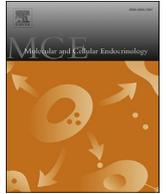




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Review

Role of bioactive lipid mediators in obese adipose tissue inflammation and endocrine dysfunction

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ABSTRACT

White adipose tissue is recognized as an active endocrine organ implicated in the maintenance of metabolic homeostasis. However, adipose tissue function, which has a crucial role in the development of obesity-related comorbidities including insulin resistance and non-alcoholic fatty liver disease, is dysregulated in obese individuals. This review explores the physiological functions and molecular actions of bioactive lipids biosynthesized in adipose tissue including sphingolipids and phospholipids, and in particular fatty acids derived from phospholipids of the cell membrane. Special emphasis is given to polyunsaturated fatty acids of the omega-6 and omega-3 families and their conversion to bioactive lipid mediators through the cyclooxygenase and lipoxygenase pathways. The participation of omega-3-derived lipid autacoids in the resolution of adipose tissue inflammation and in the prevention of obesity-associated hepatic complications is also thoroughly discussed.

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Abbreviations: BAT, brown adipose tissue; COX, cyclooxygenase; CYP, cytochrome P450; DHA, docosahexaenoic acid; EDPs, epoxydocosapentaenoic acids; EEs, epoxyeicosatetraenoic acids; EETs, epoxyeicosatrienoic acids; EPA, eicosapentaenoic acid; ER, endoplasmic reticulum; FFA, free fatty acid; HFD, high-fat diet; HSL, hormone sensitive lipase; IL, interleukin; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LD, lipid droplet; LOX, lipoxygenase; LT, leukotriene; LX, lipoxin; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PG, prostaglandin; PUFA, polyunsaturated fatty acids; sEH, soluble epoxide hydrolase; TAG, triacylglycerides; TNF α , tumor necrosis factor α ; WAT, white adipose tissue.

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1. Introduction

White adipose tissue is now well recognized as a highly active metabolic tissue and an important endocrine organ that plays a major role in balancing the homeostasis of our body. Unfortunately, this balance is lost in obese individuals in whom the excessive expansion of adipose tissue gives rise to a chronic state of “low-grade” inflammation. This unresolved inflammation of adipose tissue in obesity is deleterious and leads to many pathological sequelae including insulin resistance and type 2 diabetes, hypertension, dyslipidemia and non-alcoholic fatty liver disease (NAFLD).

Bioactive lipids play a major role in the inflammatory process. Among the different lipid mediators, polyunsaturated fatty acids and especially the essential omega-6 arachidonic acid are the prime precursors for the biosynthesis of inflammatory mediators, generically known as eicosanoids (from the Greek *eicos* = twenty; for 20-carbon fatty acid derivatives). Arachidonic acid is primarily found esterified in the 2-acyl position of phospholipids in all mammalian cell membranes. The intracellular levels of unesterified arachidonic acid are remarkably low and in its free form this fatty acid is readily available as a substrate for the intracellular biosynthesis of eicosanoids. With the exception of lipoxins, the majority of eicosanoids have pro-inflammatory properties. In contrast, another family of essential polyunsaturated fatty acids, the omega-3 family, is linked to the biosynthesis of lipid mediators with anti-inflammatory properties. Among the different lipid mediators generated from the omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), resolvins, protectins and maresins have attracted much attention in recent years because they act as 'braking signals' of the persistent vicious cycle leading to unremitting inflammation. An important aspect of these endogenous omega-3-derived lipid autacoids is their critical role in the dynamic resolution of tissue inflammation.

The aim of this review is to highlight the role of bioactive lipids as key protagonists of the intracellular and intercellular communication networks in white adipose tissue (WAT). Special emphasis is placed on the novel opportunities offered by omega-3-derived lipid mediators to prevent the “low-grade” state of mild inflammation present in adipose tissue of obese individuals. This review also covers different aspects of adipose tissue physiology and pathophysiology, including the metabolic consequences of adipose tissue expansion in obese subjects, the structural and storage lipid composition of adipose tissue and a detailed enumeration of the principal and most common bioactive lipids present in adipose tissue and their biosynthesis and actions on adipocytes and other insulin-sensitive cells.

2. Expansion of adipose tissue in obesity: metabolic consequences

WAT is an anatomical term for loose connective tissue composed of adipocytes or fat cells. Adipocytes are nucleated cells comprising a characteristic unilocular lipid droplet mainly

composed of triglycerides (TAG) and cholesterol esters, which occupy most of the cell, and a thin rim of cytoplasm displaced to the periphery (Redinger, 2009). The physical adaptability and the storage capacity of adipocytes are key components of their function. Indeed, during times in which energy intake is higher than the metabolic demand, adipocytes can expand nearly 1000-fold in volume and 10-fold in diameter in order to store the excess of fuel as TAG (Redinger, 2009). In contrast, in periods of food restriction or in periods demanding more energy expenditure, adipose tissue serves, via lipolysis, as the major source of energy. Under starving conditions, lipolysis is an essential mechanism whereby rate-limiting enzymes such as hormone-sensitive lipase (HSL) and monoacylglycerol lipase (MAGL) catalyze the hydrolysis of TAG to release free fatty acids (FFA) into the circulation (Carmen and Victor, 2006). Circulating FFA are subsequently taken up via the fatty acid binding protein (FABP) and fatty acid translocase (FAT/CD36) by metabolically active and insulin-sensitive tissues (primarily skeletal muscle and liver). These tissues use FFA as substrates for the generation of the high-energy nucleotide adenosine triphosphate (ATP) (Redinger, 2009).

The expansion of WAT occurring in obese individuals leads to prevailing high levels of hypoxia and chronic inflammation in this tissue. This inflammation is described as “metainflammation” and is characterized by a “low-grade”, “long-term” inflammatory response triggered by nutrients and metabolic surplus (Hotamisligil, 2006). It involves the rise in pro-inflammatory cytokines (i.e. tumor necrosis factor- α (TNF- α), interleukin (IL)-6, IL-1 β , monocyte chemoattractant protein-1 (MCP-1)) and adipokines (i.e. leptin and resistin) (Ouchi et al., 2011). In parallel, a reduction in anti-inflammatory and insulin-sensitizing adipokine adiponectin signals the onset of metabolic dysfunction in obese individuals (Ouchi et al., 2011). Among the metabolic consequences of this persistent state of inflammation insulin resistance leading to type-2 diabetes and hepatic steatosis leading to NAFLD are the most clinically relevant (Hotamisligil, 2006; Ouchi et al., 2011).

2.1. Insulin resistance and type 2 diabetes

Insulin resistance is one of the most important sequelae of obesity. Insulin resistance is defined as a reduced response of target tissues, such as the skeletal muscle, liver, and adipose tissue, to insulin, compared with subjects with normal glucose tolerance without a family history of diabetes (DeFronzo and Tripathy, 2009). Although skeletal muscle is the predominant site of insulin-mediated glucose uptake in the postprandial state, adipose tissue plays a major role in the development of peripheral insulin resistance. In fact, in obese subjects, the degree of insulin resistance is directly correlated with the serum levels of pro-inflammatory adipokines (i.e. TNF α , IL-6, and MCP-1) (Ouchi et al., 2011; de Luca and Olefsky, 2008). In parallel to the heightened secretion of inflammatory adipokines, there is an activation of the c-jun-N-terminal kinase (JNK) and inhibitor of κ kinase (IKK) pathways and their downstream signaling cascades by stress sensors through classical receptor-mediated mechanisms (Shoelson et al., 2006).

JNK and IKK activation in turn induces insulin resistance by disrupting tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1), a protein that connects the insulin receptor to the phosphoinositide 3-kinase (PI3K) signaling cascade (DeFronzo and Tripathy, 2009). In addition, the increased release of FFA by obese adipose tissue is a major determinant of impaired insulin-stimulated glucose uptake into muscle (Ebbert and Jensen, 2013).

2.2. Hepatic steatosis and NAFLD

Dysregulated adipose tissue function also has negative consequences in the liver. In fact, adipose tissue and the liver have immediate access to a vast network of blood vessels that implicate direct connection between these two organs. This connection is exemplified by the observation that NAFLD is one of the major metabolic consequences of obesity (Angulo, 2002; Sanyal, 2005). NAFLD is a condition ranging from simple accumulation of TAG in the cytoplasm of hepatocytes (steatosis or fatty liver) to steatosis combined with inflammation (steatohepatitis or NASH) (Angulo, 2002; Sanyal, 2005). Although generally asymptomatic, hepatic steatosis is no longer regarded as a neutral bystander, but rather as a pre-morbid condition that increases the vulnerability of this organ to progress to steatohepatitis and to more severe forms of liver damage (Angulo, 2002; Sanyal, 2005). Indeed, steatotic livers are more susceptible to the tissue-damaging effects of oxidative stress and inflammatory mediators, and transition to steatohepatitis represents a critical step in the progression to hepatic fibrosis and cirrhosis (Angulo, 2002; Sanyal, 2005). Although the exact mechanisms linking adipose tissue dysfunction and NAFLD have not been completely delineated, the exacerbated secretion of FFA and pro-inflammatory and insulin resistant adipokines (TNF α and IL-6) accompanied by reduced release of adiponectin by adipose tissue has a direct impact on liver cells (Angulo, 2002; Sanyal, 2005). Moreover, altered hepatic insulin sensitivity is a driving force for impaired hepatic FFA oxidation and *de novo* lipogenesis, which also contribute to the development of NAFLD (Tilg and Moschen, 2008).

3. Composition of adipose tissue in structural and storage lipids

The lipid composition of adipose tissue is strongly dependent on the diet. Differences in adipose tissue composition reported between racial groups, infant vs. adult and gender rapidly disappear when a diet of similar fatty acid composition is consumed (Damsgaard et al., 2013; Field et al., 1985). This section describes the lipid composition of fat cells categorized as structural lipids (i.e. lipids located within the cell membranes) or storage lipids (located within the unilocular lipid droplet).

3.1. Cell membranes

As with any other type of cell in the body, adipocytes are bound by a plasma membrane composed of carbohydrates, proteins and especially lipids. The carbohydrates in the cell membranes appear on the outside bound to lipids (glycolipids, such as cerebrosides and gangliosides) or to proteins (glycoproteins) forming the glycocalyx that provides adhesion properties to the cell and participates in lymphocyte homing (Dejana et al., 1994; Ekyalongo et al., 2015). Apart from their structural and biophysical membrane functions, membrane lipids bound to carbohydrates have no bioactive effects on the cell, and therefore are not discussed in this review. Proteins are the second most abundant component of the cell after lipids. They can be transmembrane proteins with an extracellular part that interacts with the extracellular environment and an intracellular domain interacting with signal transducers or with cytosolic

proteins in the cytoplasmic layer of the membrane (Harvey Lodish et al., 2000). There are also proteins that temporally interact with the membrane, including phospholipases (PL) A1 and A2 (PLA1 and PLA2) that release fatty acids in the SN1 and SN2 positions from the phospholipids; PLC, which releases diacylglycerol (DAG) from phospholipids; and sphingomyelinase (SMase), which hydrolyzes sphingomyelin to ceramide (see Section 4) (Balsinde and Dennis, 1997).

Phospholipids are the most abundant lipid components of the cell membrane. Phospholipids are amphipathic molecules containing both hydrophilic and hydrophobic moieties. For example, phosphoglycerides or glycerophospholipids are composed of a glycerol backbone with two fatty acids esterified to the SN1 and SN2 positions, and a phosphate group bound to the third hydroxyl group. This phosphate group is esterified to another hydroxyl group on another hydrophilic compound, such as choline, ethanolamine, serine or inositol, forming different phospholipids with unique properties (Balsinde et al., 1997). The fatty acids in glycerophospholipids can be saturated or unsaturated, and within these either mono or polyunsaturated, or a combination of both. Phospholipids are the most important precursors of fatty acids released intracellularly upon the action of PLA1 and PLA2. FFAs within the cytoplasm are toxic and are rapidly converted into biologically active lipid mediators by lipoxygenases and cyclooxygenases. The different derivatives and biological actions of these lipid mediators are extensively discussed in Section 4 of this review. On the other hand, sphingolipids such as sphingomyelin are formed by ceramide and phosphocoline or phosphoethanolamine that lacks the glycerol backbone. In this case, lipids are bound to a single sugar residue or to an oligosaccharide forming cerebrosides or gangliosides, respectively (Kolter et al., 1999). SMase activity hydrolyzes sphingomyelin into ceramide, sphingosine and phosphorylcholine (See Section 4.6 for more details). Finally, sterols are also lipid components of the cell membranes. Sterols are composed of a four-ring hydrocarbon structure with different groups at the two ends of the structure (Cantafora and Blotta, 1996). The most common sterol is cholesterol, which has a hydroxyl substituent on one end of the ring and a six-carbon tail with two methyl groups at positions 1 and 5 in the other. Membrane cholesterol may exert some biological activity since this lipid can post-translationally modify hedgehog signaling (Alcedo and Noll, 1997; Beckers et al., 2007).

3.2. Lipid droplets

Lipid droplets (LD) (also called lipid bodies, oil bodies or adiposomes) are considered a *bona fide* organelle present in almost all vertebrate cells, some plant cells and several yeasts and prokaryotes (Waltermann and Steinbuchel, 2005; Murphy, 2001). LD are composed of a hydrophobic core, mainly consisting of neutral lipids such as TAG and cholesterol esters surrounded by a phospholipid monolayer (as opposed to the normal bilayer of the other organelles) (Fujimoto and Parton, 2011). The hydrophilic phosphate group of phospholipids faces the aqueous cytoplasmic space, whereas the hydrophobic acylic tails are towards the inner part of the LD in contact with lipids accumulated in its core (Thiam et al., 2013). Several proteins are associated with LD, giving structural stability to its phospholipid monolayer. These proteins are implicated with lipid metabolism and signaling (Brasaemle, 2007). Interestingly, some proteins that are normally associated with the cytoplasm have been identified to be located in the LD core; but how their structure or function remains active in such a hydrophobic environment is unclear (Robenek et al., 2005). The major role of LD is the storage of lipids and cholesterol for energy purposes and for the formation and renewal of membranes (Thiam et al., 2013). LD can also participate in the inflammatory response

and are potentially involved in the pathogenesis of metabolic disorders such as obesity and atherosclerosis (Greenberg et al., 2011; Bozza and Viola, 2010; Krahmer et al., 2013).

The most widely accepted model of LD formation establishes the cellular origin in the endoplasmic reticulum (ER), where the enzymes catalyzing the end-steps of neutral lipid biosynthesis are located (Murphy, 2001; Buhman et al., 2001; Martin and Parton, 2006; Robenek et al., 2004). In the ER, nascent neutral lipids accumulate in the leaflets of the ER membrane forming a protuberance at the outer leaflet of the membrane that closes forming the LD surrounded by a phospholipid monolayer serving as an emulsifying agent (Thiam et al., 2013). Although the exact mechanisms are not yet clear, it is likely that several proteins contribute to the stabilization and release of the nascent LD. Among them, it has been proposed that members of the perilipin family (or PAT family) including perilipin, adipophilin and TIP47 control LD lipolysis and stabilization. Perilipin 1 (Plin1) was the first member of the PAT family described and is the best characterized. Upon formation, Plin1 is recruited to LD where it has a half-life exceeding 70 h under basal non-lipolytic conditions (Kovsan et al., 2007). Plin1 activates fat-specific protein 27 (Fsp27, or CIDEC) which promotes droplet fusion, emptying small LD into large droplets (Gong et al., 2011). Another protein of the PAT family that is present in the nascent LD after budding is TIP47 (or perilipin 3) (Wolins et al., 2005, 2003), which is recruited to the nascent LD on the ER surface when cells are incubated with fatty acids (Skinner et al., 2009). As the droplet starts growing, it migrates from the ER to the center of the adipocyte gradually losing TIP47 content while gaining adipophilin (Wolins et al., 2005). Adipophilin (or perilipin 2) is only stable while in contact with the LD, and it is rapidly degraded by the proteasome in the cytoplasm (Gross et al., 2006; Masuda et al., 2006; Xu et al., 2005). As the LD grows further, perilipin 1 replaces the other proteins in such a way that the mature adipocyte unilocular LD is coated almost exclusively by perilipin 1 (Wolins et al., 2005).

In the cell, LD store TAG and cholesteryl esters, which are hydrolyzed when cholesterol or fatty acid levels are depleted. Cholesterol is released for the production of steroid hormones and for renewal of the cellular membrane (Hu et al., 2010). On the other hand, fatty acids serve either as scaffolds of the membrane phospholipids, for energy production through β -oxidation or for the biosynthesis of bioactive lipid mediators. HSL is the first and best characterized enzyme involved in TAG hydrolysis (lipolysis) (Holm et al., 1988). HSL is highly expressed in adipocytes and exerts hydrolytic activity over TAG, diacylglycerol (DAG) and cholesteryl and retinol esters (Fredrikson et al., 1981; Pittman et al., 1975; Wei et al., 1997). For decades HSL was thought to be the major adipocyte lipase until some studies unexpectedly revealed that HSL null mice retain TAG lipase activity with accumulation of DAG, suggesting that other lipases are implicated in TAG lipolysis (Haemmerle et al., 2002; Osga et al., 2000; Wang et al., 2001). This controversy was solved when adipose TAG lipase (ATGL) was later identified (Jenkins et al., 2004; Zimmermann et al., 2004). ATGL hydrolyzes TAG to DAG releasing a FFA, whereas HSL hydrolyzes DAG to monoacylglycerol (MAG) again releasing another fatty acid. Finally, another enzyme acting downstream and designated MAG lipase converts MAG into a fatty acid and glycerol (Yang et al., 2010). Plin1 and PKA appear at the center of this process regulating the activity of both HSL and ATGL either directly or indirectly. PKA-mediated phosphorylation of HSL induces the docking of HSL to the LD monolayer in close association with Plin1, thus favoring lipolysis (Sztalryd et al., 2003; Granneman et al., 2007). Under basal conditions, Plin1 is associated with CGI-58 on the LD surface, and when Plin1 is phosphorylated by PKA, CGI-58 is released and can interact with ATGL, thereby increasing its activity (Lass et al., 2006). Fsp27 also plays a double role in the regulation of ATGL activity: in the LD

it inhibits lipolysis by binding to ATGL (Grahn et al., 2014), whereas in the nucleus it potentiates Erg1-negative regulation of the ATGL promoter (Singh et al., 2014).

The increased release of FFA from LD by TAG lipolysis in obese adipose tissue contributes to a great extent to the development of insulin resistance. For example, a reduction in Plin1 expression is associated with an increased rate of lipolysis that promotes systemic insulin resistance (Greenberg et al., 2011). In this regard, adipocytes from Plin1-null mice have an increased rate of lipolysis, and despite these mice being leaner than wild-type mice, they develop insulin resistance with aging (Tansey et al., 2001; Martinez-Botas et al., 2000). In humans, three individuals carrying a missense heterozygous mutation in the Plin1 gene (*PLIN1*) showed partial lipodystrophy, with loss of adipose tissue, along with insulin-resistant diabetes, hypertriglyceridemia and hepatic steatosis (Gandotra et al., 2011).

In addition to Plin1, knockdown of FSP27 expression increases the rate of basal lipolysis, an effect that is reversed by over-expressing FSP27 (Puri et al., 2007; Keller et al., 2008; Liu et al., 2009; Nordstrom et al., 2005; Ranjit et al., 2011; Kim et al., 2008a). Moreover, FSP27-null mice have a similar phenotype to that of Plin1-null mice, having reduced fat mass and increased lipolysis (Nishino et al., 2008). In humans, a homozygous nonsense mutation in FSP27 has been reported in a patient with lipodystrophy, insulin-resistant diabetes, hypertriglyceridemia, and hepatic steatosis. Another two proteins (seipin and caveolin-1) related to LD biology are involved in the development of lipodystrophy. Mutations in the seipin gene reduce TAG storage capacity in adipocytes, with a nearly complete absence of adipose tissue and with insulin resistance, diabetes, hypertriglyceridemia and hepatic steatosis (Magre et al., 2001). Similar features have been reported in a patient with a homozygous nonsense mutation in the gene coding for caveolin-1, which is part of the LD proteome (Kim et al., 2008b).

It has been proposed that LD have a role in the production of inflammatory and anti-inflammatory lipid mediators (Bozza and Viola, 2010; Dichlberger et al., 2013). In this regard, the number of LD has been shown to increase during the interaction of macrophages with pathogens, such as parasites (Melo et al., 2003), bacteria (Peyron et al., 2008; Daniel et al., 2011; Cardona et al., 2000; Tanigawa et al., 2008; Cao et al., 2007) and viruses (Barba et al., 1997; Samsa et al., 2009). Moreover, during infection, LD are mobilized into phagosomes, so the pathogen can use them as energy sources and for increased production of inflammatory mediators.

4. Bioactive lipids: biosynthesis and actions on WAT

Bioactive lipid mediators have been increasingly recognized as important endogenous regulators of key cellular processes. Fig. 1 illustrates a schematic representation of the most commonly described lipid mediators generated by adipocytes. The majority of these bioactive mediators originate from the cleavage of lipid constituents of cellular membranes under the activity of PLs, in particular PLA1 and PLA2, which release fatty acids from phospholipids, and PLC, which generates DAG from membrane phospholipids. In the free form, fatty acids are toxic in the cytosol, and are therefore readily converted into a number of lipid mediators, including omega-6 and omega-3 derivatives, fatty acid hydroxyl fatty acids (FAFH), nitroalkenes and endocannabinoids (Fig. 1). On the other hand, sphingolipids found in animal cell membranes are converted by the enzyme SMase into ceramide, which is subsequently hydrolyzed by ceramidase into a sphingosine molecule plus a FFA. Both ceramide and sphingosine are phosphorylated into ceramide 1-phosphate or sphingosine 1-phosphate, respectively (Fig. 1). In addition to cell membrane-derived lipids, TAG stored in

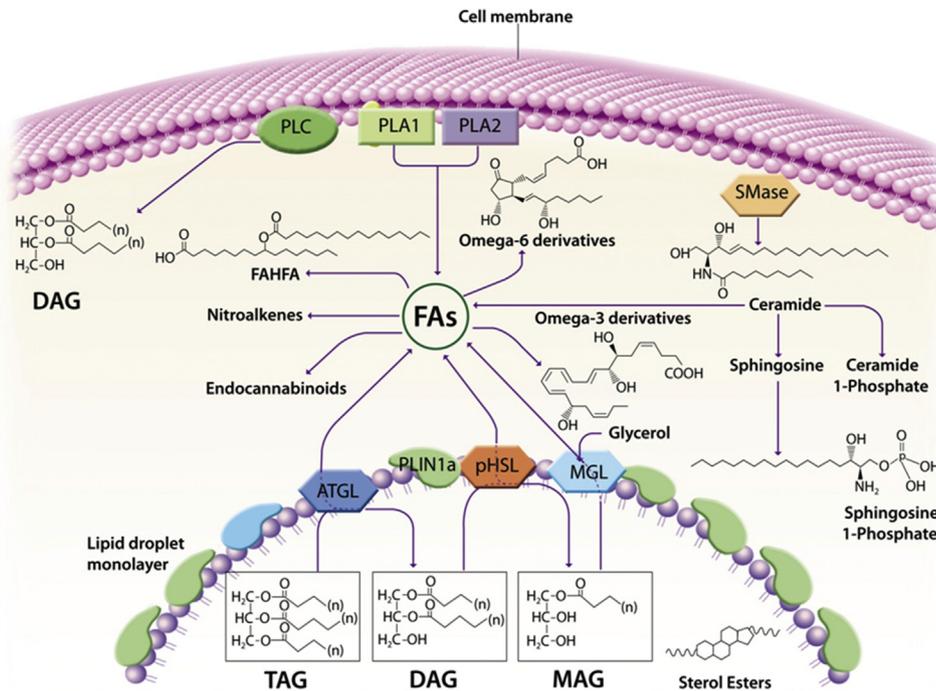


Fig. 1. Representative bioactive lipid mediators in adipocytes. Most of the bioactive lipids endogenously generated by adipocytes are primarily derived from cell membrane phospholipids and sphingolipids and secondarily from neutral lipids stored inside monolocular lipid droplets. Fatty acids (FAs), especially omega-6 and omega-3 polyunsaturated FAs, released from membrane phospholipids by phospholipase (PL) A1 and 2 (PLA1 and PLA2) are readily transformed by cyclooxygenases, lipoxygenases and cytochrome P450 epoxygenases into a broad spectrum of omega-6 and omega-3 derivatives. FA modifications also occur in the cytoplasm including nitrations (nitrated FAs or nitroalkenes), esterifications (fatty acid-hydroxy fatty acids, FAHFA), or ethanolamide additions (endocannabinoids). In the cell membrane, sphingomyelin is a substrate for sphingomyelinase (SMase), releasing ceramide to the cytoplasm. Ceramide can be phosphorylated into ceramide 1-phosphate or enzymatically hydrolyzed releasing a fatty acid and sphingosine (which can be phosphorylated to sphingosine 1-phosphate). In the cell membrane, PLC also hydrolyzes phospholipids to release diacylglycerol (DAG) that participates in different signaling pathways. FAs are also released from triacylglycerides (TAG) in perilipin 1a (PLIN1a)-coated lipid droplets. In the lipid droplet monolayer, adipose triclyceride lipase (ATGL) converts TAG into DAG by losing a FA. DAG is subsequently hydrolyzed by phosphorylated hormone-sensitive lipase (pHSL) to monoacylglycerol (MAG) releasing another FA. MAG is finally hydrolyzed into a third FA and glycerol by the actions of monoacylglycerol lipase (MGL).

the unilocular LD of adipocytes can release FFA into the cytosol by the concerted activities of ATGL, HSL and MGL present in the phospholipid monolayer coating the LD (Fig. 1).

4.1. Polyunsaturated fatty acid (PUFA)-derived lipid mediators

PUFAs cannot be synthesized *de novo* by mammalian cells and are therefore termed as “essential” because they must be obtained in adequate amounts from the diet (Lopez-Vicario et al., 2015a; Simopoulos, 1999). PUFAs are of utmost importance for mammalian cellular processes as they are the precursors of most cell-signaling molecules bearing a lipid structure, that is, lipid mediators. Indeed, PUFAs are unique fatty acids in the sense that they have multiple double bonds with a low dissociation energy rendering them very reactive to become easily oxidized to hydroperoxy and hydroxy derivatives (Lopez-Vicario et al., 2015a). There are two families of PUFAs depending on the carbon position of the first double bond from the methyl end (omega end): omega-6 and omega-3. In general terms, lipid mediators derived from omega-6-PUFA exert inflammatory, atherogenic and prothrombotic effects whereas those derived from omega-3-PUFA are anti-inflammatory and pro-resolving. Given that the current Western diet is very high in omega-6 and the ratio of omega-6/omega-3 PUFAs has risen to up to 20–30:1 (Simopoulos, 1999), pro-inflammatory and pro-thrombotic eicosanoids generated from omega-6 fatty acids are produced in larger quantities than those derived from omega-3 fatty acids (Lopez-Vicario et al., 2015a; Schmitz and Ecker, 2008). This explains why dietary changes characterized by a lower

consumption of omega-3-PUFA and modern agriculture (animals fed on diets rich in omega-6s) are believed to be the origin of the higher incidence of thrombotic, inflammatory and carbohydrate and lipid disorders in our society (Schrör, 1990; Bagga et al., 2003; Calder, 2006). The biosynthetic and signaling pathways and the cellular actions of lipid mediators derived from essential omega-6 and omega-3 fatty acids are described in detail in the following paragraphs.

4.1.1. Omega-6-derived lipid mediators

Arachidonic acid, an essential omega-6 PUFA, is the precursor of the biosynthesis of eicosanoids (Astudillo et al., 2012). There are two classical routes of eicosanoid biosynthesis in mammals: the cyclooxygenase (COX) pathway that results in the formation of prostaglandins (PGs) and thromboxane (TX); and the lipoxygenase (LOX) pathway that catalyzes the formation of leukotrienes (LTs) and hydroxyeicosatetraenoic acids (HETEs) (Fig. 2) (Samuelsson et al., 1987; Romano and Claria, 2003). Apart from the COX and LOX pathways, arachidonic acid can also be converted into biologically active mediators by cytochrome P-450 (CYP) epoxygenases (Fig. 2) (Spector and Norris, 2007). CYP epoxygenases are the so-called third branch of arachidonic acid metabolism and add oxygen across one of the four double bonds of this PUFA to generate three-membered ethers known as epoxyeicosatrienoic acids (EETs) (Spector and Norris, 2007). These epoxides act in an autocrine and paracrine fashion regulating vascular tone, inflammation, hyperalgesia and organ and tissue regeneration (Zeldin, 2001; Panigrahy et al., 2013). Finally, the eicosanoid family includes the lipoxins (LXs), a unique class of potent bioactive lipid mediators resulting

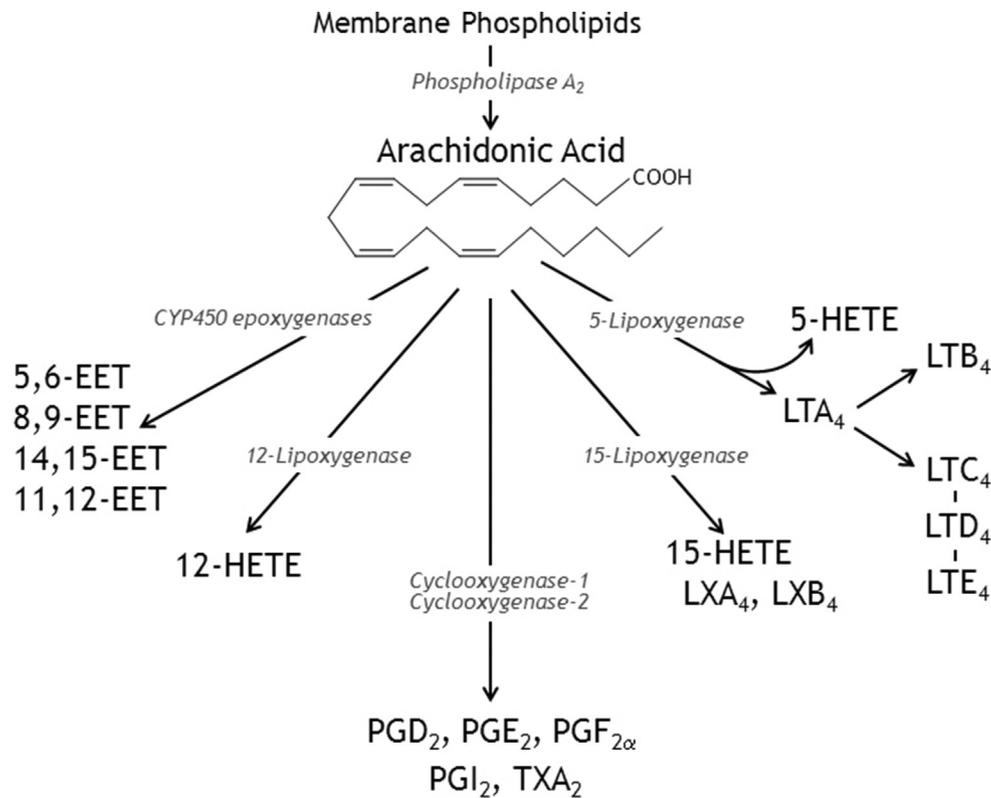


Fig. 2. Schematic diagram summarizing the biosynthesis of eicosanoids derived from the omega-6 polyunsaturated fatty acid arachidonic acid. Upon activation of phospholipase A₂, arachidonic acid is released from membrane phospholipids and converted into biologically active eicosanoids through the cyclooxygenase and lipoxygenase pathways. The cyclooxygenase pathway comprises two isoforms (cyclooxygenase-1 and -2) that convert arachidonic acid into prostaglandin (PG) D₂, PGE₂, PGF_{2α}, PGI₂ and thromboxane (TX) A₂. On the other hand, the lipoxygenase pathway comprises three different dioxygenases (5-, 12- and 15-lipoxygenases) that catalyze the oxygenation of the 5-, 12- or 15-carbon atoms of arachidonic acid resulting in the formation of the respective hydroxyeicosatetraenoic acids (i.e. 5-, 12- and 15-HETEs). 5-lipoxygenase also gives rise to the unstable allylic epoxide leukotriene (LT) A₄, which is either hydrolyzed to LTB₄ or converted into LTC₄/LTD₄/LTE₄. During cell–cell interactions, mechanisms involving transcellular routes can transform 15-HETE into lipoxin (LX) A₄ and LXB₄, which, contrary to PGs and LTs, are potent endogenous anti-inflammatory eicosanoids. A so-called third branch of arachidonic acid metabolism is represented by the CYP450 epoxygenases, which convert this fatty acid into epoxyeicosatrienoic acids (EETs).

from the interaction between individual LOXs and, in the presence of aspirin, between COX-LOX interactions (Fig. 2) (Samuelsson et al., 1987).

4.1.1.1. The COX pathway. COX, the key enzyme in the biosynthesis of PGs, has two different isoforms: COX-1, which is constitutively expressed, and COX-2, which is inducible (Kujubu et al., 1991; Xie et al., 1991). Both COX isoforms convert arachidonic acid into PGG₂ and subsequently into PGH₂, which is finally converted by specific terminal synthases into PGs of the D₂, E₂, F₂ and I₂ series as well as into TXA₂ (Chandrasekharan and Simmons, 2004). Both PGI₂ and TXA₂ have a very short half-life and are rapidly hydrolyzed to the inactive compounds 6-keto-PGF_{1α} and TXB₂, respectively. PGD₂ is also readily dehydrated to the cyclopentenone PGs of the J₂ series (PGJ₂ and 15-deoxy-Δ^{12,14}-PGJ₂ (15d-PGJ₂)) (Chandrasekharan and Simmons, 2004). COX products act as autocrine or paracrine hormones, maintaining homeostasis within their cells of origin or in neighboring cells in the tissue. These eicosanoids bind to at least ten types and subtypes of prostanoid receptors belonging to the family of the seven transmembrane G protein-coupled receptors. Four of the receptor subtypes bind PGE₂ (EP1, EP2, EP3 and EP4), two bind PGD₂ (DP1 and DP2), two bind TXA₂ (TPα and TPβ) and the rest are single receptors for PGF_{2α} and PGI₂ (FP and IP, respectively) (Breyer et al., 2001).

4.1.1.2. The LOX pathway. There are three major LOXs in humans: 5-, 12- and 15-LOX. 5-LOX converts arachidonic acid into 5(S)-

hydroxyeicosatetraenoic acid (5(S)-HETE) and LTs whereas 12- and 15-LOXs generate the corresponding 12- and 15-HETEs, respectively (Fig. 2). The best characterized and most relevant LOX is arachidonate 5-LOX. Arachidonate 5-LOX is a 674-amino acid protein, which upon cellular activation translocates to the nuclear envelope where it interacts with five lipoxygenase-activating protein (FLAP), an 18 kDa resident integral protein which functions as a transfer protein facilitating the binding of arachidonic acid to 5-LOX (Dixon et al., 1990). In the nuclear envelope, 5-LO transforms arachidonic acid into 5(S)-HpETE, which is subsequently reduced to either 5(S)-HETE or converted to the highly unstable allylic epoxide LTA₄ (Rouzer et al., 1986). Once formed, LTA₄ is rapidly transformed to either LTB₄ by LTA₄ hydrolase or to LTC₄ by LTC₄ synthase (Radmark et al., 1984). LTC₄ is subsequently deaminated into LTD₄ and LTE₄ (Fig. 2). These 5-LOX products bind G-protein coupled receptors (GPCRs), in particular B-LT₁ and B-LT₂ receptors for LTB₄ and Cys-LT₁ and Cys-LT₂ for LTC₄ and LTD₄ (Back et al., 2014).

On the other hand, 15-LOX exists in two isoforms: 15-LOX-1 and 15-LOX-2, which transform arachidonic acid into 15(S)-HETE (Kuhn et al., 2015). 12/15-LOX is the murine ortholog of human 15-LOX-1 (Kuhn et al., 2015). The physiologic role of 15-LOX is dependent on the context in which it is expressed, but this pathway is essential for the formation of products able to antagonize and properly resolve inflammatory responses (see Section 4.1.3). Regarding 12-LOX, this enzyme exists in three isoforms designated after the cells in which they were first identified: platelet-type, which metabolizes arachidonic acid into 12(S)-HETE; leukocyte-type, which converts

arachidonic acid or linoleic acid into 12(S)-HETE and also small quantities of 15(S)-HETE; and epithelial- or epidermis-type, that catalyzes the synthesis of both 12(S)- and 15(S)-HETE from arachidonic acid (Kuhn et al., 2015; Cole et al., 2013).

The interaction between individual LOX gives rise to the formation of lipoxins (LXs) by transcellular biosynthesis, eicosanoids that exert potent anti-inflammatory and immunoresolving actions in mammalian cells (Chiang et al., 2005). Three routes of transcellular LX biosynthesis have been described. The first route is initiated by the release of the epoxide intermediate LTA₄ formed by 5-LOX in activated leukocytes, which is then converted by platelet 12-LOX to LXA₄ and LXB₄ (Serhan and Sheppard, 1990). The second route takes place mainly in tissues in which endothelial and epithelial cells expressing 15-LOX can interact with 5-LOX-containing leukocytes (Chiang et al., 2005). Finally, a third major route of LX biosynthesis initiated by aspirin has been described (Claria and Serhan, 1995). Aspirin acetylates COX-2 and switches its catalytic activity from a PG synthase to a 15-LOX in such a way that PG biosynthesis is inhibited and arachidonic acid is instead transformed to 15(R)-HETE (Claria and Serhan, 1995). 15(R)-HETE is subsequently transformed by activated leukocytes possessing 5-LOX to a new series of carbon-15 epimers of LXs that carry their 15 alcohol in the R configuration (15-epi-LXs) (Claria and Serhan, 1995). The formation of these lipid mediators is specific for aspirin treatment, and the term aspirin-triggered LXs, abbreviated as AT-LXs, has been coined for these compounds (Claria and Serhan, 1995).

4.1.2. Biosynthesis and actions of omega-6-derived lipid mediators in WAT

The ability of WAT to generate bioactive lipid mediators was first described in the late 1960s when Shaw and Ramwell identified a group of hydroxyl C20 carboxylic acids, later identified as PGs derived from the oxygenation of arachidonic acid by COX in rat epididymal fat pads (Shaw and Ramwell, 1968). Among the different COX-derived products, PGE₂ was recognized as one of the most abundant PGs in WAT. This finding was consistent with studies pointing to PGE₂ as a negative regulator of hormone-stimulated lipolysis (Steinberg et al., 1963). Along these lines, preincubation of adipocytes with COX inhibitors has been reported to enhance lipolysis (Chatzipanteli et al., 1992). Given that the lipolytic actions of catecholamines are mediated by cAMP, which in turn activates HSL, the anti-lipolytic actions of PGE₂ are likely associated with the modulation of adipocyte cAMP levels (Kather et al., 1985). PGE₂ has also been shown to suppress 3T3-L1 adipocyte differentiation by binding to EP4 and eliciting an increase in intracellular cAMP levels in preadipocytes (Tsuboi et al., 2004). Recently, we gathered data supporting a coordinated negative regulation between PGE₂ and PPARγ (Garcia-Alonso et al., 2013). Indeed, mice deficient in PPARγ showed increased expression of COX-2 and mPGES-1 and augmented PGE₂ levels, whereas the addition of exogenous PGE₂ suppressed PPARγ expression (Garcia-Alonso et al., 2013). Opposite effects were seen after the inhibition of endogenous PGE₂ biosynthesis with a selective mPGES-1 inhibitor (Garcia-Alonso et al., 2013). Of note, PGE₂ diverted preadipocyte differentiation to beige/brite mature adipocytes accompanied by up-regulation of UCP1, whereas a selective pharmacological mPGES-1 inhibitor and a siRNA directed against mPGES-1 resulted in the reduction of browning markers (i.e. UCP1, CIDEA and PGC-1α) and browning determination factors (i.e. PRDM16) in preadipocytes (Garcia-Alonso et al., 2013).

In addition to PGE₂, it has been postulated that another COX-derived product, 15-deoxy-Δ^{12,14}-prostaglandin J₂ (15d-PGJ₂), plays a relevant role in adipose tissue by regulation of the adipogenic process. 15d-PGJ₂ is a cyclopentenone metabolite produced

by dehydration of PGD₂ (Bell-Parikh et al., 2003). The predominant enzymatic source of 15d-PGJ₂ formation *in vivo* is COX-2, and unlike other PGs, no specific membrane receptor has been identified for this lipid mediator (Forman et al., 1995). Instead, 15d-PGJ₂ exerts its anti-inflammatory and adipogenic actions through binding and activation of the nuclear receptor PPARγ (Forman et al., 1995). Exposure of human adipocytes to 15d-PGJ₂ inhibits the secretion of pro-inflammatory adipokines and stimulates the production of macrophage inhibitory cytokine-1, a protective adipokine, by adipose tissue (Ding et al., 2009). In addition, a significant down-regulation in the expression and secretion of the pro-inflammatory adipokine leptin has been reported in adipocytes exposed to exogenous 15d-PGJ₂ (Sinha et al., 1999). Importantly, 15d-PGJ₂ stimulates adipogenesis (Sinha et al., 1999) and also exerts proadipogenic actions in fibroblasts, although in this case lymphocytes are the source of this cyclopentenone PG (Feldon et al., 2006). Surprisingly, an impaired adipogenic program has been identified in 3T3-L1 cells with stable transfection of PGD synthase and appreciably higher levels of endogenous PGD₂-derived metabolites, suggesting a complex regulatory interaction between PPARγ and pro-adipogenic lipid mediators (Hossain et al., 2012).

Apart from COX products, WAT also has the ability to produce and release LOX products, especially LTB₄, which apparently is the predominant LOX metabolite in this tissue (Horrillo et al., 2010). In this regard, WAT expresses all the enzymes necessary for the formation of 5-LOX products (5-LOX, FLAP, LTA₄ hydrolase, and LTC₄ synthase), as well as all the receptors involved in LT signaling (BLT-1, BLT-2, CysLT1, and CysLT2) (Horrillo et al., 2010). LTB₄ has been identified as an inflammatory factor in WAT, and FLAP overexpression and excessive generation of 5-LOX products is a common finding in WAT of obese patients and animals with insulin resistance (Horrillo et al., 2010; Li et al., 2015; Pardo et al., 2015). Moreover, a direct relationship has been reported between LTB₄ and enhanced release of inflammatory adipokines (i.e. MCP-1 and IL-6) in obese WAT (Horrillo et al., 2010). Consistent with this finding, mice deficient in the LTB₄ receptor BLT-1 show reduced monocyte recruitment to hypertrophied adipose tissue, whereas inhibition of the 5-LOX pathway with a selective FLAP inhibitor or genetic deletion of the BLT-1 receptor alleviates adipose tissue inflammation and insulin resistance in obesity (Horrillo et al., 2010; Spite et al., 2011).

4.1.3. Omega-3-derived lipid mediators

EPA and DHA are the archetypal omega-3-PUFAs that are substrates of the same COX and LOX pathways described previously for omega-6-PUFA. However, in the case of EPA and DHA, they are converted into potent anti-inflammatory and pro-resolving mediators, generically known as specialized pro-resolving mediators (SPM). This family includes a number of functionally distinct mediators such as resolvins, protectins and maresins (Serhan, 2014; Serhan and Chiang, 2013). These novel bioactive lipid mediators are further classified as either resolvins of the E-series if the biosynthesis is initiated from EPA or resolvins of the D-series if they are generated from DHA (Serhan et al., 2000). Protectins and maresins are also biosynthesized from DHA (Serhan et al., 2006, 2009). A schematic diagram of DHA and EPA-derived lipid mediators is shown in Fig. 3. The biosynthesis of omega-3-derived lipid mediators and their role in the metabolic syndrome and related liver disease have been described in detail in a recent review by our group (Lopez-Vicario et al., 2015a).

4.1.4. Biological actions of omega-3-derived lipid mediators in WAT

Human and mouse WAT express all the enzymes necessary for the biosynthesis of resolvins, protectins and maresins derived from omega-3 PUFAs, as well as all the receptors necessary for their

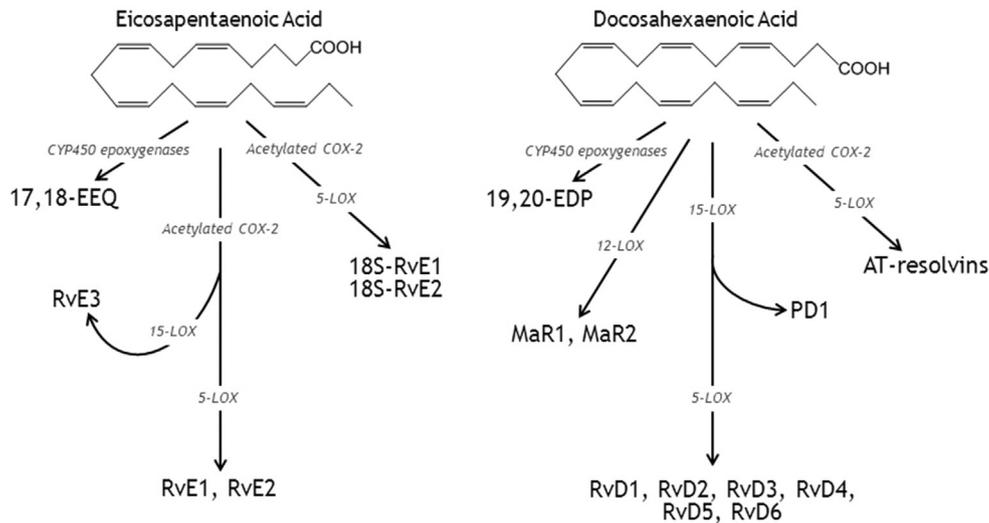


Fig. 3. Schematic diagram summarizing the biosynthesis of lipid mediators from the omega-3 polyunsaturated fatty acids eicosapentaenoic acid and docosahexaenoic acid. Eicosapentaenoic acid is converted by aspirin-acetylated cyclooxygenase-2 (COX-2) into 18R-HEPE (not shown), which is subsequently transformed by 5-lipoxygenase (5-LOX) into resolvin E1 (RvE1) and RvE2. Conversion of 18R-HEPE via the 15-LOX pathway gives rise to a novel member of the E-series resolvin family, RvE3. Members of the 18S-RvE series, including 18S-RvE1 and 18S-RvE2 derived from eicosapentaenoic acid, have also been identified. In addition, CYP epoxygenases convert eicosapentaenoic acid into a predominant epoxide form, 17,18-epoxyeicosatetraenoic acid (17,18-EEQ). On the other hand, docosahexaenoic acid is converted to 17-HDHA (not shown) by 15-LOX, which is subsequently transformed by 5-LOX into the D-series resolvins (i.e. RvD1, RvD2, RvD3, RvD4, RvD5 and RvD6). 15-LOX-derived 17-HDHA can also be converted into a dihydroxy-containing derivative termed protectin D1 (PD1). In macrophages, lipoxygenation of docosahexaenoic acid by 12-LOX gives rise to maresins (MaR1 and MaR2). Alternatively, CYP450 epoxygenases can convert docosahexaenoic acid into a predominant epoxide derivative, 19,20-epoxydocosapentaenoic acid (19,20-EDP). Finally, docosahexaenoic acid can be metabolized by aspirin-acetylated COX-2 and 5-LOX into the so-called aspirin-triggered (AT)-resolvins.

signaling (reviewed in (Spite et al., 2014)). In the setting of obesity, prevailing data support an unbalanced formation of these omega-3-derived lipid mediators in obese WAT. Indeed, a deficit in tissue SPM levels (RvD1, PD1 and 17-HDHA) has been characterized in inflamed visceral and subcutaneous fat compartments from obese *ob/ob* and obese/diabetic *db/db* mice (Gonzalez-Periz et al., 2009; Claria et al., 2012; Neuhofer et al., 2013). In humans, a deficit in PD1 and its precursor 17S-HDHA has been reported in subcutaneous fat from patients with peripheral vascular disease in whom the inflammatory status in adipose tissue is remarkably exacerbated compared with healthy subcutaneous fat (Claria et al., 2013). Moreover, LC-MS/MS-based metabolo-lipidomic analyses of fat from selected human anatomic locations have identified unique signature profiles in the content of bioactive lipids (Claria et al., 2013). Importantly, these analyses demonstrated a heterogeneous capacity for SPM biosynthesis among different adipose tissue depots, with higher activation of resolution circuits in perivascular fat compared with subcutaneous fat (Claria et al., 2013). This is relevant for vascular pathologies, with perivascular adipose tissue playing an emerging role in vascular biology homeostasis because of its tissue mass and anatomic proximity surrounding systemic vessels.

The compromised capacity to produce local SPM in obese tissues with a heightened pro-inflammatory phenotype could be the consequence of a structural deficiency in the tissue content of omega-3-PUFAs as established substrates for SPM biosynthesis. Indeed, there is evidence that SPM are generated in humans taking omega-3 dietary supplements and that SPM levels are increased above those produced normally in transgenic *fat-1* mice (Hudert et al., 2006). This is consistent with the observation that transgenic restoration of omega-3 fatty acids in *fat-1* mice with high-fat diet (HFD)-induced obesity reversed their inefficient resolution capacity and produced anti-inflammatory and pro-resolution actions in adipose tissue (Lopez-Vicario et al., 2015b; White et al., 2010). Alternatively, the loss of SPM in obesity may reflect accelerated tissue SPM conversion and clearance to inactive further

metabolites because 15-PG-dehydrogenase/eicosanoid oxidoreductase, the key enzyme in SPM inactivation, is markedly up-regulated in obese adipose tissue (Claria et al., 2012). In this tissue, omega-3-derived SPM are readily converted metabolically into oxo-resolvin products, some of which are biologically inactive (Claria et al., 2012). In addition, sEH, the enzyme that catalyzes the rapid hydrolysis of omega-6 and omega-3 epoxides by converting them into inactive or less active diols is invariably over-expressed in HFD-induced obese mice (Lopez-Vicario et al., 2015b). Collectively, these findings are consistent with the notion that unresolved chronic inflammation in obese adipose tissue is the result of an inappropriate SPM resolution-capacity allowing the inflammatory response to proceed without controlled checkpoints.

The use of synthetic SPM in different *in vivo*, *ex vivo*, and *in vitro* studies has provided clues of the role of SPM in adipose tissue homeostasis. In this regard, the administration of nanogram amounts of RvD1 to obese/diabetic *db/db* mice improves glucose tolerance, decreases fasting blood glucose, and increases insulin-stimulated Akt phosphorylation in adipose tissue (Hellmann et al., 2011). This SPM also reduces the formation of macrophage-containing crown-like structures in adipose tissue (Hellmann et al., 2011). Similarly, intraperitoneal injection (nanogram amounts) of RvE1 to obese *ob/ob* mice confers significant insulin-sensitizing effects by mechanisms related to the AMPK-adiponectin axis and the induction of GLUT-4 and IRS-1 expression (Gonzalez-Periz et al., 2009). In addition, 17S-HDHA treatment (intraperitoneal injection of nanogram doses) reduces adipose tissue expression of inflammatory cytokines (MCP-1, TNF α , IL-6 and osteopontin), increases adiponectin expression and improves glucose tolerance in parallel with insulin sensitivity in obese/diabetic *db/db* mice (Neuhofer et al., 2013). Similar beneficial actions in adipose tissue physiology have been described for LXA₄ in an experimental model of adipose tissue inflammation associated with aging (Borgeson et al., 2012). *Ex vivo*, in fat explants, both RvD1 and RvD2 rescue the impaired phenotype of obese adipose tissue by enhancing the expression and secretion of adiponectin in

parallel with decreasing the secretion of pro-inflammatory adipokines/cytokines including leptin, TNF α , IL-6 and IL-1 β (Claria et al., 2012). *In vitro*, nanomolar concentrations of RvD1 stimulate macrophage nonphlogistic phagocytosis, a critical process in the resolution of inflammation, and enhance the phagocytic activity of macrophages isolated from the adipose tissue stromal vascular cell fraction (Titos et al., 2011). In human monocyte-adipocyte co-incubations, both RvD1 and RvD2 reduce MCP-1 and LTB $_4$ -stimulated monocyte adhesion to adipocytes as well as monocyte transadipose migration, which are critical for the recruitment of monocytes/macrophages into the inflamed adipose tissue (Claria et al., 2012).

In line with SPM-protective actions against excessive macrophage recruitment, RvD1 skews polarization of adipose tissue macrophages from a classical activation inflammatory profile (M1 phenotype) toward an alternative anti-inflammatory M2-like state (Titos et al., 2011). This phenotypic switch is characterized by a reduction of secreted pro-inflammatory adipokines, such as TNF α and IL-6 accompanied by an up-regulation of a complete panel of M2 markers including IL-10, CD206, RELM- α and Ym1 (Titos et al., 2011). In addition, RvD1 remarkably increases arginase-1 expression, a well-established M2 marker, while attenuating IFN γ /LPS-induced Th1 cytokine secretion (Titos et al., 2011). Of particular interest, changes in the expression of M1/M2 markers appear to be confined to the adipose tissue stromal vascular fraction, which is highly populated by macrophages (Titos et al., 2011). These results are in agreement with those reported by Hellmann et al. (2011), who showed the ability of RvD1 to improve insulin resistance in obese-diabetic mice by reducing macrophage F4/80 $^+$ CD11c $^+$ cell accumulation and increasing the percentage of F4/80 $^+$ cells expressing the M2 marker Mgl-1 in adipose tissue. The switch of recruited macrophages toward a M2 phenotype is interpreted as anti-inflammatory and pro-resolving (Olefsky and Glass, 2010). Of particular interest is the fact that when leukocytes exit the inflamed site or exudate, they traverse perinodal adipose tissue *en route* to local lymph nodes (Schwab et al., 2007). Excessive and persistent inflammation during this lipo-passage or failure of leukocytes to reach the lymphatics and hence, getting stuck while activated within adipose, can lead to adipose inflammation that may contribute to the metabolic syndrome. Finally, in a recent study, we used *fat-1* mice as an optimal model of omega-3 tissue enrichment, in which the stabilization of the CYP-derived 19,20-EDP epoxide by a sEH inhibitor down-regulated obesity-induced ER stress and autophagy in adipose tissue (Lopez-Vicario et al., 2015b). Since inhibition of autophagic function in adipose tissue is related to reduced fat mass and improved insulin sensitivity (Singh et al., 2009), these findings can be regarded as beneficial in terms of lipid homeostasis and metabolic control.

Apart from adipose tissue, SPM also exert beneficial roles in other insulin-sensitive tissues such as the liver. Indeed, hepatocytes from transgenic *fat-1* mice, which have increased levels of resolvins, and wild-type hepatocytes incubated with nanomolar concentrations of RvD1, show a reduction in neutral lipid accumulation (steatosis) as well as inflammation (Lopez-Vicario et al., 2015b, 2014). In addition, PD1 and 17 β -HDHA are able to attenuate DNA damage and oxidative stress in hepatocytes and reduce TNF α release in macrophages (Gonzalez-Periz et al., 2006), whereas LXA $_4$ and AT-LXA $_4$ efficiently block IL-8 secretion by hepatocytes (Planaguma et al., 2002). Moreover, in precision-cut liver slices, an *ex vivo* model that overrides the influence of extrahepatic circulating factors, Rius and collaborators have demonstrated that RvD1 reduces hypoxia-induced mRNA and protein expression for inflammatory genes including COX-2, IL-1 β , IL-6 and CCR7 (Rius et al., 2014). Of interest, the anti-inflammatory actions of RvD1 were completely absent in tissue

slices in which macrophages were depleted with chlodronate liposomes (Rius et al., 2014), a finding that highlights the critical role of macrophages in the resolution phase of inflammatory response. Finally, the DHA derived 19,20-EDP epoxide was shown to restore autophagy in hepatocytes with the subsequent reduction of ER stress in these liver cells (Lopez-Vicario et al., 2015b). In summary, these findings highlight the potential of small bioactive lipid mediators to not only modulate lipid homeostasis and inflammation in insulin sensitive tissues, but also to serve as templates for the exploitation of cellular housekeeping processes (i.e. autophagy) in therapeutic interventions against obesity-related hepatic co-morbidities.

4.2. DAG

Diacylglycerol (DAG) biosynthesis is initiated from glycerol-3-phosphate generated by glycolysis in the cytoplasm of liver or adipose tissue cells (Li et al., 2010). Glycerol-3-phosphate is acylated with acyl-CoA to form lysophosphatidic acid (LPA), which is again acylated to give phosphatidic acid (PA). Subsequently, PA dephosphorylation forms DAG (Li et al., 2010). DAG is the precursor of TAG which is generated by another acylation catalyzed by diglyceride acyltransferase. This synthetic pathway can be reversed, and by the action of lipases (ATGL or HSL) TAG is hydrolyzed to DAG. Moreover, phospholipase C (PLC) can directly release DAG from phospholipids, by a hydrolytical reaction between the phosphate and the glycerol backbone (Gresset et al., 2012). All these reactions give rise to the 1,2 or the 2,3 DAG isoform; however, in some edible oils DAG can be found as a minor constituent in its 1,3 isoform, which is produced during high temperature, manufacturing processes (Flickinger and Matsuo, 2003). PLC can generate DAG from phosphatidylinositol 4,5-bisphosphate (PIP2) hydrolysis. This reaction releases inositol triphosphate (IP3) to the cytosol (Gresset et al., 2012), which stimulates calcium release. On the other hand, DAG is hydrophobic and remains in the membrane, acting as a signal messenger for activation of protein kinase C (PKC), and facilitates its translocation to the cellular membrane. DAG-mediated PKC activation in adipocytes through β -adrenergic receptors, in turn, increases glycogenolysis and gluconeogenesis (Lafontan et al., 1997).

Compared with TAG oils, dietary DAG oils suppress postprandial hypertriglyceridemia and decrease body fat mass (Nagao et al., 2000; Yamamoto et al., 2006). In animal studies this anti-obesity effect was attributed to an increase in β -oxidation of fatty acids, major energy expenditure and suppression of TAG synthesis (Meng et al., 2004; Kimura et al., 2006; Murase et al., 2001). DAG enriched structural lipids containing conjugated linoleic acid and capric acid (a medium chain fatty acid, MCFA) given in the diet to Sprague–Dawley rats, lowered the concentration of plasma TAG and decreased fat pads, simultaneously enhancing lipoprotein lipase activity (Kim et al., 2006). On the other hand, dietary supplementation with α -linoleic acid-rich DAG induced the up-regulation of β -oxidation of fatty acids, resulting in reduced body weight and fatty liver (Murase et al., 2002, 2005). For further information on this class of lipids see reference (Finck and Hall, 2015).

4.3. Endocannabinoids

The endocannabinoid system is involved in the regulation of WAT metabolism, energy homeostasis and appetite. The two classical endocannabinoids are anandamide (AEA) and 2-arachidonoglycerol (2-AG), both derived from the omega-6-PUFA arachidonic acid (sn-1 and sn-2 positions for AEA and 2-AG, respectively) (Bab et al., 2009). Three routes for AEA synthesis have been described. The major route is by arachidonic acid cleavage

from phosphatidylethanolamine and involves an acyltransferase and a specific phospholipase D (Fezza et al., 2005). The second route includes the action of phospholipase C and the formation of a phosphorylated intermediate that is then hydrolyzed by a phosphatase to form AEA. A third route involving arachidonic acid and ethanolamine condensation pathway has been described. The enzyme fatty acid amide hydrolase is a reversible enzyme that normally cleaves AEA to AA and ethanolamine, but it can also catalyze the AA and ethanolamide condensation into AEA. Three pathways have been described for 2-AG synthesis. It can be synthesized from phosphatidylinositol hydrolysis by phospholipase A that yields lysophosphatidylinositol, that is further hydrolyzed by phospholipase C to produce 2-AG. A second pathway involves phospholipase C action generating DAG with AA in its composition, which is further hydrolyzed by DAG lipase releasing 2-AG. The third pathway for 2-AG formation is catalyzed by a monoacylglycerol kinase acting over 2-arachidonoyl lysophosphatidic acid forming 2-AG (Sugiura et al., 1995).

Endocannabinoids exert their functions by binding to two cannabinoid receptors: CB-1 and CB-2 (Nogueiras et al., 2009). Apart from regulating appetite, and thus food intake, endocannabinoids participate in the control of lipid and glucose metabolism, and its dysregulation in obesity contributes to fat accumulation and associated metabolic disorders (Bluher et al., 2006; Di Marzo, 2008). Circulating levels of 2-AG are increased in obese compared to lean individuals (Bluher et al., 2006; Cote et al., 2007), and their levels are correlated with BMI and intra-abdominal adiposity (Cote et al., 2007; Cable et al., 2011). The expression of the CB-1 receptor is also correlated with BMI and the metabolic syndrome (Sarzani et al., 2009). Overall the endocannabinoid system is dysregulated in peripheral tissues in obesity, altering lipid and glucose metabolism (Pagano et al., 2007; You et al., 2011; Izzo et al., 2009). In visceral adipose tissue there is greater mRNA expression of CB-1 than in subcutaneous adipose tissue (Bluher et al., 2006). Moreover, in obese individuals, 2-AG, CB-1 and MGL are up-regulated in abdominal adipose tissue, whereas their expression is down-regulated in gluteal adipose tissue (Pagano et al., 2007; You et al., 2011). Collectively, current evidence indicates that the endocannabinoid system is dysregulated in obesity and greatly influences the storage of energy in different adipose tissue depots. For further information on endocannabinoids see reference (Silvestri and Di Marzo, 2013).

4.4. Nitroalkenes of fatty acids

Nitro fatty acids are formed by nitration of unsaturated fatty acids. For this process, the formation of $\bullet\text{NO}_2$ during gastric acidification or in the presence of nitric oxide ($\bullet\text{NO}$) and nitrite (NO_2^-) is necessary (Bonacci et al., 2012). The nitration of PUFAs results in the formation of electrophilic fatty acid nitroalkene derivatives (NO₂-FA) with biological properties including nitro-oleic acid (NO₂-OA), nitro-linoleic acid (NO₂-LA) and nitro-conjugated linoleic acid (NO₂-CLA). NO₂-FAs have been detected in plasma and urine from healthy subjects at nano- to micromolar concentrations (Baker et al., 2005; Khoo and Freeman, 2010; Schopfer et al., 2011). Transcriptional responses to NO₂-FAs account for a broader array of signaling events than fatty acid derivatives generated by enzymatic oxygenation (Rudolph and Freeman, 2009; Kansanen et al., 2009). This is due to the pleiotropic effects of the Michael addition reaction by which the electrophilic NO₂-FAs can react with the nucleophilic center of a protein (for example a cysteine or histidine residue) that regulates their structure, function and subcellular distribution (Schopfer et al., 2010).

NO₂-OAs display anti-inflammatory properties *in vitro* and *in vivo*. Indeed, NO₂-OAs limit LPS-induced inflammation and

multi-organ dysfunction and have a reduced expression of MCP-1, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, xanthine oxidase, inducible NO synthase and COX-2 (Wang et al., 2010a; Kelley et al., 2008). NO₂-FAs have been reported to inhibit NF- κ B-regulated gene expression, as a consequence of adduction of a cysteine in the p65 subunit (Cui et al., 2006). NO₂-FAs also mediate the adduction of a cysteine residue in Keap1, an Nrf2 regulatory protein, activating Nrf2-dependent phase 2 gene expression, thereby protecting the cells against oxidative damage and inflammation (Kansanen et al., 2009). NO₂-FAs can regulate glucose and lipid metabolism by binding to PPAR γ (Li et al., 2008; Schopfer et al., 2005). Recently, NO₂-FAs were reported to inactivate the 5-LOX enzyme, resulting in a lower production of inflammatory eicosanoids (Awwad et al., 2014). More recently, Kelley et al. have reported that NO₂-FAs improve glucose tolerance and reduce the expression of inflammatory cytokines and circulating leptin levels while increasing adiponectin in a HFD model of obesity (Kelley et al., 2014). In a previous study, Wang and collaborators administered NO₂-OA to obese Zucker rats to reduce body weight, TAG and FFA levels, and TBARS and proteinuria (Wang et al., 2010b). For further information on this class of lipids see reference (Rubbo, 2013; Narala et al., 2014).

4.5. Fatty acid-hydroxy fatty acids (FAHFA)

A new class of fatty acid derivatives designated as FAHFA has recently been identified by Yore et al. (2014). In WAT, these lipid mediators are synthesized in response to carbohydrate-responsive element-binding protein (ChREBP) and released to the blood, enhancing insulin secretion and glucose uptake (Yore et al., 2014). These authors identified FAHFA in adipose tissue of AG4OX mice, a transgenic model of Glut-4 over-expression, using an untargeted mass spectrometry lipidomic approach. Among the 16 species of FAHFA identified, palmitic acid-hydroxy stearic acid (PAHSA) was the most up-regulated. Eight isomers of this branched fatty acid (depending on the carbon position of the ester) were detected, among which the most relevant were 5- and 9-PAHSA (Yore et al., 2014). In this study, PAHSA levels were reduced in mice and humans with obesity and insulin resistance, and oral administration of 5- and 9-PAHSA was able to enhance glucose tolerance (Yore et al., 2014). Additionally, PAHSA increased Glp-1 secretion in intestinal enteroendocrine cells and enhanced pancreatic insulin secretion. Apart from these metabolic effects, PAHSA exhibited anti-inflammatory properties (Yore et al., 2014). Apparently, PAHSA exert all the above-described biological activities by binding to the long-chain fatty acid receptor GPR120 (Yore et al., 2014). Nonetheless, it remains unclear whether FAHFA biosynthesis is limited to adipocytes or it is produced in other tissues as well.

4.6. Sphingolipids

Sphingolipids contain a backbone of sphingosine and other aliphatic amino alcohols. Sphingolipids play different roles in the cell as structural lipids of the cell membrane by forming a stable and chemically resistant outer protective layer as well as in cell recognition and intracellular signaling. Ceramide is released from the hydrolysis of sphingomyelin (located in the cell membrane), which in turn can be converted to sphingosine and sphingosine-1-phosphate (S1P) (Fig. 1). Both ceramide and S1P are involved in different signaling cascades that participate in proliferation, differentiation, senescence, stress response, necrosis, apoptosis, autophagy, and inflammation.

Apart from the mentioned hydrolytic formation of ceramide from sphingomyelin by the action of acid or neutral SMases

(Hannun and Obeid, 2008), ceramide can be biosynthesised *de novo*. In this case, ceramide biosynthesis is initiated by the condensation of serine and palmitoyl CoA by serine palmitoyl-transferase, and subsequent actions of 3-ketosphinganine reductase, ceramide synthase and dihydroceramide desaturase. Alkaline or acid ceramidase deacetylates ceramide to generate sphingosine, and sphingosine kinase phosphorylates sphingosine to S1P. Similarly, ceramide kinase phosphorylates ceramide to ceramide 1 phosphate (C1P) (Sugiura et al., 2002). The availability of free fatty acids and inflammatory cytokines increases ceramide synthesis (Samad et al., 2006; Schilling et al., 2013), suggesting that ceramide metabolism may be altered in obesity. In obese rodents and humans ceramide is elevated in the liver, the hypothalamus and skeletal muscle (Adams et al., 2004; Holland et al., 2007). In leptin-deficient ob/ob mice, total sphingomyelin and ceramide levels in adipose tissue are reduced, whereas circulating levels of sphingomyelin, ceramide, sphingosine and S1P are increased in plasma, since ceramide secretion by adipose tissue is increased (Samad et al., 2006). In addition, the inflammatory status associated with obesity overlaps with ceramide production. TNF- α administration to mice results in an up-regulation of ceramide synthetic enzymes in adipose tissue, thus increasing ceramide production (Samad et al., 2006).

Adiponectin, the levels of which are generally reduced in obesity and diabetes (Liu et al., 2007), is linked to sphingolipid metabolism. The receptors for adiponectin contain ceramidase activity, thereby reducing ceramide levels (Holland et al., 2011), an activity that depends on adiponectin levels and binding to the receptors. This ceramidase activity leads to the release of a fatty acid and sphingosine that can be phosphorylated to S1P which has anti-apoptotic and anti-diabetic effects. S1P is released and through S1P receptors elevates intracellular calcium and activates AMPK, which participates in FA oxidation (Fang and Sweeney, 2006; Matsuzawa, 2010), thus alleviating lipotoxicity and reducing metabolic dysregulation. Moreover, adiponectin transgenic mice have better insulin tolerance under a HFD (Luo et al., 2010).

Obesity is associated with insulin resistance and type 2 diabetes. Ceramide appears to be elevated in these conditions, correlating positively with the degree of insulin resistance (Haus et al., 2009). *In vitro*, ceramide and sphingosine can inhibit insulin signaling by inhibiting Akt and AMPK (Hajduch et al., 2001; Liu et al., 2004; Summers, 2006). *In vivo*, the administration of myricin, a serine palmitoyltransferase inhibitor, results in an improvement in insulin resistance in different disease models due to the inhibition of *de novo* ceramide biosynthesis (Holland et al., 2007). Heterozygous deficiency of dihydroceramide desaturase, another protein of the ceramide synthetic pathway, results in improved insulin sensitivity, and protection against dexamethasone-induced insulin-resistance (Holland et al., 2007). In 3T3-L1 adipocytes, ceramide blocks the phosphorylation of Akt and IRS-1 (Summers et al., 1998; Chavez et al., 2003); activates protein phosphatase 2A and PKC ζ ; and inhibits Akt translocation to the membrane (Powell et al., 2003, 2004). In NAFLD patients, ceramide biosynthesis and levels are also significantly increased (Kolak et al., 2007). Moreover, in ob/ob mice hepatic ceramide levels correlated with the degree of steatosis (Kolak et al., 2007). For further information on this class of lipids see reference (Hla and Dannenberg, 2012; Larsen and Tennagels, 2014).

4.7. Short- and medium-chain fatty acids

Short-chain fatty acids (SCFA) and MCFA are not generated within adipose tissue and are generally derived from fiber fermentation in the colon. These fatty acids enter the blood directly through the portal vein during lipid digestion, as opposed

to long chain fatty acids which require proper absorption into the blood circulation (Papamandjaris et al., 1998). An important feature of SCFA and MCFA is that they remarkably differ in the number of carbons. In this regard, MCFA contain 8-10 carbon atoms, as in caprylic (C8:0) and capric (C10:0), whereas SCFA contain less than 8 carbons in their structure. Relevant members of the SCFA are formic acid, acetic acid, propionic acid, butyric acid and valeric acid, among others. Among these, butyric acid is the best known for its biological functions. Butyric acid is a substrate for growth and regeneration of cells in the large intestine; it has anti-cancer properties in colon cancer, probably enhancing apoptosis of tumoral cells, and more importantly for the purpose of this review, it increases thermogenesis, energy expenditure and contributes to the reduction of body weight and other factors present in the metabolic syndrome (Goncalves and Martel, 2013; Liu et al., 2011; Xue et al., 2009).

5. Concluding remarks

Much progress has been made in identifying some of the triggers of adipose tissue inflammation in obesity. Among the factors that are involved in this uncontrolled “low-grade” inflammatory response, lipid mediators play a pivotal role. Indeed, a number of lipid mediators derived from membrane phospholipids, including PUFA derivatives, are emerging as key regulators of adipose tissue homeostasis. Any strategy targeting mediators of inflammation such as omega-6 derivatives (i.e. PGs and LTs) and sphingolipids (i.e. LPA, S1P and ceramide) would be beneficial in reducing obesity-associated comorbidities. Another strategy to combat inflammation in adipose tissue is based on fostering the endogenous production of anti-inflammatory and pro-resolving mediators derived from omega-3 fatty acids, such as resolvin, protectins and maresins. Alternatively, the exogenous administration of stable analogs of this novel functional set of lipid autacoids would promote the timely resolution of inflamed tissues.

Interestingly, other fatty acid-derived molecules have come into focus in the last few years, giving us more tools to regulate obesity-related metabolic diseases. For example, nitroalkene derivatives such as nitro-oleic acid have been reported to exert pleiotropic effects, which overall reduce the inflammatory state and improve glucose tolerance. Another example is the recently identified fatty acid hydroxy fatty acids described by Yore et al. in adipose tissue. These authors have reported some metabolic effects of these novel lipids, such as enhanced glucose tolerance, and anti-inflammatory actions. Nonetheless, more studies are needed to demonstrate their potential. However, not only have these novel lipids opened and expanded new avenues in the field of lipid mediators, but they have also encouraged the search for new therapeutic molecules, thereby providing more options for the pharmacological regulation of obesity related diseases.

In summary, the current review provides up-to-date insight on the wide variety of lipid mediators present in mammalian cells, with special emphasis on the role of these bioactive lipids in the regulation of adipose tissue homeostasis.

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