Chapter 6
Function and Regulation of Macrophage Stearoyl-CoA Desaturase in Metabolic Disorders

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Introduction

Macrophages are key members of the innate immune system, which reside in most tissues of the body. The primary function of macrophages was traditionally considered to be phagocytosis and killing of foreign pathogens. More recently, a preponderance of evidence from cell to human studies suggests that macrophages play an important role in metabolic homeostasis as well (Bhargava and Lee 2012). For example, macrophages in adipose tissue and skeletal muscle regulate local inflammatory responses and insulin sensitivity, while macrophages in arterial walls are involved in atherosclerotic plaque formation. Further, macrophages in the liver, also known as Kupffer cells, are responsible for hepatic inflammation, steatosis, and insulin resistance. Therefore, macrophages play a key role in the pathogenesis of metabolic disorders such as type-2 diabetes and atherosclerosis.

Stearoyl-CoA desaturase (SCD) is a microsomal enzyme which facilitates the formation of monounsaturated fatty acids (MUFA) from saturated fatty acid (SFA) precursors (discussed in previous chapters). More specifically, SCD converts palmitoyl-CoA and stearoyl-CoA to palmitoleoyl-CoA and oleoyl-CoA, respectively (Mauvoisin and Mounier 2011). Of the two human SCD isoforms (SCD1 and SCD5), macrophages mainly express SCD1. While mice have four SCD isoforms, only SCD1 has been widely studied in macrophages, with a few studies reporting the expression of SCD2 as well (Saez et al. 2007; Sun et al. 2003).

Interestingly, macrophages isolated from subjects with type 2 diabetes have a higher linoleic acid content and fatty acid profiles consistent with increased SCD

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activity compared to control subjects (Senanayake et al. 2007). Moreover, incubation of human macrophages in serum isolated from dyslipidemic subjects leads to increased expression of SCD1 (Wong et al. 2011). Macrophages from obese animal models also express higher levels of SCD1 (Leroux et al. 2012). Therefore, it is likely that SCD plays an important role in the pathogenesis of macrophage-mediated metabolic disorders. This chapter discusses the functions of macrophages in relation to metabolic derangements, regulation of macrophage SCD expression, and effects of macrophage SCD expression in metabolic disorders.

Role of Macrophages in Metabolic Disorders

Macrophages and Obesity-Associated Insulin Resistance

Adipose tissue is considered as an endocrine organ (discussed in a separate chapter in this book), which consists of adipocytes and a stromal vascular fraction. The latter contains blood cells, endothelial cells, adipose tissue precursors, and macrophages (Kalupahana et al. 2012). Adipose tissue from a lean, normal-weight person contains macrophages which are of the M2 type. These are adipose tissue-resident macrophages (Rull et al. 2010), which have anti-inflammatory functions (Rull et al. 2010; Mosser and Edwards 2008). Adipose tissue of an obese individual is characterized by increased adipocyte (fat cell) numbers (hyperplasia) and cell size (hypertrophy). Obesity and adipocyte hypertrophy can cause lack of nutrients for cells, hypoxia, and endoplasmic reticulum stress, which can lead to adipocyte death via necrosis and apoptosis. Dead adipocytes are surrounded by macrophages, which can be identified microscopically as a "crown-like structure" (Yudkin 2007). The majority of macrophages in expanded adipose tissue are of the M1 type, which are mainly induced and recruited by proinflammatory cytokines. Expanded adipose tissue has an increased local inflammatory response. Monocyte chemoattractant protein 1 (MCP-1) is a chemokine secreted by adipocytes, macrophages, and activated endothelial cells in expanded adipose tissue. MCP-1 promotes the recruitment of monocytes into adipose tissue. Subsequent exposure of the monocytes to macrophage colony-stimulating factor causes differentiation to macrophages, which can lead to secretion of more MCP-1 (Kanda et al. 2006). M1 type macrophages in expanded adipose tissue secrete not only MCP-1 but also other proinflammatory cytokines including tumor necrosis factor α (TNFα), interleukin (IL)-6, IL-1, and IL-8, which can further amplify the local inflammatory response and decrease adipocyte insulin sensitivity (Coppack 2001; Zeyda and Stulnig 2009).

Obesity and increased fat mass are also accompanied with hepatic steatosis and inflammation. Since hypertrophic, insulin-resistant adipocytes have increased lipolytic rates, expanded adipose tissue continuously releases free fatty acids into the blood stream. These fatty acids can be taken up by the liver, skeletal muscle, and other tissues. Increased uptake of free fatty acids from adipose tissue and triglyceride-rich lipoproteins including chylomicrons and very low-density lipoproteins

(VLDLs) can increase fat accumulation in the liver, resulting in hepatic steatosis (Maher et al. 2008). Excess fat accumulation can recruit more inflammatory cells into the liver. These immune cells and Kupffer cells can secrete more inflammatory factors and amplify this inflammatory response, which can lead to hepatic insulin resistance (Huang et al. 2010; Neyrinck et al. 2009). Kupffer cells in obese rodents also express high levels of lipogenic genes such as SCD1, fatty acid synthase (FAS), and diacylglycerol acyltransferase 2 (DGAT2) (Leroux et al. 2012). As a consequence, these cells have elevated lipid content and recruit more immune cells, producing high levels of inflammatory factors.

Macrophages play an essential role in skeletal muscle repair during tissue damage and exercise (Chazaud et al. 2009). Increased blood free fatty acid concentrations can cause elevated fat content in skeletal muscle, which may recruit more immune cells including macrophages. This fat accumulation and inflammation can decrease insulin sensitivity in the muscle (Trayhurn et al. 2011).

Macrophages and Atherosclerosis

Macrophages play an important role in atherosclerotic lesion progression by facilitating cholesterol accumulation and amplifying the local inflammatory responses in blood vessel walls (Kunjathoor et al. 2002; Ludewig and Laman 2004). As early as in 1958, experimental data in rabbits suggested that the increase in white blood cells adhering to the vessel wall signaled an early stage of atherosclerotic lesion progression (Lusvarghi et al. 1958). It was likewise demonstrated that fatty streaks, the earliest detectable atherosclerotic lesions, contain macrophage-derived foam cells (MDFC) which were differentiated from blood monocytes. Monocytes adhere to the blood vessel wall by inflammatory signals such as vascular cell adhesion molecule-1 (VCAM-1), P-selectin, and E-selectin (Hope and Meredith 2003). Under normal conditions the endothelial monolayer of the vasculature resists adhesion of blood-borne monocytes. The presence of VCAM-1, P-selectin, and E-selectin increases the adhesion of monocytes to the blood vessel wall. Once adherent to the endothelial monolayer, the monocytes migrate between endothelial cells at their junction to penetrate the intimal layer (Parker et al. 2001). Modified lipoprotein particles, especially high levels of low-density lipoprotein (LDL) and low levels of high-density lipoprotein (HDL), have been shown to increase the expression of VCAM-1 (Lopez-Garcia et al. 2005; Baker et al. 1999). MCP-1, a chemoattractant cytokine (chemokine), also plays an important role in the recruitment of monocytes into the arterial intima (Sheikine and Hansson 2004).

After monocyte migration into the arterial intima, these monocytes differentiate into macrophages in response to macrophage colony-stimulating factor (Tojo et al. 1999). Macrophages express many scavenger receptors and membrane proteins, which can regulate cellular cholesterol and fat content. Macrophage scavenger receptor 1 (MSR1) and CD36 are membrane proteins involved in the uptake of cholesterol-rich modified lipoproteins (Kunjathoor et al. 2002; de Winther et al. 2000). Two important macrophage membrane proteins involved in cholesterol

efflux are ATP-binding cassette transporter A1 (ABCA1) and scavenger receptor B class 1 (SR-B1). ABCA1 promotes cholesterol and phospholipid efflux from cells to HDL, while SR-B1 mediates the selective efflux of cellular cholesterol to HDL (Vedhachalam et al. 2004; Baranova et al. 2002). Cholesteryl ester (CE) in HDL is then selectively taken up by hepatocytes and used to synthesize bile acids or excreted into the bile completing a process termed reverse cholesterol transport. When macrophage cholesterol influx is greater than cholesterol efflux, cholesterol homeostasis in the macrophages is disturbed and CE accumulates in cytoplasmic droplets. These lipid-laden macrophages are known as MDFC. Both macrophage- and smooth muscle cell-derived foam cells characterize the early atherosclerotic lesion (Guyton and Klemp 1996). This cholesterol accumulation in the vessel intima leads to the formation of a cholesterol core, characteristic of advanced atherosclerotic lesions. MDFC in the atheroma secrete several inflammatory factors and proteases involved in lesion progression. Secretion of MCP-1 and matrix metalloproteinases promotes the progression of the atherosclerotic lesion formation.

Regulation of Macrophage SCD Expression

Only a few studies have investigated the regulation of SCD1 expression in macrophages. These studies indicate that macrophage SCD1 is regulated mainly by transcription factors and polyunsaturated fatty acids (PUFA).

Several transcription factors regulate SCD1 expression in macrophages. For example, activation of liver X receptor (LXR)/retinoid X receptor (RXR) via 22(R)-OH cholesterol and 9-*cis*-retinoic acid leads to increased expression of SCD1 and SCD2 in peritoneal macrophages (Martin-Fuentes et al. 2009). CCAAT/enhancer-binding protein (CEBP) β is a transcription factor which represses SCD1 expression (Zhang et al. 2012). The peroxisome proliferator-activated receptor (PPAR) γ agonist troglitazone suppresses macrophage SCD1 expression (Wang et al. 2004). Atorvastatin, an inhibitor of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, also suppresses SCD1 expression in THP-1-derived macrophages. β-Amyloid peptide is an important mediator of Alzheimer's disease (AD), which induces inflammation in brain macrophages (microglia). One study has shown that this peptide can increase SCD1 expression in microglial cells, suggesting that it is a positive regulator of SCD1 in macrophages (Uryu et al. 2003).

Similar to its regulation in other tissues, macrophage SCD1 expression is repressed by PUFA. For example, alpha linolenic acid (ALA), an n-3 PUFA, reduces SCD1 expression in THP-1 MDFC (Zhang et al. 2011). The mechanism of ALA-induced SCD1 repression is as follows. ALA activates the nuclear receptor farnesoid-X-receptor (FXR), which increases the expression of small heterodimer partner (SHP), which in turn decreases LXR-dependent sterol regulatory element-binding protein 1c (SREBP1c) transcription, leading to repression of SCD1 expression (Zhang et al. 2012). Conjugated linoleic acid (CLA) also suppresses SCD1 in macrophages (Wang et al. 2004).

SCD and Macrophage Biology in Metabolic Disorders

Role of Macrophage SCD in the Pathogenesis of Obesity-Related Inflammation

Macrophages play a key role in the pathogenesis of adipose tissue inflammation and obesity-associated metabolic disorders such as type-2 diabetes and atherosclerosis. While obesity promotes a proinflammatory macrophage phenotype, the key molecules and the molecular signaling pathway (s) involved in this process are not clearly known. Interestingly, macrophages from subjects with type-2 diabetes exhibit higher accumulation of linoleic acid and fatty acid profiles consistent with increased SCD activity compared to control subjects (Senanayake et al. 2007). Recent studies have found that peritoneal macrophages from global C/EBPβ deletion exhibit significantly higher SCD1 gene expression and attenuated the expression of palmitate-induced inflammatory cytokines including TNFα (Rahman et al. 2012). Thus, it is reasonable to propose that forced expression of macrophage SCD1 might be protective against high-fat diet-induced macrophage lipotoxicity.

The assertion that macrophage SCD1 expression is unlikely to promote an inflammatory phenotype is also supported by findings from SCD1 knockout mice. While SCD1 deficiency in obese mouse models such as Agouti and high-fat diet-fed mice prevents inflammation in white adipose tissue and adipocytes, it does not prevent the inflammatory activation of peritoneal macrophages (Liu et al. 2010). Moreover, adipocytes isolated from SCD1 knockout adipose tissue show a blunted response to lipopolysaccharide (LPS) stimulation. However, peritoneal macrophages isolated from SCD1 knockout and wild-type (WT) mice show similar expression of inflammatory genes when challenged with LPS. These results suggest that the modulation of inflammation by SCD1 is cell type-specific. In order to assess a paracrine connection between adipocytes and macrophages, Liu et al. collected conditioned medium (CM) from WT and SCD1 knockout adipocytes and tested its effects on inflammation in RAW264.7 macrophage cells. The induction of proinflammatory genes TNFα and IL-1β was significantly lower in RAW264.7 macrophages treated with SCD1-deficient conditioned medium (CM), compared with the treatment with WT CM. These data indicate that adipocyte-derived soluble factors are the likely mediators of inflammation in macrophages and that the levels of these factors are lower in SCD1-deficient CM.

Macrophage SCD as a Mediator of Atherosclerosis

Macrophage-mediated inflammation also plays a critical role in the pathogenesis of atherosclerosis, a leading cause of cardiovascular morbidity and mortality in the world. Macrophages play a central role in atherogenesis through regulation of accumulation of cholesterol and inflammation (discussed above). As discussed earlier in

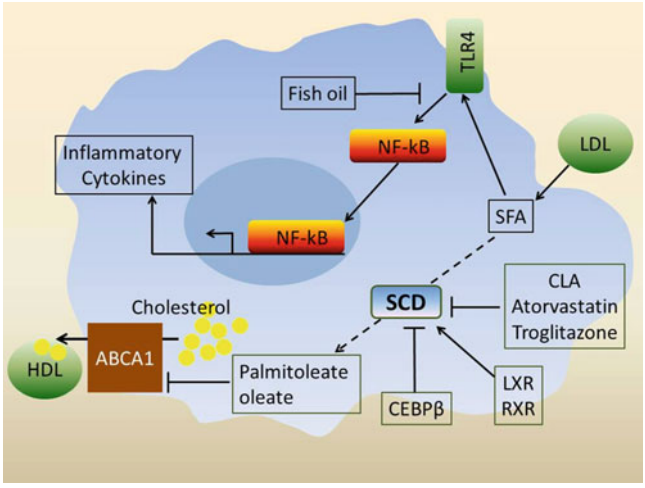

Fig. 6.1 Regulation and functions of macrophage SCD. Macrophage SCD expression is induced by activation of LXR/RXR transcription factors, while repressed by CEBPβ. SCD activity is also inhibited by PUFA, Atorvastatin, and PPARγ agonist troglitazone. SCD catalyzes MUFA formation from SFA, which in turn destabilize ABCA1 leading to reductions in cholesterol efflux. Therefore, SCD inhibition leads to increased cholesterol efflux. However, SCD inhibition leads to accumulation of SFA, which can activate TLR4 and thereby the NF-kB signaling pathway, leading to production of proinflammatory cytokines, which can aggravate atherogenesis. Fish oil can prevent this effect, probably via inhibition of the NF-kB pathway. *SCD* stearoyl-CoA desaturase, *LXR* liver X receptor, *RXR* retinoid X receptor, *CEBP* CCAAT/enhancer-binding protein, *PUFA* polyunsaturated fatty acids, *PPAR* peroxisome proliferator-activated receptor, *MUFA* monounsaturated fatty acids, *SFA* saturated fatty acids, *ABCA1* ATP-binding cassette transporter A1, *TLR4* toll-like receptor-4, *NF-kB* nuclear factor-kB

this chapter, ABCA1 is an important cholesterol efflux receptor, which promotes cholesterol and phospholipid efflux from macrophages to HDL. When macrophage cholesterol influx is greater than cholesterol efflux, cholesterol homeostasis in the macrophage is disturbed and cholesteryl ester accumulates in cytoplasmic droplets. These lipid-laden macrophages are known as MDFC, which characterize the early atherosclerotic lesion (Vedhachalam et al. 2004). Cholesterol efflux from these foam cells provides protection against the progression of the plaque.

Because of the promising role of SCD in the regulation of metabolic functions, much effort has been directed in elucidating the role of SCD in atherosclerosis. A summary is given in Fig. 6.1. Sun et al. have shown that SCD1 and SCD2 are induced in peritoneal macrophages after treatment with LXR/RXR activators, 22(R)-OH cholesterol and 9-*cis*-retinoic acid. This induction is associated with inhibition of ABCA1 (Sun et al. 2003). Other studies also report the LXR-mediated induction of SCD gene expression and subsequent reduction of ABCA1 in macrophages (Wang et al. 2004). Conversely, SCD inhibitors, CLA and troglitazone attenuate the ABCA1 destabilization induced by palmitate and stearate but not by linoleate. These results suggest that LXR/RXR ligands activate SCD, which in turn promote the production

of MUFA from SFA precursors, which destabilize ABCA1. However, there is a body of literature showing that LXR agonists increase both ABCA1 and ATP-binding cassette subfamily G member 1 (ABCG1) gene transcription and cholesterol efflux in macrophages (Larrede et al. 2009; Zhou et al. 2010). These studies, however, do not clarify whether LXR activation-mediated increase of ABCA1 and ABCG1 gene expression and therefore cholesterol efflux in macrophages is dependent on SCD expression (Beyea et al. 2007; Teupser et al. 2008). Thus, the role of SCD in LXR activation-mediated induction of ABCA1 and ABCG1 remains unclear. Further work in this area to determine the exact relationship between LXR agonism, SCD1 expression, and cholesterol efflux is certainly warranted.

Consistent with the effect of SCD inhibitors on attenuating SFA-induced ABCA1 destabilization, SCD inhibition also promotes cholesterol efflux from foam cells. For example, ALA treatment and siRNA-mediated knockdown of SCD1 significantly reduce SCD1 expression in macrophage foam cells with concomitant increases in cholesterol efflux and reductions in intracellular cholesterol storage in these cells (Zhang et al. 2012). SCD1 knockdown also reduces fatty acid content, increases ABCA1 protein levels, and increases cholesterol efflux in cultured human macrophages (Wong et al. 2011). Taken together, this suggests a negative effect of macrophage SCD expression on cholesterol efflux, thereby potentially promoting atherogenesis. Interestingly, the anti-atherogenic pharmacological agent atorvastatin is also known to suppress SCD gene expression in macrophages. In one such study, Martín-Fuentes et al. assessed the effects of atorvastatin on oxidized low-density lipoprotein (oxLDL)-loaded human macrophage cells (THP-1). They found a significant reduction in the percentage of palmitoleic and oleic acids in THP-1 cells incubated with atorvastatin, which was associated with marked reduction of SCD and sterol regulatory element-binding protein 1 (SREBP1) gene expression (Martin-Fuentes et al. 2009).

Since increased macrophage SCD expression is associated with reduced cholesterol efflux, SCD inhibition could possibly have a favorable effect on atherogenesis. Paradoxically, rodent studies have indicated otherwise. Brown et al. used antisense oligonucleotides (ASO) to inhibit SCD1 in a mouse model of hyperlipidemia and atherosclerosis (LDLr−/−Apob100/100) and showed that inhibition of SCD1 attenuated diet-induced obesity, insulin resistance, and hepatic steatosis but promoted aortic atherosclerosis, which was not reversed by dietary oleate (Brown et al. 2008). Furthermore, these mice had increased levels of SFA in plasma and tissues, reduced plasma triglycerides, and normal LDL cholesterol levels. Next, they examined whether increased SFA availability in this model affected toll-like receptor-4 (TLR4) activation. As expected, mice with SCD1 inhibition exhibited hypersensitivity to TLR4 agonists. It is possible that inhibition of SCD1 in the liver leads to secretion of VLDL particles that are enriched in SFA-rich cholesteryl esters (CE), giving rise to SFA-CE-rich LDL particles. Since the macrophages also have reduced SCD1 expression, they are unable to convert the SFA delivered to them via LDLs to MUFA, and therefore are exposed to high levels of SFA. This in turn will activate TLR4 which can further activate the nuclear factor-kB (NF-kB) pathway, leading to transcription of proinflammatory cytokines (Fig. 6.1). This proinflammatory environment promotes atherogenesis, especially in hyperlipidemic conditions.

This model is further supported by the finding that the atherosclerosis in LDLr−/− Apob100/100 mice with SCD1 knockdown can be prevented by the co-treatment with fish oil (Brown et al. 2010). We and others have previously shown that eicosapentaenoic acid (EPA), an n-3 PUFA found in fish oil, can inhibit the NF-kB pathway, possibly via activation of the G protein-coupled receptor 120 (Siriwardhana et al. 2012; Oh et al. 2010). It is plausible that fish oil attenuates the SFA-induced activation of TLR4 and subsequent activation of the NF-kB pathway and transcription of proinflammatory cytokines in the LDLr−/−Apob100/100 mice treated with SCD1 ASO, providing protection against the development of atherosclerosis.

Other studies have also shown that SCD1 deficiency promotes atherosclerosis under hypercholesterolemic conditions. For example, low-density lipoprotein receptor (LDLr)-deficient mice with SCD1 deficiency have increased atherosclerosis when fed a Western-type diet (Macdonald et al. 2009). In addition, SCD1 deletion in bone marrow cells of LDLr−/− mice also does not prevent atherosclerotic lesion formation. However, SCD1 knockdown in the chronic intermittent hypoxia mouse model, a model of obstructive sleep apnea which exhibits atherosclerosis, is protected from atherosclerosis. This discrepancy of the effects of SCD1 knockdown on atherosclerosis could indicate that under hypercholesterolemic conditions, SCD might protect against SFA-mediated inflammation (Liu et al. 2011). Taken together, this indicates that while macrophage SCD deficiency seems to promote cholesterol efflux, the proinflammatory environment induced by SFA-mediated TLR4 activation promotes atherogenesis.

Conclusion

SCD plays a pivotal role in metabolic function and exerts diverse cell-specific patterns of function and regulation. SCD is nutritionally and hormonally regulated and is altered in various metabolic and inflammatory disorders including obesity and diabetes. The role of SCD in macrophages in obesity and atherosclerosis is not fully understood and very limited studies have addressed its regulation in immune cells. Most of the studies were conducted either in RAW macrophages or in peritoneal macrophages isolated from global SCD1−/− mice. Several isoforms of SCD exist (Liu et al. 2011) and their comparative role in macrophage inflammation and lipotoxicity in response to obesity and its associated disorders have not been addressed. Future studies with isoform-specific roles of SCDs in macrophages might shed new insights into SCD's role in obesity-induced macrophage lipotoxicity and metabolic disorders.

References

Baker PW, Rye KA, Gamble JR, Vadas MA, Barter PJ (1999) Ability of reconstituted high density lipoproteins to inhibit cytokine-induced expression of vascular cell adhesion molecule-1 in human umbilical vein endothelial cells. J Lipid Res 40:345–353

Baranova I, Vishnyakova T, Bocharov A, Chen Z, Remaley AT, Stonik J, Eggerman TL, Patterson AP (2002) Lipopolysaccharide down regulates both scavenger receptor B1 and ATP binding cassette transporter A1 in RAW cells. Infect Immun 70:2995–3003

Beyea MM, Heslop CL, Sawyez CG, Edwards JY, Markle JG, Hegele RA, Huff MW (2007) Selective up-regulation of LXR-regulated genes ABCA1, ABCG1, and APOE in macrophages through increased endogenous synthesis of 24(S),25-epoxycholesterol. J Biol Chem 282:5207–5216

Bhargava P, Lee CH (2012) Role and function of macrophages in the metabolic syndrome. Biochem J 442:253–262

Brown JM, Chung S, Sawyer JK, Degirolamo C, Alger HM, Nguyen T, Zhu X, Duong MN, Wibley AL, Shah R, Davis MA, Kelley K, Wilson MD, Kent C, Parks JS, Rudel LL (2008) Inhibition of stearoyl-coenzyme A desaturase 1 dissociates insulin resistance and obesity from atherosclerosis. Circulation 118:1467–1475

Brown JM, Chung S, Sawyer JK, Degirolamo C, Alger HM, Nguyen TM, Zhu X, Duong MN, Brown AL, Lord C, Shah R, Davis MA, Kelley K, Wilson MD, Madenspacher J, Fessler MB, Parks JS, Rudel LL (2010) Combined therapy of dietary fish oil and stearoyl-CoA desaturase 1 inhibition prevents the metabolic syndrome and atherosclerosis. Arterioscler Thromb Vasc Biol 30:24–30

Chazaud B, Brigitte M, Yacoub-Youssef H, Arnold L, Gherardi R, Sonnet C, Lafuste P, Chretien F (2009) Dual and beneficial roles of macrophages during skeletal muscle regeneration. Exerc Sport Sci Rev 37:18–22

Coppack SW (2001) Pro-inflammatory cytokines and adipose tissue. Proc Nutr Soc 60:349–356

de Winther MP, van Dijk KW, Havekes LM, Hofker MH (2000) Macrophage scavenger receptor class A: a multifunctional receptor in atherosclerosis. Arterioscler Thromb Vasc Biol 20:290–297

Guyton JR, Klemp KF (1996) Development of the lipid-rich core in human atherosclerosis. Arterioscler Thromb Vasc Biol 16:4–11

Hope SA, Meredith IT (2003) Cellular adhesion molecules and cardiovascular disease. Part II. Their association with conventional and emerging risk factors, acute coronary events and cardiovascular risk prediction. Intern Med J 33:450–462

Huang W, Metlakunta A, Dedousis N, Zhang P, Sipula I, Dube JJ, Scott DK, O'Doherty RM (2010) Depletion of liver Kupffer cells prevents the development of diet-induced hepatic steatosis and insulin resistance. Diabetes 59:347–357

Kalupahana NS, Moustaid-Moussa N, Claycombe KJ (2012) Immunity as a link between obesity and insulin resistance. Mol Aspects Med 33:26–34

Kanda H, Tateya S, Tamori Y, Kotani K, Hiasa K, Kitazawa R, Kitazawa S, Miyachi H, Maeda S, Egashira K, Kasuga M (2006) MCP-1 contributes to macrophage infiltration into adipose tissue, insulin resistance, and hepatic steatosis in obesity. J Clin Invest 116:1494–1505

Kunjathoor VV, Febbraio M, Podrez EA, Moore KJ, Andersson L, Koehn S, Rhee JS, Silverstein R, Hoff HF, Freeman MW (2002) Scavenger receptors class A-I/II and CD36 are the principal receptors responsible for the uptake of modified low density lipoprotein leading to lipid loading in macrophages. J Biol Chem 277:49982–49988

Larrede S, Quinn CM, Jessup W, Frisdal E, Olivier M, Hsieh V, Kim MJ, van Eck M, Couvert P, Carrie A, Giral P, Chapman MJ, Guerin M, le Goff W (2009) Stimulation of cholesterol efflux by LXR agonists in cholesterol-loaded human macrophages is ABCA1-dependent but ABCG1-independent. Arterioscler Thromb Vasc Biol 29:1930–1936

Leroux A, Ferrere G, Godie V, Cailleux F, Renoud ML, Gaudin F, Naveau S, Prevot S, Makhzami S, Perlemuter G, Cassard-Doulcier AM (2012) Toxic lipids stored by Kupffer cells correlates with their pro-inflammatory phenotype at an early stage of steatohepatitis. J Hepatol 57:141–149

Liu X, Miyazaki M, Flowers MT, Sampath H, Zhao M, Chu K, Paton CM, Joo DS, Ntambi JM (2010) Loss of stearoyl-CoA desaturase-1 attenuates adipocyte inflammation: effects of adipocyte-derived oleate. Arterioscler Thromb Vasc Biol 30:31–38

Liu X, Strable MS, Ntambi JM (2011) Stearoyl CoA desaturase 1: role in cellular inflammation and stress. Adv Nutr 2:15–22

Lopez-Garcia E, Schulze MB, Meigs JB, Manson JE, Rifai N, Stampfer MJ, Willett WC, Hu FB (2005) Consumption of trans fatty acids is related to plasma biomarkers of inflammation and endothelial dysfunction. J Nutr 135:562–566

Ludewig B, Laman JD (2004) The in and out of monocytes in atherosclerotic plaques: balancing inflammation through migration. Proc Natl Acad Sci U S A 101:11529–11530

Lusvarghi E, Bellesia L, Mucci P (1958) Osmotic resistance of white blood cells in different circulatory districts (renal, intestinal, hepatic and peripheral) in the rabbit. Blut 4:254–260

Macdonald ML, van Eck M, Hildebrand RB, Wong BW, Bissada N, Ruddle P, Kontush A, Hussein H, Pouladi MA, Chapman MJ, Fievet C, van Berkel TJ, Staels B, McManus BM, Hayden MR (2009) Despite antiatherogenic metabolic characteristics, SCD1-deficient mice have increased inflammation and atherosclerosis. Arterioscler Thromb Vasc Biol 29:341–347

Maher JJ, Leon P, Ryan JC (2008) Beyond insulin resistance: innate immunity in nonalcoholic steatohepatitis. Hepatology 48:670–678

Martin-Fuentes P, Garcia-Otin AL, Calvo L, Gomez-Coronado D, Civeira F, Cenarro A (2009) Atorvastatin decreases stearoyl-CoA desaturase gene expression in THP-1 macrophages incubated with oxidized LDL. Lipids 44:115–123

Mauvoisin D, Mounier C (2011) Hormonal and nutritional regulation of SCD1 gene expression. Biochimie 93:78–86

Mosser DM, Edwards JP (2008) Exploring the full spectrum of macrophage activation. Nat Rev Immunol 8:958–969

Neyrinck AM, Cani PD, Dewulf EM, de Backer F, Bindels LB, Delzenne NM (2009) Critical role of Kupffer cells in the management of diet-induced diabetes and obesity. Biochem Biophys Res Commun 385:351–356

Oh DY, Talukdar S, Bae EJ, Imamura T, Morinaga H, Fan W, Li P, Lu WJ, Watkins SM, Olefsky JM (2010) GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects. Cell 142:687–698

Parker C III, Vita JA, Freedman JE (2001) Soluble adhesion molecules and unstable coronary artery disease. Atherosclerosis 156:417–424

Rahman SM, Janssen RC, Choudhury M, Baquero KC, Aikens RM, de la Houssaye BA, Friedman JE (2012) CCAAT/enhancer-binding protein beta (C/EBPbeta) expression regulates dietary-induced inflammation in macrophages and adipose tissue in mice. J Biol Chem 287:34349–34360

Rull A, Camps J, Alonso-Villaverde C, Joven J (2010) Insulin resistance, inflammation, and obesity: role of monocyte chemoattractant protein-1 (or CCL2) in the regulation of metabolism. Mediators Inflamm 2010

Saez F, Chabory E, Cadet R, Vernet P, Baron S, Lobaccaro JM, Drevet JR (2007) Liver X receptors and epididymal epithelium physiology. Asian J Androl 9:574–582

Senanayake S, Brownrigg LM, Panicker V, Croft KD, Joyce DA, Steer JH, Puddey IB, Yeap BB (2007) Monocyte-derived macrophages from men and women with Type 2 diabetes mellitus differ in fatty acid composition compared with non-diabetic controls. Diabetes Res Clin Pract 75:292–300

Sheikine Y, Hansson GK (2004) Chemokines and atherosclerosis. Ann Med 36:98–118

Siriwardhana N, Kalupahana NS, Fletcher S, Xin W, Claycombe KJ, Quignard-Boulange A, Zhao L, Saxton AM, Moustaid-Moussa N (2012) n-3 and n-6 polyunsaturated fatty acids differentially regulate adipose angiotensinogen and other inflammatory adipokines in part via NF-kappaB-dependent mechanisms. J Nutr Biochem 23:1661–1667

Sun Y, Hao M, Luo Y, Liang CP, Silver DL, Cheng C, Maxfield FR, Tall AR (2003) Stearoyl-CoA desaturase inhibits ATP-binding cassette transporter A1-mediated cholesterol efflux and modulates membrane domain structure. J Biol Chem 278:5813–5820

Teupser D, Kretzschmar D, Tennert C, Burkhardt R, Wilfert W, Fengler D, Naumann R, Sippel AE, Thiery J (2008) Effect of macrophage overexpression of murine liver X receptor-alpha (LXR-alpha) on atherosclerosis in LDL-receptor deficient mice. Arterioscler Thromb Vasc Biol 28:2009–2015

Tojo N, Asakura E, Koyama M, Tanabe T, Nakamura N (1999) Effects of macrophage colony-stimulating factor (M-CSF) on protease production from monocyte, macrophage and foam cell in vitro: a possible mechanism for anti-atherosclerotic effect of M-CSF. Biochim Biophys Acta 1452:275–284

Trayhurn P, Drevon CA, Eckel J (2011) Secreted proteins from adipose tissue and skeletal muscle—adipokines, myokines and adipose/muscle cross-talk. Arch Physiol Biochem 117:47–56

Uryu S, Tokuhiro S, Oda T (2003) beta-Amyloid-specific upregulation of stearoyl coenzyme A desaturase-1 in macrophages. Biochem Biophys Res Commun 303:302–305

Vedhachalam C, Liu L, Nickel M, Dhanasekaran P, Anantharamaiah GM, Lund-Katz S, Rothblat GH, Phillips MC (2004) Influence of ApoA-I structure on the ABCA1-mediated efflux of cellular lipids. J Biol Chem 279:49931–49939

Wang Y, Kurdi-Haidar B, Oram JF (2004) LXR-mediated activation of macrophage stearoyl-CoA desaturase generates unsaturated fatty acids that destabilize ABCA1. J Lipid Res 45:972–980

Wong BX, Kyle RA, Myhill PC, Croft KD, Quinn CM, Jessup W, Yeap BB (2011) Dyslipidemic diabetic serum increases lipid accumulation and expression of stearoyl-CoA desaturase in human macrophages. Lipids 46:931–941

Yudkin JS (2007) Inflammation, obesity, and the metabolic syndrome. Horm Metab Res 39:707–709

Zeyda M, Stulnig TM (2009) Obesity, inflammation, and insulin resistance—a mini-review. Gerontology 55:379–386

Zhang J, Grieger JA, Kris-Etherton PM, Thompson JT, Gillies PJ, Fleming JA, Vanden Heuvel JP (2011) Walnut oil increases cholesterol efflux through inhibition of stearoyl CoA desaturase 1 in THP-1 macrophage-derived foam cells. Nutr Metab (Lond) 8:61

Zhang J, Kris-Etherton PM, Thompson JT, Hannon DB, Gillies PJ, Heuvel JP (2012) Alpha-linolenic acid increases cholesterol efflux in macrophage-derived foam cells by decreasing stearoyl CoA desaturase 1 expression: evidence for a farnesoid-X-receptor mechanism of action. J Nutr Biochem 23:400–409

Zhou X, Yin Z, Guo X, Hajjar DP, Han J (2010) Inhibition of ERK1/2 and activation of liver X receptor synergistically induce macrophage ABCA1 expression and cholesterol efflux. J Biol Chem 285:6316–6326