenase 2		
Endothelium - Vasculature - Tissue specific regulatory functions				
↓	VAP-1	Vascular adhesion protein - 1	Decrease recruitment of T cells and rolling monocytes	Calkin et al. 2006; Cheng et al. 2010; Varga et al. 2011

adipose tissue, colon, heart, muscle, kidney, pancreas, and spleen (see functions in Table 3) (Brown and Plutzky 2007). Thus, the PPARs are highly expressed in tissues heavily dependent on lipids both for energy and maintenance. For example, in the CNS, glial cells use more lipids than any other tissue in the body. Glial cells, in particular oligodendrocytes, rely heavily on peroxisomal and mitochondrial oxidation of VLCFAs, both for fuel and structural maintenance, such as myelin synthesis (Braissant et al. 1996).

Each PPAR regulates genes by binding the PPAR/RXR heterodimer to a promoter region known as peroxisome proliferator response element, or PPRE, of a gene. PPARs are also activated by extracellular stimuli: PPARα is activated during starvation and cold acclimatization, PPARγ is activated in well-fed states, and the activation of PPARβ/δ is linked to the consumption of energy, thermogenesis, and CNS maintenance (Varga et al. 2011).

The transcriptional function of the PPARs is also induced by a series of ligands, which act as activators of PPAR binding to the PPRE, increasing the expression of target genes. Polyunsaturated fatty acids, such as

linoleic and arachidonic acids, as well as prostaglandin-related compounds, such as 15-deoxy-Δ12,14-prostaglandin (15d-PGJ2), are known to be powerful endogenous ligands to the PPARs (Kota et al. 2005).

PPARs are nodal points among the immune system, the transcriptional regulation of energy, and lipid homeostasis because they sense intracellular lipid levels and modify lipid metabolism under specific conditions in both major organs and peripheral cells (see Figure 3) (Evans et al. 2004; Khovidhunkit et al. 2004; Brown and Plutzky 2007; Varga et al. 2011). As such, they play a major role in the etiology of MS, as described in detail below.

PATHOPHYSIOLOGY OF MS: LINKS TO
LIPID HOMEOSTASIS AND
ATHEROSCLEROSIS

The pathways to inflammation and plaque formation in MS and atherosclerosis parallel each other. Lipid dysregulation through either diet or endogenous mechanisms is clearly linked to atherosclerosis, but MS is construed as an immune system dysfunction.

TABLE 2
Regulatory functions of PPAR β/δ

PPARβ/δ				
Genes		Protein/enzyme	Effects	References
Lipid metabolism - Extracellular				
↑	PON1	Paraoxonase 1	Stimulates the prevention of oxidation of LDL by HDL	Khovidhunkit et al. 2004; Brown and Plutzky 2007; Marsillach et al. 2009
↑ ↓	Apo B	Apolipoprotein B	Regulates the formation of chylomicrons and VLDLs (Up during fasting state, down during postprandrial state)	Bishop-Bailey and Bystrom 2009
Lipid Metabolism - Intracellular - peroxisomes/mitochondrion				
↑ ↓	ACS2	Acyl-CoA synthetase-2	Regulates the conversion of FA into acyl-CoA derivatives, affecting posttranslational modification of myelin synthesis	Hall et al. 2008
↑ ↓	CPTI	Carnitine palmitoyltransferase I	Regulates the transfer of long-chain FA from the cytosol to the mitochondrial (Up during fasting and inflammatory state; down during postprandrial state)	Dressel et al. 2003;
↑ ↓	CPTII	Carnitine palmitoyltransferase II		Khovidhunkit et al. 2004; Wagner and Wagner 2010
↑ ↓	CACT	carnitine-acylcarnitine translocase		
↑	MCAD	Medium-chain acyl-CoA dehydrogenase	Stimulates the first step in β-oxidation of medium-chain FA	Wagner and Wagner 2010
↑	ME	Malic enzyme	Stimulates malate decarboxylation, providing NADPH for FA synthesis	Bishop-Bailey and Bystrom 2009; Varga et al. 2011
↑	PEPCK	Phosphoenolpyruvate carboxykinase	Stimulates gluconeogenesis and glyceroneogenesis	Moller and Berger 2003; Ehrenborg and Krook 2009
↓	ACC	acetyl-CoA carboxylase	Decreases acetyl-CoA carboxylase	Khovidhunkit et al. 2004; Lunde et al. 2007
↓	FAS	Fatty acid synthase	Decreases FA synthesis	Barbier 2002; Dressel et al. 2003
↓	SREBP	Sterol Regulatory Element-Binding Protein	Decreases de novo lipogenesis	Dressel et al. 2003; Ehrenborg and Krook 2009
Lipid metabolism - Adipocytes - Tissue specific - Energy production				
↑	FABP	Fatty acid-binding protein	Stimulates adipocyte differentiation and binding of FA	Bocher et al. 2002; Dressel et al. 2003; Sprecher et al. 2007; Ehrenborg and Krook 2009; Wagner and Wagner 2010

continued

TABLE 2
Continued

PPARβ/δ			
Genes	Protein/enzyme	Effects	References
↑	C/EBP	CCAAT/enhancer-binding protein	Bocher et al. 2002; Takata et al. 2002; Glazer et al. 2008
↑	UCP	Thermogenin	Stimulate energy production
↑	GLUT4	Glucose transporter type 4	Stimulates glucose transport
↑	TXNIP	Thioredoxin-binding protein-2	
Inflammation - Pathways			
↓	NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells pathway	Khovidhunkit et al. 2004; Varga et al. 2011
↓	MAPK/ERK	Mitogen-activated protein (MAP) kinases/ extracellular-signal-regulated kinases pathway	Decreases transcription of inflammatory enzymes
↑	BCL-6	B-cell lymphoma 6 protein	Increases the modulation of the transcription of STAT-dependent interleukin responses of B cells
Inflammation - Cytokines - Chemokines - ROS			
↓	IFN-γ	Interferon gamma	Decreases the transcription of inflammatory enzymes, oxidants and chemoattractant ligands
↓	TNα	Tumor necrosis factor-alpha	and decreases the stimulation of platelet activation, cell proliferation, extracellular matrix synthesis, and glucose metabolism
↓	IL-1β	Interleukin-1 beta	
↓	IL-6	Interleukin-6	
↓	Isg20	Interferon-stimulated gene 20 kDa protein	
↓	GM-CSF		
↓	MCP-1/CCL2	Monocyte-specific chemokine 2/ Chemokine (C-C motif) ligand 2	
↓	MCP-3/CCL7	Monocyte-specific chemokine 3/ Chemokine (C-C motif) ligand 7 (CCL7)	
↓	MCP-5/CCL12	Monocyte-specific chemokine 5/ Chemokine (C-C motif) ligand 12 (CCL12)	
↓	CXCL7	Chemokine (C-X-C motif) ligand 7	
↓	CCL21	Chemokine (C-C motif) ligand 21	
↓	CCR2	Chemokine receptor 2	

continued

TABLE 2
Continued

PPARβ/δ				
Genes	Protein/enzyme		Effects	References
↑	RGS4	Regulator of G protein signaling 4	Stimulates G-protein signaling	Barish et al. 2008; Bishop-Bailey and Bystrom 2009
↑	RGS5	Regulator of G protein signaling 5		
↑	TIMP3	Metalloproteinase inhibitor 3	Increases the inhibition of matrix metalloproteinase inflammatory functions	Rock et al. 2004; Bishop-Bailey and Bystrom 2009; Wagner and Wagner 2010
↑	SOCS3	Suppressor of cytokine signaling 3	Increases the inhibition of cytokine signaling	Thomas et al. 2006; Qin et al. 2007; Bishop-Bailey and Bystrom 2009
↑	SOD1	Superoxide dismutase	Increases the decomposition of superoxide radicals	Hou et al. 2005; Bishop-Bailey and Bystrom 2009
↑	CAT	Catalase	Increases the decomposition of hydrogen peroxide to water and oxygen in the peroxisomes	Hou et al. 2005; Bishop-Bailey and Bystrom 2009; Marsillach et al. 2009; Wagner and Wagner 2010
↑	TXN	Thioredoxin	Increases the antioxidant functions of this oxidoreductase enzyme	Bishop-Bailey and Bystrom 2009; Marsillach et al. 2009; Wagner and Wagner 2010
↑	YWHAH/14-3-3a	Tyrosine 3-monooxygenase / tryptophan 5-monooxygenase activation protein, alpha polypeptide	Stimulates synthesis of the dopamine (DOPA), norepinephrine (noradrenaline), and epinephrine (adrenaline) precursors	Coker et al. 1988; Kim et al. 2001
Endothelium - Vasculature - Tissue specific regulatory functions				
↓	VCAM-1 (CD106)	Vascular cell adhesion protein 1	Maintain the plasticity, flexibility, and permeability of blood vessels and decrease adhesion of rolling monocytes and agglutination of platelets	Assmann and Grotto 2004; Bishop-Bailey and Bystrom 2009
↓	ICAM-1 (CD54)	Inter-Cellular Adhesion Molecule 1		
↓	E-selectin (CD62)	CD62 antigen-like family member E/ Endothelial-leukocyte adhesion molecule 1 (ECAM-1)		
↓	GROα/CXCL1	Chemokine (C-X-C motif) ligand 1 (CXCL1)	Decreases the migration of oligodendrocyte precursors, angiogenesis, inflammation, and tumorigenesis	Bishop-Bailey and Bystrom 2009
↑	VEGF	Vascular endothelial growth factor	Increases vasculogenesis and angiogenesis	Ritter et al. 2006; Bishop-Bailey and Bystrom 2009; Wagner and Wagner 2010

continued

TABLE 2
Continued

PPARβ/δ				
Genes	Protein/enzyme		Effects	References
↑	Akt	Akt-protein kinase	Induces cellular survival pathways by inhibiting apoptotic processes. Induces skeletal muscle hypertrophy, and general tissue growth, including angiogenesis	Kota et al. 2005; Glazer et al. 2008; Bishop-Bailey and Bystrom 2009; Wagner and Wagner 2010
↑	TGFβ	Transforming growth factor beta	Induces TGF pathway that inhibits cell proliferation, induces differentiation, and promotes apoptosis	Yang and Frucht 2001; Bishop-Bailey and Bystrom 2009
↓	CN Aβ	Calcineurin Aβ	Stimulates muscle growth and angiogenesis	Wagner and Wagner 2010
↓	PGC-1α	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha	Stimulates activation of PGC-1α in skeletal muscles	Wagner and Wagner 2010

Understanding MS in the same context as atherosclerosis explains aspects of MS better than the immune dysfunction model by providing a unifying physiological framework. A rapidly increasing body of literature documents how lipids or lipid regulators produce oxidative damage and inflammation in MS (Witherick et al. 2010; Chrast et al. 2011; Varga et al. 2011). The parallels between the mechanisms described for MS and atherogenesis are striking. Although atherosclerosis is localized to the artery walls and MS to the central nervous system (CNS), lesions in both diseases are essentially the same, and parallel mechanisms underlie their formation. These mechanisms can be summarized as: 1) dysregulation of cholesterol compound formation; 2) differentiation of macrophages into cytotoxic foam cells; 3) inflammatory response; and 4) accumulation of foam cells and formation of lesions.

Where atherosclerosis and MS differ is in the exposure of particular tissues to foam cells, inflammation, and lesion formation (steps 2 through 4). The CNS and the brain are shielded by the blood brain barrier (BBB), a specific high-density endothelial layer that restricts the passage of solutes from the bloodstream. The CNS has its own mac-

rophages, the microglia, which are very similar in morphology and immunophenotype to the macrophages of the peripheral/perivascular tissues involved in atherogenesis. The origin of microglial cells is still debated (Kofler and Wiley 2011), but the CNS contains a highly stable pool of microglia formed during embryonic development. Microglia permanently monitor the integrity of the CNS tissues in normal conditions (Wake et al. 2009). Through a highly ramified system of receptors, they can detect the state of cells in their neighborhood and respond quickly to the ATP release of distressed cells, or an excess of oxLDL (Davalos et al. 2005; Nimmerjahn et al. 2005; Monk and Shaw 2006; Wake et al. 2009). During inflammation, bone marrow-derived rolling monocytes differentiate into microglial cells and infiltrate the blood brain barrier in a process similar to the formation of perivascular macrophages (Rock et al. 2004; Ladeby et al. 2005). The functions of the microglia are similar to bone marrow-derived perivascular macrophages in atherosclerosis, although they differ in their location-specific potential neurotoxicity when activated (Malchiodi-Albedi et al. 2008). Under normal circumstances, an autoregulatory mecha-

TABLE 3
Regulatory functions of PPAR γ

PPAR γ				
Gene		Protein/Enzyme	Effects	References
Lipid metabolism – Extracellular				
↑	ABCG1	ATP-binding cassette G1	Stimulates reverse cholesterol efflux	Rubic et al. 2004; Brown and Plutzky 2007; Fruchart 2007; Duan et al. 2008
↑	ABCA1	ATP-binding cassette A1		
↑ ↓	CD36	Scavenger receptor	Regulates entry of FA and lipoproteins in cells under specific lipid stimulation	Barbier 2002; Khovidhunkit et al. 2004; Rubic et al. 2004; Fruchart 2007; Sprecher et al. 2007; Ahmed et al. 2009
↑ ↓	SR-B1	Scavenger receptor		
↑	Apo E	Apolipoprotein Epsilon	Stimulates the formation of chylomicrons and binding of lipoproteins to the liver for catabolism	Rai et al. 2008
Lipid Metabolism - Intracellular - peroxisomes/mitochondrion				
↑	CYP4A6 (P450)	Cytochrome P450 enzyme	Stimulates FA ω -hydrolase	Davidson 2006; Zordoky and El-Kadi 2010
↑	HMG-CoAS	Mitochondrial 3-hydroxy-3-methylglutaryl CoA synthase	Stimulates liver ketogenesis	Khovidhunkit et al. 2004; Malchiodi-Albedi et al. 2008
↑	ME	Malic enzyme	Stimulates malate decarboxylation, providing NADPH for FA synthesis	Moller and Berger 2003
↑	PEPCK	Phosphoenolpyruvate carboxykinase	Stimulates gluconeogenesis and glyceroneogenesis	Davidson 2006
↓	ACC	acetyl-CoA carboxylase		
↓	FAS	Fatty acid synthase	Decreases acetyl-CoA carboxylase	Schoonjans et al. 1996; Khovidhunkit et al. 2004; Brown and Plutzky 2007
↓	FAS	Fatty acid synthase	Decreases FA synthesis	Yang and Frucht 2001; Bocher et al. 2002
↓	SREBP	Sterol Regulatory Element-Binding Protein	Decreases de novo lipogenesis	Davidson 2006; Sundaram and Yao 2010; Chrast et al. 2011
Lipid metabolism - Adipocytes				
↑	FABP	Fatty acid-binding protein	Stimulates adipocyte differentiation	Barbier 2002; Moller and Berger 2003; Khovidhunkit et al. 2004; Varga et al. 2011
↑	C/EBP	CCAAT/enhancer-binding protein		
↑	ADPN	Adiponectin	Stimulates glucose regulation and FA catabolism	Singh et al. 2007; Glazer et al. 2008; Tufekci et al. 2011; Varga et al. 2011
↑	ADN	Adipsin	Stimulates synthesis of C3 convertase in the alternative complement pathway	Auwerx et al. 1996; Schoonjans et al. 1996; Handschin et al. 2003; Moller and Berger 2003; Hammarstedt et al. 2005; Sharma and Staels 2007; Stefano et al. 2007; Cho et al. 2008; Wagner and Wagner 2010
↑	GLUT4	Glucose transporter type 4	Stimulates glucose transport	
↑	TXNIP	Thioredoxin-binding protein-2		

continued

TABLE 3
Continued

PPAR γ			
Gene	Protein/Enzyme	Effects	References
Inflammation – Pathways			
↓ NF- κ B	Nuclear factor kappa-light-chain-enhancer of activated B cells	Decreases transcription of inflammatory enzymes	Moller and Berger 2003; Khovidhunkit et al. 2004; Calkin et al. 2006; Paintlia et al. 2006; Duan et al. 2008
↓ STAT-1	JAK-STAT signaling pathway	Decreases transcription of inflammatory enzymes	Khovidhunkit et al. 2004; Drew et al. 2008; Duan et al. 2008
↓ AP-1	Activator protein 1	Decreases differentiation, proliferation, and increases apoptosis	Drew et al. 2008; Mirabelli-Badenier et al. 2011; Raman et al. 2011
Inflammation - Cytokines - Chemokines			
↓ IFN- γ	Interferon gamma		Harris and Phipps 2001; Barbier 2002; Bocher et al. 2002; Takata et al. 2002; Khovidhunkit et al. 2004; Paintlia et al. 2006; Brown and Plutzky 2007; Xu et al. 2007; Drew et al. 2008; Duan et al. 2008; Glazer et al. 2008;
↓ MHC II	Major Histocompatibility Complex, Class II	Decreases the transcription of inflammatory enzymes, oxidants, and chemoattractant ligands (MHC II, CXCLs)	Malchiodi-Albedi et al. 2008; Blecharz et al. 2010; Sundaram and Yao 2010; Yousefipour et al. 2010; Raman et al. 2011
↓ TN α	Tumor necrosis factor- α		
↓ IL-1 β	Interleukin-1 beta		
↓ IL-6	Interleukin-6		
↓ MMP-9	Matrix metalloproteinase 9		
↓ MMP-6	Matrix metalloproteinase 6		
↓ IP-10/CXCL10	Interferon gamma-induced protein 10 (CXCL10)		
↓ Mig/CXCL9	Monokine induced by gamma interferon (CXCL9)		
↓ I-TAC/CXCL11	Interferon-inducible T-cell alpha chemoattractant (CXCL11)		
Endothelium - Vasculature - Tissue specific regulatory functions			
↑ eNO	Endothelial nitric oxide	Maintains the plasticity, flexibility, and permeability of blood vessels and decreases adhesion and recruitment of rolling monocytes and agglutination of platelets	Yang and Frucht 2001; Barbier 2002; Takata et al. 2002; Moller and Berger 2003; Khovidhunkit et al. 2004; Calkin et al. 2006; Brown and Plutzky 2007; Sahni 2007; Drew et al. 2008; Duan et al. 2008; Glazer et al. 2008; Malchiodi-Albedi et al. 2008; Yousefipour et al. 2010; Mirabelli-Badenier et al. 2011
↓ ET-1	Endothelin-1		
↓ VCAM-1 (CD106)	Vascular cell adhesion protein 1		
↓ ICAM-1 (CD54)	Inter-Cellular Adhesion Molecule 1		

nism prevents potential neurotoxicity by the apoptosis of the activated microglial cells (Lee et al. 2003). Crucial for understanding MS pathogenesis, the gene expression of activated microglia induces molecular alterations of pathways of metabolism of lipids and

membranes (Carson et al. 2004; Qin et al. 2007). It is precisely the infiltrating macrophages—the perivascular microglia—that contribute the most to neurodegeneration in MS, rather than the resident parenchymal microglia (Carson et al. 2004). The role

FIGURE 3. REGULATORY FUNCTIONS OF THE PEROXISOME PROLIFERATOR ACTIVATED RECEPTORS (PPARs)

The side arrows indicate the feedback from the regulated systems and enzymes on the functions of the PPARs. A full list of the PPAR-regulated elements is given in Tables 1, 2, and 3.

of perivascular microglia in neurodegeneration highlights the mechanistic similarity of atherosclerosis and multiple sclerosis.

Another line of evidence pointing to the similarities between atherosclerosis and multiple sclerosis is a recent development in MS treatment. Atherosclerosis-specific drugs, such as statins and, more recently, PPARs agonists, are currently used to treat MS symptoms (Assmann and Gotto 2004; Rubic et al. 2004; DeAngelis and Lublin 2008; Heinecke 2009; Mandosi et al.

2010; Chrast et al. 2011; Mirabelli-Badenier et al. 2011; Rinaldi et al. 2011), highlighting the shared pathways underlying inflammatory events in the two diseases. Statins and PPAR agonists taken separately can successfully treat specific symptoms (Brown and Plutzky 2007). The new framework for understanding MS suggests that instead of inhibition or increase of single targets, modulation of target expression through a careful combination of both kinds of drugs would be more beneficial to patients. A systemic approach to treat-

ment based on lipid metabolism feedbacks can more readily attenuate MS degeneration than the current approach of treating the disease as a collection of symptoms to be relieved (Brown and Plutzky 2007).

Inflammatory pathways are, however, not the only shared features of atherosclerosis and multiple sclerosis: the same disequilibrium in lipid homeostasis leads to both diseases and suggests a model mechanism for the etiology of MS.

LIPID METABOLISM DURING THE ACUTE-PHASE RESPONSE IN MS

The similarity between the lipid profile of MS patients and that of patients suffering from infection or inflammation was observed early on, although researchers could not explain the link between the two at the time (Holman et al. 1989). The immune response to an infectious agent or trauma is costly to the host in terms of lipid catalysis. Indeed, acute-phase responses to infection and inflammation produce dramatic changes in lipid metabolism by increasing: adipose tissue lipolysis; hepatic TG and FA synthesis (by increasing levels of HMG-CoA reductase); and hepatic cholesterol synthesis (VLDLs); and decreasing both hepatic clearance of the VLDLs and reverse cholesterol transport (Calder et al. 1999; Khovidhunkit et al. 2004). This reduction in lipid storage and increased lipolysis helps deploy lipids in the immune system, either as anti-inflammatory agents or as building blocks of new cells.

Changes in lipid metabolism during infection or inflammation mirror the lipid profile of MS patients in elevated plasma cholesterol content (Cunnane et al. 1989), elevated levels of lipid hydroperoxides (Ferretti et al. 2005), elevated levels of oleic, palmitic, and palmitoleic acids, and low levels of Apo A1 (Sladkova et al. 2011). As in pathogenic and trauma-related inflammation, the acute and advanced stages of MS are characterized by lower levels of linoleic acids in plasma cholesterol esters (Love et al. 1974; Cunnane et al. 1989; Marshall 1991). Some of the shared features of inflammatory responses and MS directly involve lipid metabolism; e.g., impaired metabolism of polyunsaturated fatty acids, evident by reduced levels of omega-3

fatty acids in plasma and in cell membranes (Aupperle et al. 2008; Mehta et al. 2009); and compensation for low levels of polyunsaturated fatty acids by endogenous synthesis of lower-melting, short-chain, saturated, and monounsaturated nonessential fatty acids (Cunnane et al. 1989; Holman et al. 1989). In short, the lipid profile of MS patients is indicative of both inflammation and a dysregulation of the metabolism of lipids.

THE PPAR/RXR HETERODIMERS: AT THE CROSSROAD BETWEEN LIPID AND IMMUNE SYSTEM HOMEOSTASIS

The PPAR/RXR heterodimers regulate key enzymes involved in the intake, synthesis, cleavage, oxidation, and efflux of lipids, which are also involved in the immune system acute-phase response (see Tables 1, 2, and 3). The role of these PPARs-regulated enzymes is to accelerate lipolysis and endogenous lipogenesis so lipids can be redirected to immune cells and repair sites. Thus, a dysregulation of lipids, such as a rise of oxidized lipid/phospholipids either through a high fat/carbohydrate diet or genetic predisposition (or both), alters the regulatory functions of these lipidsensing nuclear receptors dramatically, leading to the breakdown of homeostasis of both lipid metabolism and the immune system (Kota et al. 2005; Varga et al. 2011).

The PPARs contribute to lipid homeostasis in the three main pathways of fat metabolism: the exogenous, endogenous, and cholesterol efflux pathways. At the exogenous levels, the PPARs play a critical role in regulating the synthesis of chylomicrons, by regulating the production of the microsomal triglyceride transfer protein (MTP) and apolipoproteins B and E (Stefano et al. 2007; Rai et al. 2008; Bishop-Bailey and Bystrom 2009). PPAR α and β/δ also regulate lipolysis through regulation of the synthesis of apolipoprotein CII (Peters et al. 2003). PPARs also play a vital role in the intake and digestion of carbohydrates by regulating glucose transport and glycogen synthesis through the glucose transporter type 4 (GLUT4) and thioredoxin-binding protein (TXNIP), and glucogenesis through the phosphoenolpyruvate carboxykinase (PEPCK), adiponectin (ADPN), and adipisin (AND) (Auwerx et

al. 1996; Schoonjans et al. 1996; Moller and Berger 2003; Hammarstedt et al. 2005; Sharma and Staels 2007; Stefano et al. 2007; Cho et al. 2008; Wagner and Wagner 2010). PPARs are also responsible for the regulation of both morphology and functions of adipocytes, by upregulating lipolysis during a fasting state or inflammatory state, and down-regulating lipolysis and stimulating TG storage during the postprandial state (PPAR γ), as well as by stimulating adipocyte differentiation and binding of FA through regulation of the fatty acid-binding protein (FABP) (Bocher et al. 2002; Sharma and Staels 2007).

In the endogenous pathways, PPARs regulate key enzymes involved in the intake, oxidation, and de novo synthesis of fatty acids (Schoonjans et al. 1996; Moller and Berger 2003; Evans et al. 2004; Roberts et al. 2004; Shi and Burn 2004; Sundaram and Yao 2010). PPARs regulate the intake and activation of fatty acids in cells (more markedly in hepatocytes), through regulation of: a) the fatty acid transporter protein (FATP) for entry into cells; b) acyl-CoA synthetase (ACS) for activation of fatty acids prior to β -oxidation; c) the carnitine palmitoyltransferase I and II (CPTI and CPTII) for transports of fatty acid carnitine derivatives into the mitochondria; d) carnitine-acylcarnitine translocase (CACT) for reactivation of carnitine derivatives into acyl-CoAs; and e) acetyl-CoA carboxylase (ACC), which regulates the synthesis of malonyl-CoA, a known regulator of the CPT functions (Schoonjans et al. 1996; Herzig et al. 2003; Sharma and Staels 2007; Shi and Burn 2004; Stefano et al. 2007; Lim et al. 2010). The β -oxidation of lipids, both in the peroxisomes and the mitochondria is, in great part, controlled by regulation of key enzymes in the reaction by PPARs (Figure 2). The PPARs control the expression of: a) acyl-CoA oxidase (ACO), the first enzyme of β -oxidation in the peroxisome; b) enoyl-CoA hydratase/3-hydroxyacyl-CoA dehydrogenase (HD), the third and second step of β -oxidation in the peroxisome; and c) the medium-chain acyl-CoA dehydrogenase (MACD), which oxidize medium chain fatty acids into medium acetyl-CoA in the mitochondria (Schoonjans et al. 1996). PPARs also control many of the enzymes active in lipogenesis and in ketogene-

sis, such as the fatty acid synthase (FAS), the malic enzyme (ME), the sterol regulatory element binding protein (SREBP)—all three leading to de novo fatty acid synthesis, and the HMG-CoA synthase (HMG-CoAS) leading to ketone bodies synthesis (Peters et al. 2003; Khovidhunkit et al. 2004; Sharma and Staels 2007; Cho et al. 2008; Chrast et al. 2011).

The PPARs also play a crucial role in the cholesterol efflux from peripheral macrophages. PPARs regulate the synthesis and function of cholesterol molecules, which intake excess oxLDL from lipid-laden macrophages. Faulty PPAR regulation caused by environmental triggers and/or genetic predisposition disable lipid homeostasis through the dysregulation of the three pathways of lipid metabolism, in turn leading to a toxic accumulation of oxLDL, both in plasma and in peripheral macrophages (Figure 4). This triggers responses that further compromise lipid metabolism, resulting in a feedback loop. The dysregulated PPARs accelerate monocyte differentiation into toxic macrophages/microglial cells (Yu and Cooper 2001; Malchiodi-Albedi et al. 2008) and compromise the integrity of the blood brain barrier (Airas et al. 2006). OxLDLs can now more freely cross into the endothelial layers where an increased amount of CNS macrophages (microglia) absorb them in excess through the overexpression of the PPARs-regulated SR-B1/CD36 scavenger receptors. This leads to the differentiation of cytotoxic microglia into foam cells. The accumulation of foam cells causes oxidative damage, and the anti-inflammatory responses to excess oxLDL, usually mediated by the PPARs, fails to prevent both the expression of interleukin 6 (IL-6), NF- κ B, and C/EBP, and the synthesis of free radicals (Khovidhunkit et al. 2004; Witherick et al. 2010; Haider et al. 2011). The apoptosis of the now highly cytotoxic microglial foam cells, also regulated by the PPAR/RXR heterodimers (Harris and Phipps 2001; Yang and Frucht 2001; Qin et al. 2007; Glazer et al. 2008), no longer occurs, generating more inflammation, and the fatty streaks plaques observed in MS lesions (Pau- men et al. 1997; Boullier et al. 2001). The oxidative injuries and accumulation of

Environmental factors (e.g. Diet rich in terrestrial animal fat/carbohydrate and poor environmental access to vitamin D3) and/or genetic predisposition

FIGURE 4. LOOP MECHANISM OF THE ETIOLOGY OF MS

foam cells lead to demyelination through the oxidation of myelin phospholipids by circulating free radicals, and indiscriminate phospholipid endocytosis by the cytotoxic microglial and T cells.

The dysregulation of the immune system, which relies entirely on lipids for repair and to prevent/stave off inflammation, follows from the disequilibrium in lipid metabolism (and not the other way around). I propose that the mechanism of pathogenesis of MS originates in a dysregulation of lipid homeostasis, due to the dual action of faulty PPAR genes (or specific faulty alleles regulated or

linked to the PPARs) and environmental triggers, such as diet and pathogens, accentuating this dysregulation in a loop.

THE ROLE OF LIPID METABOLISM AND THE NUCLEAR RECEPTORS IN THE INTAKE OF OXIDIZED LIPIDS BY DYSFUNCTIONAL MICROGLIAL CELLS: THE PATHOGEN-TRIGGER THEORY OF MS ETIOLOGY

Lipids, and specifically oxLDLs, are the core agents of the immune system during the acute-phase response to infection/inflammation

(Khovidhunkit et al. 2004). The oxLDLs bind to the lipopolysaccharide (LPS) membrane of the infectious agent (bacteria, virus, or parasite), allowing endocytosis by the macrophages via the scavenger receptors (SR-B1, CD36, ABCA1). In the nonacute phase, all three major receptors, regulated by the PPAR/RXR heterodimers, work toward removing excessive amounts of TG from the plasma. This action regulates the endogenous lipid metabolism, including cholesterol efflux by HDL.

All scavenger receptors have a high affinity for cholesterol and oxidized phospholipids, a property that explains their involvement in immune system response to pathogens (Janabi et al. 2000; Van Eck et al. 2004; Svensson et al. 2005; Vergeer et al. 2011). Binding to the damaged, oxidized, infected macrophages initiates phagocytosis in a process similar to that of removal of foam cells from the endothelial layers of blood vessels. But an overexpression of the two main scavenger receptors, SR-B1 and CD36, is deleterious. PPAR γ -regulated CD36 overexpression in microglia increases free radicals, increasing the levels of oxLDLs, turning on the overexpression of the receptors in a feedback loop (Cho et al. 2005).

In MS, CD36 overexpression is associated with both acute relapsing episodes (Ferrandi et al. 2011) and ischemic brain (Cho et al. 2005), linking this scavenger receptor to CNS damage. Under hyperlipidemic conditions, platelet-expressed CD36 sense oxidative stress and modulate platelet reactivity, leading to vascular atrophy and thrombosis (Podrez et al. 2000). By increasing platelet aggregation, CD36 alters the structure and permeability of the BBB, increasing the adherence of platelets to microvascular beds and activating the neurotoxic cytokines (Cotter et al. 2006). This inflammatory mechanism of CD36 has been well described in the context of parasitic and microbial infections (Febbraio and Hajjar 2001; Huang and Jong 2001; Combes et al. 2006). MS patients have significantly higher platelet activity (Sheremata et al. 2008), suggesting this mechanism is implicated in the pathogenesis of MS.

The expression of SR-B1, mediated by PPAR/RXR heterodimers, also increases the intake of free fatty acids by the endothelial

macrophages. SR-B1 expression appears to be beneficial in atherosclerosis (Ahmed et al. 2009) and polymorphisms in the PPAR/RXR-regulated SR-B1 coding gene, SCARB1, decrease insulin-resistance and lower oxLDL in plasma in populations with a high polyunsaturated diet (Pérez-Martínez et al. 2005). But overexpression of the SR-B1 receptor induces peripheral cells into nonspecific excess intake of fatty acids (Trigatti et al. 2003; Van Eck et al. 2004).

The affinity of CD36 and the closely linked SR-B1 to a variety of pathogens, including mycobacteria and hepatitis viruses, also explains why so many pathogenic triggers for MS have been uncovered (Philips et al. 2005; Cunha-Rodrigues et al. 2007; Barth et al. 2008; Catanese et al. 2010; Hawkes et al. 2010). The binding affinity of scavenger receptors can explain the overrepresentation of specific pathogens, such as EBV, in MS lesions (Febbraio and Hajjar 2001; Cunha-Rodrigues et al. 2007; Barth et al. 2008; Catanese et al. 2010; Hawkes et al. 2010). But the autoimmunity theory of MS pathogenesis has so far failed to account for the lack of specificity of pathogenic triggers. In the context of a runaway feedback involving scavenger receptors and oxidized LDL, it is not the specific pathogens that precipitate MS etiology, but the affinity of immune cells to respond to damaged, oxidized cells that mimic the structure of infected cells or cell membranes of microbial and parasitic pathogens (Blewett 2010).

The proposed etiology of MS is either an increase of oxidized phospholipids through genetically faulty PPARs, combined with a diet high in triglycerides that lead to a dysregulation of the scavenger receptors and lipid homeostasis. A pathogen trigger exacerbates the imbalance of lipid homeostasis by shifting the lipid metabolism from energy production and lipid storage to the production of more TG by lipolysis and lipogenesis, leading to a greater number and intake of oxLDLs by peripheral macrophages. In pathogen-triggered MS, overexpression of CD36 and SR-B1 leads to nonspecific, indiscriminate binding to phospholipids via oxLDL, at first pathogenic in origin, but then turning to the native phospholipid-rich myelin. This hypo-

thetical mechanism is not exclusive to a specific pathogen as trigger of the inflammatory vicious circle observed in MS.

THE ROLE OF LIPID METABOLISM AND THE
NUCLEAR RECEPTORS IN THE
DYSREGULATION OF HDL CHOLESTEROL
EFFLUX AND COMPOSITION OF THE HDL
MEMBRANE: THE DIET-TRIGGER THEORY OF
MS ETIOLOGY

The overexpression of the CD36 and SR-B1 scavenger receptors is further exacerbated by a lack of cholesterol efflux from the macrophages. Downregulation of the Apo A1 gene, regulated by PPAR α , explains the low levels of apolipoprotein A1 (Apo A1) observed in MS patients (Burger and Dayer 2002; Sundaram and Yao 2010; Sladkova et al. 2011). A downregulation of the ABCA1 receptor and a lower level of Apo A1 in the liver and serum contribute to a saturation of macrophages with cholesteryl esters and long fatty acids. The downregulation of Apo A1 synthesis also reduces the anti-inflammatory functions of the protein (Burger and Dayer 2002), the formation of nascent HDL molecules in plasma, and impairs the functions of the ABCA1 receptors, which in turn impairs the reverse cholesterol process.

The reverse cholesterol pathway is further impaired by a shift of HDL composition. In a diet high in polyunsaturated fatty acids (PUFAs), and low in triglycerides, the PPAR α -regulated HDL phospholipids have a polyunsaturated linoleic acid (PLPC) in the β position (Fruchart 2001, 2007). These PLPC-HDL inhibit the proliferation of proinflammatory LPS by binding to them and the acute phase serum amyloid A (SAA), as well as by decreasing the expression of adhesion molecule (VAP-1) in peripheral endothelial cells (Baumberger et al. 1991; Baker et al. 2000). HDL with high PLPC content is also a potent antioxidant, preventing the oxidation of LDL molecules into oxLDL (Brodeur et al. 2008). Conversely, a high triglyceride diet leads to the composition of HDL with monounsaturated oleic acid (POPC) or polyunsaturated arachidonic acid (PAPC) in the β position. POPC or PAPC-HDL has none or little of the functions of HDL described above. The an-

tioxidant properties of HDL are further inhibited by a decrease in serum levels of the paraoxonase-1 (PON1), an enzyme regulated by PPAR δ that hydrolyzes lipid peroxides, bound to HDL (Marsillach et al. 2009). A deficiency in the regulatory expression of PPAR δ decreases PON1 expression, decreasing HDL synthesis, and depressing the LDL antioxidant function of HDL. All of these changes lead to more oxLDLs in both plasma and macrophages (Ferretti et al. 2005). All of the PPAR-mediated lipid metabolism dysfunctions—high oleic acid, high oxLDL, high SAA expression, high VAP-1 expression, low PON1, and low PUFA—characterize the observed lipid and enzymatic profile of MS patients (Jamroz-Wisniewska et al. 2009).

The low levels of PUFAs in MS patients are consistent with the dietary/lipid homeostatic origin of the disease and directly relate to the function of PPARs. The new framework explains why treating MS patients with a diet high in omega-3 fatty acids has been an effective way of lowering demyelination and inflammation (Cunnane et al. 1989; Zhang et al. 2000; Besler et al. 2002; Habek et al. 2010). PUFAs are known activators of the PPARs, which in turn regulate the lipogenesis-controlling sterol receptor element binding protein-1c (SREBP-1c) (Yoshikawa et al. 2003). Reduced expression of SREBP-1c leads to the upregulation of fatty acid oxidation in hepatocytes, and enhances the catabolism of glucose to glycogens through downregulation of nuclear factor HNF4 α (Davidson 2006). The oxidation of fatty acids in both adipocytes and plasma decreases VLDL synthesis. In a fasting state and under severe inflammation, the cAMP response element-binding (CREB) downregulates hepatic PPAR γ expression, thus activating gluconeogenic and fatty acid oxidation by stimulating expression of the nuclear hormone receptor coactivator PGC-1 (Herzig et al. 2003; Sue et al. 2009). Modulation in the expression of the PPAR α and γ leads to the opposite effect: lower FA oxidation in the peroxisome, higher FA oxidation in the mitochondria, and the release of SREBP-1 and de novo lipogenesis. This lipid profile results in high nonoxidized VLCFAs in cells and serum, high VLDL syn-

thesis, and high levels of oxLDLs both in circulation and in the lesions of MS and atherosclerosis patients.

Diet, therefore, plays a role in the etiology and course of MS. A diet high in terrestrial animal fat and/or carbohydrates leads to a modulation of PPARs, which can then lead to MS in the presence of an inflammatory trigger, whether pathogen or trauma.

THE ROLE OF LIPID METABOLISM AND THE PPARs IN MS CNS INFLAMMATION

Permeability of the Blood Brain Barrier

MS patients have severe vascular abnormalities that reduce brain blood flow. These vascular abnormalities are in fact part of the feedback loop of the dysregulation of lipids and inflammatory response of the endothelial macrophages. High levels of circulating fatty acids and triglycerides have a direct impact on the vasculature by modifying the regulatory functions of two main PPARs: PPAR β/δ and PPAR γ (Duan et al. 2008).

The expression of the PPAR β/δ in the brain regulates the integrity of the BBB by controlling the VAP-1 adhesion molecules, enhancing angiogenesis and vascular repair (Hall et al. 2008; Ehrenborg and Krook 2009; Haider et al. 2011). Deficient expression of PPAR β/δ , induced by elevated levels of free fatty acids in the serum, results in impaired vascular repair, diminished vascular flow, a reduced hyperplastic development of microvasculature, and dysregulation of the VAP-1 adhesion molecules, inducing more rolling monocytes to enter the layers of the endothelium (Hall et al. 2008). A deficient PPAR β/δ also decreases nuclear translocation of CREB in endothelial cells, thus accelerating smooth cell proliferation and the narrowing of blood vessels (Sue et al. 2009). The cerebrovascular dysfunction resulting from PPAR β/δ underexpression is compounded by dysregulation of PPAR γ activation, which increases the expression of endothelin-1 (ET-1), a potent vasoconstrictor and regulator of vascular smooth muscle cell (VSMC) proliferation, and downregulation the main vasorelaxant, nitric oxide (NO) (Duan et al. 2008).

Finally, lack of PPAR β/δ and PPAR γ activation also leads to the increased expression of inflammatory genes, increasing endothelial inflammation (Duan et al. 2008; Hall et al. 2008; Varga et al. 2011). The evidence shows that modulation of the PPARs in a dysregulated lipid metabolism makes the endothelial layers more permeable, further leaking oxLDLs and rolling monocytes across the blood brain barrier, leading to an inflammatory loop as described below.

Inflammatory Process of the CNS

The normal course of an inflammatory response is a careful balance between the recruitment of: a) lipids from diet, adipocytes, and energy production to the site of inflammation/injury; and b) cytotoxic macrophages that produce proinflammatory cytokines and free radicals, and phagocytic macrophages that remove pathogens, debris, and apoptotic cytotoxic macrophages.

The microglia maintain a highly active monitoring state in normal, noninflammatory conditions (Nimmerjahn et al. 2005; Wake et al. 2009). Through the expression of proteinase activated (PAR) and purinergic receptors (PR), microglia can sense environmental cues such as vascular depression in the BBB and adenosine triphosphate (ATP) in damaged cells (Carson et al. 2004; Wake et al. 2009). Stimuli such as trauma, pathogens, and even psychological stress induce the microglia to produce proinflammatory enzymes such as free radicals, and pathogen-inhibiting cytokines and chemokines (Davalos et al. 2005; Chen et al. 2010). Phagocytic microglia, and T cells, then remove pathogens and debris from the CNS and undergo a self-regulated apoptotic mechanism to prevent injury to the CNS from their own proinflammatory enzymes (Rock et al. 2004; Drew et al. 2008; Allen and Barres 2009).

In MS, the disequilibrium of lipid homeostasis leads to an imbalance between the cytotoxic and the phagocytic microglia/T cells. Since oxLDLs circulate in high concentration and cross the BBB, the microglia are chronically activated into cytotoxic cells in a feedback loop, where excess of circulating oxLDLs leads to inflammation, producing

more oxLDLs. Permanently highly activated, the glial cells lack the self-regulatory apoptotic mechanism that would prevent an accumulation of toxic foam cells, and neurodegeneration.

The activation of cytotoxicity in microglia, through the NF- κ B, JAK-STAT, and MAPK signaling pathways, induces the expression of immune response genes responsible for the release of chemoattractant cytokines, such as IL-1, IL-6, TN- α , IFN- γ , and TNF- α , as well as small lipid molecules such as the leukotrienes and prostaglandins, reactive oxygen species (ROS) and chemokines (Hoon Lee et al. 2005). This acute-phase response induces the liver to produce the C-reactive protein (CRP), the serum amyloid A (SAA), as well as fibrinogen and plasminogen activators. During inflammation, the microglia express MHC class-I/II proteins, thereby becoming effective recruiters of T cells that then fulfill a variety of roles, from forming an immune memory, to becoming cytotoxic (Davalos et al. 2005; Nimmerjahn et al. 2005; Wake et al. 2009; Chen et al. 2010). The expression of MHC class-II proteins by activated microglial cells explains the strong association of MS to allelic variants in the HLA DR and DQ complexes of MHC (Tienari et al. 2006; Svejgaard 2008; Ramagopalan et al. 2009; Isobe et al. 2010). The variants provide stronger ligands for microglia to recruit potentially cytotoxic T cells than wild-type alleles.

Activation of the inflammatory response of microglia is intricately tied to the metabolism of lipids. The acute inflammatory response generates a shift from lipid storage to lipid sequestration by the immune system. Most of these changes can be traced to the transcription of genes regulated by the nuclear PPAR receptors. Activation of PPARs prevents activation of the proinflammatory enzymes produced by the microglia and T cells (Cosulich et al. 2000; Rusyn et al. 2000; Hoon Lee et al. 2005; Paintlia et al. 2006). Downregulation of all three PPARs precludes the inhibition of the expression of the inflammatory response proteins and pathways (see Tables 1, 2, and 3 for a complete list): nuclear factor- κ B (NF- κ B), acute phase C reactive protein, IL-6, monocyte chemoat-

tractant protein-1 (MCP-1), plasminogen activator inhibitor-1, soluble CD40 ligand, matrix metalloproteinase-9 (MMP 9), and cyclooxygenase 2 (COX-2) (Yang and Frucht 2001; Kota et al. 2005; Collino et al. 2006; Fruchart 2007; Barish et al. 2008; Bishop-Bailey and Bystrom 2009; Wagner and Wagner 2010).

The consequences of individual PPAR downregulation are also relevant to MS pathogenesis. Downregulated PPAR β/δ prevents the release of the B-cell lymphoma (BCL-6) protein, thus reducing the expression of regulator of G-protein signaling (RGS) genes, which leads to the releasing of the signal transduction of chemokine receptors, thereby increasing inflammation (Barish et al. 2008). PPAR γ activation induces the expression of the suppressor of cytokine signaling protein-3 (SOCS-3), the negative regulator of the inflammatory response of the immune system in the CNS (Qin et al. 2007). Downregulation presumably leads to overexpression of the SOCS-3-regulated inflammatory pathways. Activation of PPAR γ results in apoptosis of the cytotoxic microglia. Without such activation (e.g., by a lack of PPAR γ -ligand interaction), apoptosis does not happen, leading to an accumulation of cytotoxic macrophages (Harris and Phipps 2001; Yang and Frucht 2001).

Thus, the activation of microglial cells leads to the recruitment of monocytes and helper T cells, which quickly become cytotoxic, but further, are not evacuated either through an apoptotic mechanism, or by phagocytosis. Instead, the microglial cells become toxic foam cells and, together with memory-formed and cytotoxic T cells, release free radicals, chemoattractant inflammatory cytokines, and chemokines, and indiscriminately uptake phospholipids from adjacent myelin sheaths, leading to neurodegeneration.

Oxidative Damage of the CNS and Impaired Remyelination

The degradation of myelin is connected to the dysregulation of PPARs and lipid homeostasis because it results, in part, from indiscriminate phospholipid endocytosis by the scavenger receptors on macrophages (above), accumulation of cytotoxic foam

cells and low peroxisome proliferation in the CNS and liver cells, leading to oxidative damage and impaired myelin synthesis. This mechanism of myelin degradation is distinct and contradicts the hypothesis of molecular mimicry leading to erroneous immune attack (Blewett 2010).

Myelin synthesis in the CNS is concentrated in the peroxisomes of oligodendrocytes, and is also found in the peroxisome of other CNS cells. The peroxisomes play a dual role of maintenance and synthesis of myelin: they are necessary for the compaction and biogenesis of the myelin sheath by regulating oligodendrocyte differentiation and posttranslational modifications of myelin proteins, such as the myelin oligodendrocyte glycoprotein (MOG), the proteolipid protein (PLP), and the myelin basic protein (MBP) (Hall et al. 2008; Bishop-Bailey and Bystrom 2009; Wagner and Wagner 2010); to protect the axons by inhibiting the release of hydrogen peroxides by catalase and the trapping action of uric acid (Massa et al. 2009); and by β -oxidation of the neuroinflammatory leukotrienes, prostaglandins, and very long chain of fatty acids (VLCFA) (Baes and Aubourg 2009). The maintenance and protection of the CNS is not confined to the peroxisome of the CNS cells, but extends to the liver peroxisomes. Deficiency of liver peroxisomes causes myelin anomalies at the ultra and inner structural levels of the axons, severe gliosis (activation of glial cells), a toxic VLCFA accumulation in the brain and the spinal cord, as well as a higher concentration of peroxynitrite that is no longer contained due to the low synthesis of uric acid by the disabled organelle (Hulshagen et al. 2008; Dujmovic et al. 2009).

The crucial importance of whole-organism peroxisomal metabolism in maintaining the integrity of the CNS is well illustrated by the numerous neurodegenerative and demyelinating diseases in which either the whole organelle or a single mechanism is faulty (Hulshagen et al. 2008; Baes and Aubourg 2009). In MS, damage to the CNS is further compounded by lack of remyelination associated with the regulatory functions of nuclear receptors and, in particular, the expression of the retinoid receptor,

RXR. Specifically, downregulation of RXR γ reduces maturation of oligodendrocytes in areas of active remyelination (Hanafy and Sloane 2011). The role of lipid metabolism and nuclear receptors in maintaining the integrity of the CNS is therefore fivefold: 1) maintain the integrity of the blood brain barrier; 2) prevent the activation of proinflammatory pathways; 3) regulate the apoptosis of cytotoxic T and microglial cells; 4) regulate the number and efficiency of peroxisomes in both CNS and liver cells; and 5) regulate the maturation of oligodendrocytes and myelin synthesis. All five regulatory pathways are impaired in MS, through the mechanisms of lipid dysregulation described so far.

THE ROLE OF LIPID METABOLISM AND THE PPARS IN LOW VITAMIN D: THE NORTHERN HIGH LATITUDES AS TRIGGER OF MS

Vitamin D has been at the center of MS research because it links areas of high MS prevalence in the high northern latitudes where lack of sunlight reduces UV-linked Vitamin D synthesis with immune system regulation (Poser 1994; Rosati 2001; VanAmerongen et al. 2004; Broadley 2007; Oksenberg et al. 2008; Ascherio et al. 2010; Comabella et al. 2010; Grant 2010; Simon et al. 2010; van der Mei et al. 2011; Wang et al. 2011). But steroidogenesis, including the synthesis of active Vitamin D, is also intricately linked to lipid metabolism through diet. Low levels of exogenous polyunsaturated fatty acid in serum slow the regulatory function of PPARs, in particular PPAR α and PPAR γ , on the production of calcitriol (1,25(OH) $_2$ D $_3$), the bioactive form of Vitamin D. PPAR γ activated by PUFAs decreases the expression of SREBP-1c and increases expression of the microsomal cytochrome p450 27B1 (CYP27B1 25-hydroxyvitamin D $_3$ 1- α -hydroxylase), which catalyzes calcidiol to calcitriol (Li et al. 2011; Wang et al. 2011). Low expression of CYP27B1 in dendritic cells inhibits brain development (Eyles et al. 2005), and is consistent with the observed low calcitriol profile of MS patients (VanAmerongen et al. 2004). PPAR α also serves as a coregulator of the Vitamin D receptor (VDR), which recruits and heterodimerizes with the RXR β dimer to synthesize calcitriol de novo (Savkur et

al. 2005; Sertznig et al. 2009). More $1,25(\text{OH})_2\text{D}_3$ increases the expression of the Vitamin D receptor (VDR) and its heterodimerization with RXR β to synthesize more calcitriol in a loop. Therefore, an environment low in PUFAs results in a broken loop where the downregulation of the PPARs on steroidogenesis leads to low levels of calcitriol, both through low heterodimerization of the VDR to RXR, and decreased biogenesis.

This explains why the environmental risk to develop MS in populations residing in the high northern latitudes is not evenly spread, but concentrated among populations with specific diets (Tienari et al. 2006; Ascherio and Munger 2007; Ascherio et al. 2010). Low levels of UV-linked Vitamin D synthesis, compounded by a diet rich in triglycerides, carbohydrates, and low in PUFAs, are the environmental triggers. The coastal Norwegian communities, whose diet has traditionally been poor in triglycerides and carbohydrates, but high in PUFAs and Vitamin D $_3$ fish oil, showed a relatively low incidence of MS compared with their inland and Swedish counterparts until the 1980s. Since then, dietary changes toward a higher intake of terrestrial animal triglycerides and carbohydrates paralleled a threefold rise in the incidence of MS in Norway (Midgard et al. 1991).

THE ROLE OF LIPID METABOLISM AND THE PPARS IN MS MUSCULAR ATROPHY

Muscle atrophy, weakness, and spasticity, all major pathophysiological consequences of MS, can also be understood in the context of a dysregulation of lipid homeostasis and the regulatory function of the nuclear receptors, more specifically downregulation of PPAR β/δ (Tilberly et al. 1989; Haselkorn and Loomis 2005; Dalgas et al. 2009). PPARs have distinct roles in muscle cells by increasing fatty acid catabolism, cholesterol efflux, and energy expenditure of the muscles (Dressel et al. 2003; Ehrenborg and Krook 2009). The expression of PPAR β/δ increases with elevated levels of free fatty acids in serum, and also muscle activity (Lunde et al. 2007). This may explain the recent findings that MS patients improve their motor ability

through resistance-training exercises (White et al. 2004; Dalgas et al. 2009; De Souza-Teixeira et al. 2009).

Another mechanism linking muscle atrophy and spasticity to PPAR regulatory function is the synthesis of creatine. Creatine is a major component of muscle development. Altered PPAR γ expression has been observed to inhibit myogenic differentiation in skeletal muscle cells, and impair the synthesis of creatine (Singh et al. 2007). This is further confirmed by lower levels of the creatine breakdown product, creatinine, observed in both MS and diabetes 2 type patients. The lack of creatine synthesis results in muscle atrophy and reduced renal function in both diseases (Calabresi et al. 2002; Calkin et al. 2006).

PPARS, HOMOCYSTEINE, LIPID METABOLISM, AND SEX DISPARITY IN MS

Women are twice as likely to develop MS, and autoimmune diseases in general, while men are more likely to develop atherosclerosis at an earlier age than women. Sex affects the prevalence, pathological course, and severity of the disease (Greer and McCombe 2011). Biological differences in males and females, such as the differences in immune system response, morphology of the CNS, and other factors indubitably play a role in both the etiology and course of the disease. However, each of these factors and its effects has been studied as separate entities within the autoimmunity hypothesis. This framework has not linked all of the factors into one coherent mechanistic explanation of the sexual disparity seen in MS. The proposed framework can explain the sex disparity in MS prevalence in terms of the central functions of PPAR α in lipid metabolism and homocysteine synthesis.

Homocysteine (Hcy), a sulfur-containing amino acid, is formed from the metabolism of methionine, an essential amino acid acquired through diet, particularly from food rich in protein, and certain cereals and seeds, such as sesame. This amino acid is metabolized as a derivative of the methionine cycle in two ways: through remethylation or transsulfuration. Homocysteine is formed by the addition of a methyl group from methionine, and reconverted into me-

thionine, through the Vitamin B₁₂ pathway, in which Vitamin B₁₂ act as a cofactor of methionine synthase, and folates act as coenzymes (Fukagawa et al. 2000). When levels of methionine are too high, homocysteine is metabolized into cysteine by entering the transsulfuration pathway, in which Vitamin B₆ acts as cofactor for cystathionine β -synthase and cystathionine γ -ligase. Excessive levels of homocysteine are correlated with low Vitamin B₆, Vitamin B₁₂, folic acid, and low levels of creatinine (Sassi et al. 2002). High levels of Hcy have also been correlated with the risk of developing cardiovascular diseases, strokes, restenosis, and high oxidative stress, and are found in the plasma and lesions of both MS and atherosclerosis patients (Besler and Comoğlu 2003; Schwarz and Leweling 2005; Ramsaransing et al. 2006).

Sexual disparity in homocysteine levels can partially explain sexual disparity in both MS and atherosclerosis. The rate of synthesis of homocysteine is higher in men than in young women. Both sexes, however, steadily develop higher levels of Hcy with increasing age (Bostom et al. 1999; Sassi et al. 2002; Hayden and Tyagi 2004). The mechanism underlying differential rates of Hcy synthesis is still debated, but several hypotheses have been put forward to explain it. Methionine synthesis differs in men and women because the sexes may have different demands for methyl groups (Mudd and Poole 1975; Fukagawa et al. 2000). A greater rate of methionine transamination and more rapid methionine cycle in which homocysteine is both remethylated and diverted to cystathionine in premenopausal women has been linked to lower levels of homocysteine, and protection against vascular disease (Fukagawa et al. 2000).

Sex hormones influence homocysteine concentrations. In particular, estrogen lowers the concentration of homocysteine in plasma, which explains both the sexual disparity in producing Hcy, but also why women develop higher levels of Hcy with increasing age, and more markedly after menopause (Fukagawa et al. 2000; Sassi et al. 2002). Sex differences in lipid metabolism and levels of homocysteine are also linked by the transsul-

furation of homocysteine into cysteine, which requires the amino acid serine, and occurs at a higher rate in women than in men (Elshorbagy et al. 2008). Serine is generated from intermediates of glycolysis that are regulated by the PPARs (Herzig et al. 2003; Davidson 2006; Sue et al. 2009). Dysregulation of PPAR functions would result in less serine, and more homocysteine, both phenomena observed in MS patients, and would also be more marked in young women, since they tend to have a faster methionine cycle. A reduction of serine levels would also produce lower levels of sphingolipid synthesis, and impair the synthesis of myelin (Inuzuka et al. 2005). The effects of low serine levels are compounded by myelin synthesis requiring a methyl group from S-adenosylmethionine of the methionine cycle to synthesize methylarginine incorporated into myelin basic protein (MBP) (Small et al. 1981). PPAR α increases the expression of methionine-adenosyltransferase (MAT), which synthesizes methionine into S-adenosylmethionine (Luc et al. 2004). Thus, there is a secondary negative effect of a dysfunctional PPAR α : a slower production of S-adenosylmethionine, leading to a dysfunctional myelin synthesis. Higher levels of homocysteine are also associated with higher oxidative stress, in particular in the CNS, which would compound the impaired myelin synthesis with an increased inflammatory response in the cells of the CNS (Hunt and Tyagi 2002; Hayden and Tyagi 2004; Yilmaz et al. 2005; Jiang et al. 2007).

An additional link between high levels of homocysteine and the metabolism of lipids is in the interaction of homocysteine and Apo AI synthesis (Devlin and Lentz 2006). High levels of homocysteine inhibit the expression of PPAR α -regulated Apo A1, leading to a lower production of HDL and a lower lipolysis of VLDL (Mikael et al. 2006). Homocysteine may also impair PPARs by acting as an inhibitory ligand (Hayden 2008).

Dysfunction of the PPAR α , therefore, is at the center of sexual disparity in lipid metabolism, and the risk of developing MS. PPAR α mediates sexual dimorphism in lipid metabolism, specifically in the regulation of fatty acid oxidation in the liver (Jalouli et al. 2003;

Ciana et al. 2007). This sexual dimorphism underlies women having a higher removal efficiency of VLDL-triglyceride from circulation, but a greater hepatic VLDL-triglyceride secretion rate; and men having a lower VLDL-triglyceride secretion rate, but also lower removal rate from the serum (Magkos and Mittendorfer 2009). The expression of PPAR α is controlled by hormone levels, and is significantly higher in the livers of men than in those of women, partly explaining sexual dimorphism in lipid metabolism (Jalouli et al. 2003). Dunn et al. showed that PPAR α is also expressed at higher levels in male than female mice T cells, and that deficiency of the PPAR α gene selectively affects male T lymphocytes (Dunn et al. 2007). Males have a higher expression of PPAR α in naive T cells (Th2), while females have a higher expression of PPAR α in activated T cells (Th1). This disparity increases immune response and correlates to both the more robust immune system response known in women, and the greater likelihood of women to develop MS and other autoimmune diseases (Dunn et al. 2007; Voskuhl 2011). Male but not female PPAR α -deficient mice developed more severe experimental autoimmune encephalomyelitis (EAE), the animal model of MS (Dunn et al. 2007). A similar sexual difference in the course of the disease is noted in MS patients (Greer and McCombe 2011).

Here again, the PPARs act as central nodes between lipid metabolism and the immune system. A dysregulation of PPAR α would be deleterious in different ways for both sexes. High levels of homocysteine in men have a greater tendency to impact the artery walls by concentrating the amino acid's oxidative action on the endocardial endothelial cells, letting in more oxLDLs in the intima of the endothelium (McCully et al. 1990; Nygård et al. 1997; Hunt and Tyagi 2002; Jiang et al. 2007). In women, the impaired production of serine by sluggish PPAR function and a slower transsulfuration pathway translates into weakened components of the CNS, which is highly dependent on the methionine cycle methyl groups for maintenance (Small et al. 1981; Fukagawa et al. 2000). The influence of sexual hormones on both the concentration of homocysteine

and elements of lipid metabolism that are regulated by the PPARs, further accentuates the disparity between men developing atherosclerosis and women developing MS (Williams 2004; Magkos and Mittendorfer 2009; Marinou et al. 2011). These mechanisms are, however, not exclusive to either sex.

More studies are needed to explain the mechanisms underlying sexual disparity in MS. Understanding the disease as a metabolic, rather than immune, disorder provides a unifying framework for every known aspect of sexual dimorphism in MS, and may explain differential prevalence of autoimmune diseases generally.

DISCUSSION

The human diet has changed dramatically since the advent of industrialized agriculture and food processing. In 50 years, we have moved to a diet high in carbohydrates and terrestrial animal fat, with well-known health consequences: rise in cardiovascular and metabolic diseases. Autoimmune diseases have also increased over the same time span. Hypotheses linked to the autoimmune hypothesis, such as the "hygiene hypothesis," which suggests that reduced exposure to critical microorganisms has led to autoimmune disorders (Rook 2009), lack a unifying framework for all elements of the pathophysiology, genetic, and environmental triggers of MS. Lack of exposure to pathogens, or exposure to specific pathogens, are logically contradictory explanations for the rise in MS prevalence.

The new approach to understanding MS pathogenesis explains both the recent rise in incidence and all pathological, genetic, and environmental aspects of the disease. The homeostasis of lipid metabolism, regulated in great part by the PPARs, and already weakened by environmental factors such as low Vitamin D, a high fat/high carbohydrate diet, and/or defective alleles in the PPAR or PPAR-controlled genes, collapses during acute-phase response triggered by a pathogen, trauma, or stress. Modulation in the regulatory functions of PPARs in reaction to the acute-phase response starts a chain reaction. Reduced fat storage, enhanced lipolysis, higher fatty acids oxidation in both the

liver and muscles, and boosted secretion of *de novo* fatty acids and VLDLs by the liver, leads to increased levels of oxLDLs in the serum. High levels of oxLDLs circulating in the serum and across the blood brain barrier are controlled either by saturated macrophage apoptosis or by transport to the liver by HDL. But faulty PPAR regulation of both the intake and efflux of oxLDLs in peripheral microglial cells leads to the overloading of the cells with toxic lipids and the formation of cytotoxic cells. Excess of oxLDLs, now boosted by the acute-phase response *de novo* lipid synthesis, increases differentiation of rolling monocytes into microglial cells, and sluggish PPAR regulation decreases smooth cell proliferation and angiogenesis, weakening the blood brain barrier. The anti-inflammatory response activated by lipid-laden microglia, and mediated by damaged PPARs, also causes more recruitment of helper T cells, which will both form a memory of the oxLDL-laden microglia cell membranes and become cytotoxic cells through the release of free radicals. Both lipid-laden microglial cells and T cells differentiate into cytotoxic foam cells emitting free radicals, and indiscriminately attack cell membranes that contain phospholipids. The apoptotic process of removing the oxidized toxic cells is rendered inoperative by the downregulation of the TGF and AP-1 pathways by sluggish PPARs (PPAR γ and β/δ), leading to foam cell stagnation and the formation of plaques that damage the phospholipid-rich myelin sheath of adjacent axonal neurons. The repair of the myelin sheath is impaired by a lack of peroxisome functionality in oligodendrocytes, leading to a sluggish α - and β -oxidation and a toxic accumulation of nonoxidized very long chain of fatty acids in those cells. The now weakened and permeable blood brain barrier lets in more oxLDLs, which generates an inflammatory response in the peripheral microglia, sending a signal to the liver to synthesize more lipids that will become oxLDLs, in a loop-like mechanism (see Figure 4).

This proposed mechanism underlines the similarity between atherosclerosis and multiple sclerosis, and explains how both genetic and environmental triggers lead to the development of multiple sclerosis. A diet high in animal lipids and carbohydrates, which char-

acterizes the diet of industrialized countries for the past 50 years, compounded by environmental factors such as a low availability of sunlight, and genetic factors linked to the PPAR regulatory functions in lipid homeostasis and the immune system, represent a high risk background for populations to develop MS.

This new framework explains the origins of all the symptoms of MS studied here, from restenosis, neurological disorders, and muscle spasticity to weight loss at the onset of the disease and shift of lipid metabolism throughout the course of the disease and during acute relapses.

CONCLUSION

MS should be approached as a dysregulation of the homeostatic system, where dysregulation of one element in the regulation of lipid metabolism leads to a cascade involving inflammation and impairment of reparative mechanisms. The pathogenesis of atherosclerosis and MS are similar in the dysregulation of lipid homeostasis, and sex-specific differences in lipid metabolism lead to the sex disparity in prevalence of each disease. Multiple sclerosis should be thought of as a metabolic disease, the female equivalent of atherosclerosis, not as a disease of the immune system. When lipid homeostasis is no longer maintained, it leads to a cascade of similar events that predominantly lead to atherosclerosis in men, and in women leads to MS, while excluding neither sex from developing the other disease.

This framework explains why statins and PPAR agonists (fibrates) have shown so much promise in treating MS (Stüve et al. 2003; Sena et al. 2007; Xu et al. 2007; Drew et al. 2008; Goldman and Cohen 2008; Malchiodi-Albedi et al. 2008). A cure for MS will not be achieved by taking one or the other, or both, in a symptom-by-symptom approach, but by modulating the effects of both medications in order to reestablish the homeostasis of the lipid metabolism. To fully understand the influence of PPARs on MS and its therapy will require much more work. Initiatives such as the nuclear receptor signaling atlas (NURSA) are essential to this endeavor (McKenna et al. 2009). The new framework presented here makes a cure for MS closer than ever.

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