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Omega-3 fatty acids and adipose tissue biology

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ABSTRACT

This review provides evidence for the importance of white and brown adipose tissue (i.e. WAT and BAT) function for the maintenance of healthy metabolic phenotype and its preservation in response to omega-3 polyunsaturated fatty acids (omega-3 PUFA), namely in the context of diseased states linked to aberrant accumulation of body fat, systemic low-grade inflammation, dyslipidemia and insulin resistance. More specifically, the review deals with (i) the concept of immunometabolism, i.e. how adipose-resident immune cells and adipocytes affect each other and define the immune-metabolic interface; and (ii) the characteristic features of "healthy adipocytes" in WAT, which are relatively small fat cells endowed with a high capacity for mitochondrial oxidative phosphorylation, triacylglycerol/fatty acid (TAG/FA) cycling and *de novo* lipogenesis (DNL). The intrinsic metabolic features of WAT and their flexible regulations, reflecting the presence of "healthy adipocytes", provide beneficial local and systemic effects, including (i) protection against *in situ* endoplasmic reticulum stress and related inflammatory response during activation of adipocyte lipolysis; (ii) prevention of ectopic fat accumulation and dyslipidemia caused by increased hepatic VLDL synthesis, as well as prevention of lipotoxic damage of insulin signaling in extra-adipose tissues; and also (iii) increased synthesis of anti-inflammatory and insulin-sensitizing lipid mediators with pro-resolving properties, including the branched fatty acid esters of hydroxy fatty acids (FAHFAs), also depending on the activity of DNL in WAT. The "healthy adipocytes" phenotype can be induced in WAT of obese mice in response to various stimuli including dietary omega-3 PUFA, especially when combined with moderate calorie restriction, and possibly also with other life style (e.g. physical activity) or pharmacological (e.g. thiazolidinediones) interventions. While omega-3 PUFA could exert beneficial systemic effects by improving immunometabolism of WAT without a concomitant induction of BAT, it is currently not clear whether the metabolic effects of the combined intervention using omega-3 PUFA and calorie restriction or thiazolidinediones depend also on the activation of BAT function and/or the induction of brite/beige adipocytes in WAT. It remains to be established why omega-3 PUFA intervention in type 2 diabetic subjects does not improve insulin sensitivity and glucose homeostasis despite inducing various anti-inflammatory mediators in WAT, including the recently discovered docosahexaenoyl esters of hydroxy linoleic acid, the lipokines from the FAHFA family, as well as several endocannabinoid-related anti-inflammatory lipids. To answer the question whether and to which extent omega-3 PUFA supplementation could promote the formation of "healthy adipocytes" in WAT of human subjects, namely in the obese insulin-resistant patients, represents a challenging task that is of great importance for the treatment of some serious non-communicable diseases.

1. Introduction

Prevention and treatment of severe diseases that are associated with adverse lifestyle conditions, obesity or ageing represent a major challenge for the health care systems in affluent societies. The existence of multiple associations between diet and adipose tissue (**AT**) functions offer an excellent opportunity to improve health through specific dietary constituents. In this review, we focus on the interactions between dietary omega-3 polyunsaturated fatty acids (**omega-3 PUFA**) and AT, which could contribute to the known beneficial effects of these lipids on health.

AT is characterized by extreme plasticity that not only involves changes in its total mass, or weight of various fat depots, but also in

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the number of fat cells, relative numbers of various cell types contained in the tissue, or the size of adipocytes. Excessive accumulation of AT in obesity, as well as atrophy of the tissue, result in insufficient storage capacity of AT for lipids and, hence, lipotoxic damage of insulin signaling in peripheral tissues and low-grade inflammation (Herrero et al., 2010). These harmful systemic effects also reflect changes in secretory functions of AT, involving both adipose-released cytokines (**adipokines**) and lipid mediators (**lipokines**). The secretory pattern reflects changes in adiposity, with obesity promoting secretion of pro-inflammatory signaling molecules.

Emerging evidence suggests that (i) metabolism of both glucose and lipids in adipocytes can evoke major systemic effects partly independent of the amount of body fat, with the "healthy adipocyte" metabolic phenotype being linked to amelioration/prevention of obesity-associated metabolic disorders such as dyslipidemia and insulin resistance, and (ii) the "healthy adipocyte" phenotype could be induced by a number of natural factors that also contribute to healthy life-style. These factors include namely physical activity, calorie restriction, and various dietary constituents, especially omega-3 PUFA.

AT represents the best example of the mutual links between cells of the immune system, which are present in the tissue, and local tissue metabolism. We could learn here how the immune and metabolic systems are interconnected (Masoodi et al., 2015; Wahli and Michalik, 2012). Thus, the recently coined concept of immunometabolism (Kohlgruber et al., 2016; Mathis, 2013; Mathis and Shoelson, 2011) is highly relevant for the explanation of processes at the level of AT, as well as for the integrating role of AT in the control of both systemic inflammatory status and metabolism. This concept also represents the key to understand modulation of both the immune status and metabolism of AT by omega-3 PUFA and its systemic consequences. The aim of this review is to provide a synopsis of the key features of AT, which could be modulated in response to omega-3 PUFA and, therefore, affect the whole organism and improve its health.

2. Adipose tissue biology

2.1. Origin and heterogeneity of fat cells

AT is distributed in various anatomical locations around the body while demonstrating depot-specific metabolic properties. During ontogenesis, the formation of individual fat depots is linked to the development of tissue microcirculation, since adipocytes are probably derived from vascular endothelial cells (reviewed in (Algire et al., 2013; Cinti, 1999, 2002; Crandall et al., 1997; Wassermann, 1965)). Adrenergic innervation is also of great importance for the development of AT (Beranger et al., 2013; Cinti, 2012; Lafontan and Berlan, 1993) as well as for the control of its metabolic functions (Cannon and Nedergaard, 2004; Lafontan and Langin, 2009; Sponarova et al., 2005).

Under the complex influence of various external factors, intracellular signaling pathways and specific transcriptional mechanisms (reviewed in (Algire et al., 2013; Beranger et al., 2013; Farmer, 2006; Gesta et al., 2007; Kajimura et al., 2010; Rodriguez et al., 2004; Seale, 2015)), adipose precursor cells differentiate into: (i) unilocular adipocytes, the typical energy-storing cells that are contained in white AT (**WAT**) and lack uncoupling protein 1 (**UCP1**); (ii) classical multilocular brown adipocytes, which are closely related to myocytes and are found in typical depots of brown AT (**BAT**) such as the interscapular BAT, and which are responsible for the bulk of the adaptive UCP1-mediated thermogenesis; and (iii) so called '**brite**' (Petrovic et al., 2010) or '**beige**' (Wu et al., 2012) adipocytes, which are interspersed in some WAT depots and are characterized by highly inducible UCP1 expression (Cousin et al., 1992; Guerra et al., 1998; Himms-Hagen et al., 2000; Loncar et al., 1986). The existence of at least some of these cells could reflect a reversible trans-differentiation of white to brown adipocytes (Frontini and Cinti, 2010; Frontini et al., 2013; Rosenwald et al., 2013). The physiological role of brite/beige adipocytes ('**browning**') remains unclear (see Section 2.2.). Because different types of adipocytes can coexist in the same fat depot, and their brown/white phenotype could be possibly reversed (see above), Cinti and several other investigators (Barquissau et al., 2016; Cinti, 2002, 2012; Smorlesi et al., 2012) coined the term 'adipose organ', which comprises all fat depots in the body.

2.2. Brown and brite/beige adipose tissue

Both brown and brite/beige adipocytes produce heat in response to β-adrenergic stimulation. The thermogenic process occurs in mitochondria, which are abundant in these cells and contain UCP1. When activated by increased intracellular levels of fatty acids (**FA**), UCP1 mediates a proton leak across the inner mitochondrial membrane, which results in burning chemical energy of substrates and heat production (reviewed in (Nicholls, 2006)). Non-shivering thermogenesis in BAT is essential for (i) postnatal adaptation to cold extrauterine environment in most mammalian species, (ii) arousal from hibernation in some species, and (iii) sufficient defense capacity against cold in smaller mammals during their whole life. BAT thermogenesis is activated by cold to support thermal homeostasis (cold-induced thermogenesis) and also, at least in rodents, in response to energy-rich foods (diet-induced thermogenesis (Rothwell and Stock, 1979)); as a part of a complex regulatory mechanism that helps to keep body weight constant (reviewed in (Cannon and Nedergaard, 2004; Kazak et al., 2017)). Accordingly, BAT mass and capacity for UCP1-mediated thermogenesis correlates with the resistance to obesity in various mouse models (reviewed in (Seale, 2015)) as well as in adult humans (Cypess et al., 2009), where functional BAT was unexpectedly found in 2007 (Nedergaard et al., 2007). However, in lean adult humans, BAT may be only a minor source of thermogenesis in cold (Muzik et al., 2013), suggesting that mechanisms that are independent of UCP1 contribute to adaptive thermogenesis and whole-body energy balance (reviewed in (Flachs et al., 2013) and refs. (Bal et al., 2012; Blondin et al., 2017a)), including energy dissipation in adipocytes (Flachs et al., 2013; Kazak et al., 2017; Ukropec et al., 2006).

Brown as well as brite/beige adipocytes represent the terminally differentiated adipocytes (reviewed in (Algire et al., 2013; Petrovic et al., 2010; Seale, 2015; Walden et al., 2012; Wu et al., 2012); see also Section 2.1.). Since brite/beige adipocytes exist also in humans (Bostrom et al., 2012; Hondares et al., 2014; Jespersen et al., 2013; Lee et al., 2014; Wu et al., 2012), the mechanisms mediating their induction are intensively studied because it might help to reduce obesity (Algire et al., 2013; Bargut et al., 2016; Beranger et al., 2013; Bostrom et al., 2012; Kim et al., 2015, 2016; Pahlavani et al., 2017; Qiu et al., 2014; Seale, 2015; Wu et al., 2012). A vast number of studies in mice documented the up-regulation of UCP1 gene in subcutaneous WAT in response to various interventions that activate lipolysis in adipocytes (possibly including omega-3 PUFA; see Section 2.3.3.), namely the cold exposure (Algire et al., 2013; Beranger et al., 2013; Kim et al., 2016; Qiu et al., 2014; Seale, 2015). The contribution of UCP1-mediated thermogenesis in brite/beige adipocytes to total energy balance is relatively low compared to that of BAT (Nedergaard and Cannon, 2013; Shabalina et al., 2013), while the induction of this type of adipocytes might represent an adaptive mechanism to alleviate local redox pressure in WAT (Carriere et al., 2014; Jeanson et al., 2016) rather than

representing a primarily thermogenic mechanism. However, even a moderate induction of UCP1 in WAT may reduce obesity, as documented by transgenic mice with ectopic UCP1 in WAT (Kopecky et al., 1995).

2.3. White adipose tissue

WAT can represent 5%–60% of total body weight (Kissebah and Krakower, 1994; Lee et al., 2013), and thus it represents the most plastic organ among the metabolically relevant tissues. The total mass of WAT reflects the state of energy balance; however, adipocyte number is very static in adult humans and largely independent of body weight fluctuations. Adipocyte number is set during childhood and adolescence (Kissebah and Krakower, 1994), and only approximately 10% of fat cells are renewed annually in adult humans (Spalding et al., 2008).

2.3.1. Gross anatomy of WAT

WAT depots are similarly located in mice and in humans (Chusyd et al., 2016; Cinti, 2012; Gesta et al., 2007; Lee et al., 2013), except for the absence of epididymal WAT in men (Frontini and Cinti, 2010). Intraabdominal/visceral fat includes intraperitoneal fat (omental, mesenteric and epiploic fat) and retroperitoneal fat (Lee et al., 2013). Accumulation of visceral fat (upper body obesity) correlates with the incidence of the metabolic syndrome (Despres and Lemieux, 2006). Especially men, unlike women, accumulate fat centrally in both subcutaneous and visceral depots (Enzi et al., 1986). Major depots of subcutaneous fat in humans are located in abdominal, gluteal and femoral regions (Lee et al., 2013). Deep and superficial subcutaneous fat depots, which are separated by a connective tissue layer, differ in their metabolic properties, with the deep subcutaneous fat having a stronger link to insulin resistance (Kelley et al., 2000; Markman and Barton, 1987). Subcutaneous fat is not associated with metabolic complications and may even be protective against metabolic disorders associated with obesity (Chusyd et al., 2016; Frayn, 2000, 2005; Kwok et al., 2016; Unger, 2003). Accordingly, women who tend to accumulate more subcutaneous fat (i.e. lower body obesity) are more resistant than men to development of adverse metabolic disorders linked to obesity (Chusyd et al., 2016; Kwok et al., 2016).

AT depots are organized into lobules that are separated by extracellular matrix (**ECM**; ref. (Wassermann, 1965)), which consists of a fibrillary network of proteins, mainly fibronectin and collagens. These components provide both mechanical support and create micro-domains as the basis of cellular signaling (Vegiopoulos et al., 2017). A recent study in mice (Barreau et al., 2016) revealed a marked heterogeneity of fat depots, namely of the inguinal fat, with the core structured into segmented lobules, whereas the periphery appeared unsegmented; in the animals exposed to cold, brite/beige adipocytes were induced only in the core area. Hypertrophy of AT in obesity is associated with proliferation of ECM, which is mutually linked with low-grade inflammation of the tissue, and could eventually lead to tissue fibrosis. Proliferation of ECM and fibrosis limit the “expandability” of AT, resulting in a spillover of FA and lipotoxic damage of insulin signaling in extra-adipose tissues (Van Pelt et al., 2017; Vegiopoulos et al., 2017; Virtue and Vidal-Puig, 2010). Fibrosis also limits the density of AT vessels (Spencer et al., 2011), resulting in the development of tissue hypoxia, one of the factors triggering inflammation in obesity (Vegiopoulos et al., 2017).

2.3.2. Cell types in WAT

WAT is composed of many different cell types including adipocytes, preadipocytes, endothelial cells, fibroblasts, and almost the full spectrum of immune cells defining a unique adipose-resident immune system. Macrophages have been the most frequently studied myeloid cells in the WAT since the discovery documenting their contribution to low-grade AT inflammation and insulin resistance in obesity (Cao et al., 2008; Weisberg et al., 2003; Xu et al., 2003). However, additional members of the innate and adaptive arms of the immune system have been implicated in regulating inflammatory response, WAT matrix remodeling, angiogenesis, and lipid buffering capacity (reviewed in (Mraz and Haluzik, 2014)). Recently, visceral AT-specific regulatory T cells were implicated in improving metabolic parameters in obese mice (Feuerer et al., 2009; Wensveen et al., 2015), while heterogeneous populations of adipose type innate lymphoid cells (**ILCs**) were shown to regulate AT macrophage homeostasis (Boulenouar et al., 2017; Molofsky et al., 2013; Wu et al., 2011). Moreover, AT-resident natural killer cells could regulate macrophage polarization and WAT immunological homeostasis (Lynch et al., 2015; Wensveen et al., 2015). However, the simplified concept that “pro-inflammatory” M1-like (classically activated) macrophages contribute to insulin resistance of WAT while “anti-inflammatory” M2-like (alternatively activated) macrophages ameliorate these negative effects and contribute to homeostasis in WAT is widely accepted. Macrophage polarization is a relatively dynamic process that adapts to changes in diet and maintains homeostatic tissue remodeling. Omega-3 PUFA, which exert strong anti-inflammatory effects, could support the switch from M1 to M2 phenotype (see Section 3.1. and refs. (Kuda et al., 2016b; Oh et al., 2010)). The growing evidence documenting the unique immune cell repertoire in WAT, which is adapted to local microenvironment, suggests that the immune cell populations are highly involved in the control of mature adipocyte metabolism.

2.3.3. Systemic effects of WAT metabolism

WAT stores excess energy as TAG. During exercise, fasting or cold exposure, FA and glycerol are released due to TAG hydrolysis; the rate limiting initial step in TAG hydrolysis is catalyzed by adipose TAG lipase (**ATGL**; (Zimmermann et al., 2004)). Part of liberated FA can be re-esterified back to TAG (by the action of acyl CoA:d-iacylglycerol transferase enzymes, **DGAT1** and **DGAT2**; refs. (Chitraju et al., 2017), resulting in futile TAG/FA cycling, which is one of the core biochemical activities of white adipocytes (Reshef et al., 2003). TAG synthesis requires glyceroneogenesis (Beale et al., 2002; Bederman et al., 2009; Nye et al., 2008) and is associated with *in situ* FA synthesis (*de novo* lipogenesis; **DNL** (Flachs et al., 2011; Mottillo et al., 2014)). All these activities, including FA re-esterification, require ATP that is produced by oxidative phosphorylation in adipocyte's mitochondria (Flachs et al., 2013).

Several pieces of evidence obtained in mice suggest that improvement of glucose and insulin homeostasis in response to life-style changes, including increased physical activity, caloric restriction and dietary omega-3 PUFA intake (see Section 4.4.), as well as those of antidiabetic drugs thiazolidinediones or acclimatization to cold, reflect in part the induction of “healthy white adipocytes”. These cells are relatively small, especially in the mice subjected to the combined intervention using omega-3 PUFA and caloric restriction or thiazolidinediones (Flachs et al., 2011; Kuda et al., 2009), while the small adipocytes that appeared in WAT of cold-exposed mice contained multiple lipid droplets, indicating a high lipolytic activity (Flachs et al., 2017). Also in humans, omega-3 PUFA could decrease the size of fat cells (see Section 4.4). The “healthy white adipocytes” are endowed with a high activity of TAG/FA cycling, DNL and oxidative phosphorylation (and do not contain UCP1; reviewed in (Flachs et al., 2013, 2017; Masoodi et al., 2015)). Induction of these interrelated biochemical activities in white adipocytes could help to explain why 10%–40% of obese individuals remain metabolically healthy (reviewed in (Naukkarinen et al.,

2014)). High rates of basal lipolysis, typical of obesity, has detrimental systemic effects, while inducibility of this activity by sympathetic system and/or pharmacological treatments is linked with metabolic flexibility and healthy phenotype ((Arner et al., 2011; Ryden et al., 2013; Van Pelt et al., 2017); reviewed in (Flachs et al., 2013)) and is required for thermogenesis (Blondin et al., 2017b). The "healthy adipocytes" hypothesis is supported by the findings in weight-discordant monozygotic twins (Naukkarinen et al., 2014), the existence of an inverse relationship between BMI and oxidative phosphorylation in human subcutaneous adipocytes (Fischer et al., 2015), and the fact that limited capacity of oxidative phosphorylation in white adipocytes is a hallmark of obesity in laboratory mice irrespective of their glucose tolerance status (Schottl et al., 2015). Moreover, oxygen consumption in human WAT was negatively related to age and the degree of obesity (Hallgren et al., 1989), and WAT mitochondrial content was increased by exercise (Bernlohr, 2014). That TAG/FA cycling in WAT was associated with lean and insulin-sensitive phenotype was documented in both mice (Mottillo et al., 2014) and humans (Allister et al., 2015).

Beneficial systemic effects that are associated with the "healthy white adipocyte" phenotype could reflect several mechanisms, namely (i) protection against *in situ* endoplasmic reticulum stress and related inflammatory response during activation of adipocyte lipolysis, due to FA re-esterification mediated by DGAT1 (Chitraju et al., 2017); (ii) fine and fast tuning of plasma FA levels, according to the extra-adipose tissues' energy needs (Flachs et al., 2017), because futile substrate cycling facilitates oscillation between two opposing metabolic pathways, amplifying the magnitude of small changes in the activity of pathway enzyme(s) on the net direction of the metabolic flux (Newsholme and Crabtree, 1976); (iii) protection against liver fat accumulation and related dyslipidemia due to increased hepatic VLDL synthesis; and (iv) prevention of lipotoxic damage, i.e. namely a deterioration of insulin signaling, in extra-adipose tissues (Flachs et al., 2013; Nye et al., 2008). On the other hand, energy dissipation in white adipocytes probably plays only a negligible direct role in energy balance, since energy costs of a futile TAG/FA cycling could account for only about 2%–3% of resting metabolic rate in obese humans (Flachs et al., 2013), and it was three orders of magnitude lower than the metabolic rate of cold-exposed mice (Flachs et al., 2017).

WAT is an important site of DNL in rodents, but also in humans, where up to 40% of whole-body *de novo* FA synthesis from glucose may take place in WAT (Chascione et al., 1987). DNL is associated with TAG turnover under various physiological circumstances (reviewed in (Flachs et al., 2013, 2017; Masoodi et al., 2015); see also above). Since glucose uptake in adipocytes, as well as FA synthesis associated with it, were linked to whole-body insulin sensitivity, it was postulated that some *de novo* formed lipid(s) in adipocytes could support insulin signaling in other tissues (reviewed in (Czech et al., 2013)). Indeed, it has been found recently (Yore et al., 2014) that WAT serves as a major source of novel lipid mediators, i.e. branched fatty acid esters of hydroxy fatty acids (**FAHFAs**), with some of these lipokines improving glucose tolerance, while stimulating insulin secretion in pancreas, incretin secretion in intestinal cells, and insulin-stimulated glucose transport in adipocytes, and ameliorating also obesity-associated inflammation. Recently, we have elucidated the structures of novel members of FAHFA lipokines derived from docosahexaenoic acid (**DHA**; 22:6 ω-3; ref. (Kuda et al., 2016a)), which exert anti-inflammatory and pro-resolving properties (see Section 3.1.). A novel (β) isoform of carbohydrate responsive-element binding protein (**ChREBPβ**; also referred to as MLX interacting protein-like) serves as the major determinant of synthesis of these novel signaling lipids in WAT, and its loss in adipocytes of mice causes FAHFA-dependent insulin resistance in the liver, muscle and fat (Vijayakumar et al., 2017). Free Fatty Acid Receptor 4 (**FFAR4**; also known as G protein-coupled receptor 120, **GPR120**) mediates the effects of FAHFAs on glucose transport in adipocytes, as well as the anti-inflammatory effects of these lipids, which include the change of macrophage polarization in WAT (see Section 3.1, and refs. (Vijayakumar et al., 2017; Yore et al., 2014)).

2.3.4. Immunometabolism of WAT

Metabolic flexibility, i.e. the ability to shift back and forth between the use of glucose and FA as fuels, is integral to energy homeostasis and immunity, as phenotypes of immune cells are associated with specific metabolic profiles. A unique pool of adipose-resident immune cells and adipocytes affect each other and define immune–metabolic interface (Mathis, 2013; Mathis and Shoelson, 2011). The immune cells can influence the intrinsic metabolic pathways of adipocytes via cytokines or specialized lipid mediators, while adipocytes can release lipids, specialized adipokines and lipokines, which modulate inflammatory status of the immune cells. Lean WAT contains a number of anti-inflammatory immune cells that exert a regulatory and remodeling program characterized by high oxidative phosphorylation and FA oxidation and actively participate in lipid metabolism (Huang et al., 2014; Kratz et al., 2014; Prieur et al., 2011; Shaul et al., 2010; Wernstedt Asterholm et al., 2014; Xu et al., 2013). Altered nutrient flux during obesity changes the local microenvironment, forces cells to adapt their metabolic program and change their preferred nutrients, and leads to pro-inflammatory response while inducing insulin resistance in adipocytes. Although the triggers of WAT metabolic inflammation are still being explored, the evidence suggests that not all immune cells might be able to adapt their substrate utilization when exposed to excess lipids, and therefore lose their specific functions. AT macrophages, especially those that are M2-like polarized, can partially buffer fluctuations in nutrient levels and modulate lipolysis in adipocytes (Rombaldova et al., 2017), but others like ILCs are not able to adapt to obese conditions and lose their killing ability (Boulenouar et al., 2017). The negative effects of excess lipids on macrophages could be partially ameliorated by omega-3 PUFA (see Section 3.1. and Fig. 1).

3. Omega-3 PUFA

3.1. Molecular mechanisms

Naturally occurring long-chain omega-3 PUFA, namely eicosapentaenoic acid (**EPA**; 20:5 ω-3), docosapentaenoic acid (**DPA**; 22:5 ω-3), and DHA exert multiple biological effects that are mediated either by these PUFA themselves (i.e. acting as PPARα ligands (Diep et al., 2000; Zuniga et al., 2011)) or their bioactive metabolites. These bioactive compounds could be divided into several subfamilies such as specialized pro-resolving mediators, epoxides, electrophilic oxo-derivatives, ethanolamines, acylglycerols, acylamides of amino acids or neurotransmitters, and FAHFAs (Chiang and Serhan, 2017; Claria et al., 2013, 2017; Galano et al., 2015; Kuda, 2017; Kuda et al., 2016a), exerting mostly anti-inflammatory effects (reviewed by Calder P. in this issue).

Using experiments in mice and overweight/obese patients with type 2 diabetes (**T2DM**), we elucidated the structures of novel members of FAHFA lipokines derived from DHA and linoleic acid, which were present in serum and WAT after omega-3 PUFA supplementation. These compounds contained DHA esterified to 9- and 13-hydroxyoctadecadienoic acid (**HLA**) or 14-hydroxydocosahexaenoic acid (**HDHA**), termed 9-DHAHLA, 13-DHAHLA, and 14-DHAHDHA, and were synthesized by adipocytes at concentrations comparable to those of protectins and resolvins

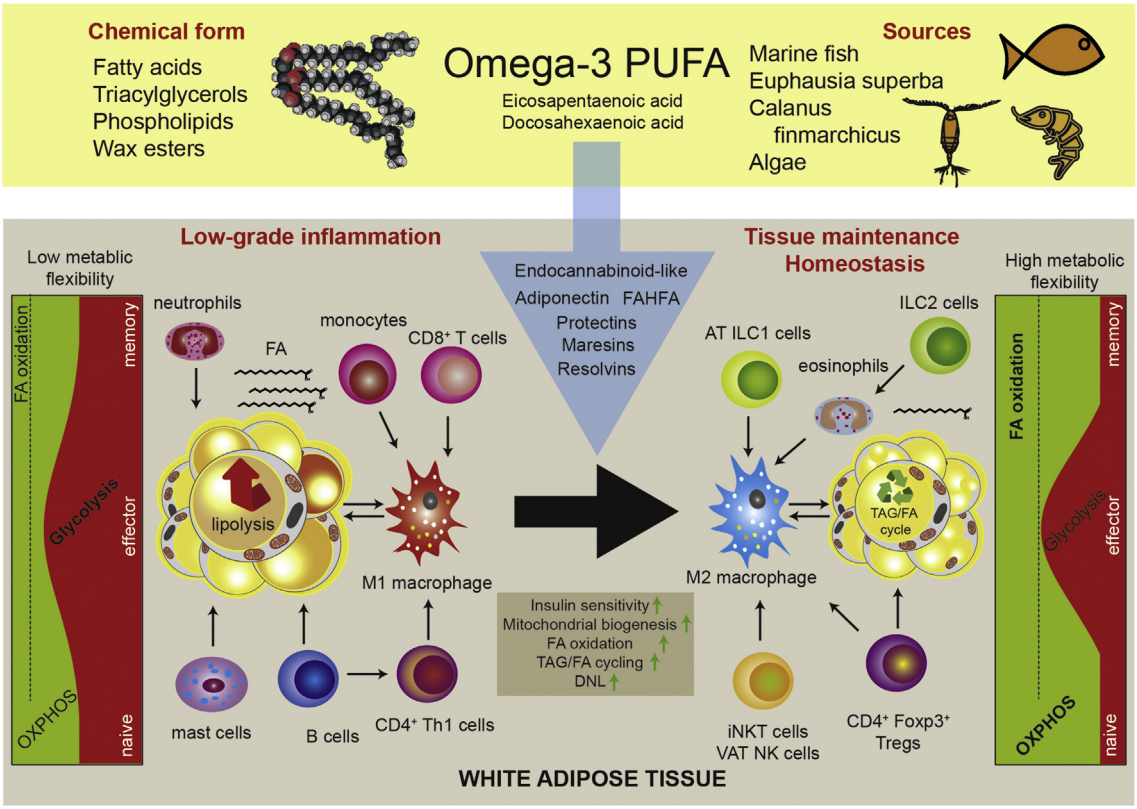

Fig. 1. Effects of omega-3 PUFA on inflamed white adipose tissue.
Omega-3 PUFA, mainly DHA and EPA, are present in various sources (fish, crustaceans, etc.) in different chemical forms, which affect their bioavailability. Omega-3 PUFA are converted to a diverse family of bioactive metabolites (resolvins, FAHFA, etc.), and stimulate secretion of adiponectin, which affects metabolism of AT. During obesity, monocytes, neutrophils, T cells, B cells and mast cells secrete pro-inflammatory signals, drive M1-macrophage polarization, and promote insulin resistance of adipocytes, i.e. low-grade AT inflammation. On the contrary, high levels of FA released from hypertrophic adipocytes limit metabolic flexibility (switch in fuel partitioning) of immune cells and inhibit their specific functions. Omega-3 PUFA, mainly via lipid mediators and stimulation of adiponectin, alleviate low-grade inflammation, promote insulin sensitivity, mitochondrial biogenesis, oxidation of FA as well as their re-esterification in adipocytes, and oxidative phosphorylation (OXPHOS). Eosinophils, adipose type 1/2 innate lymphoid cells (AT ILC2s), invariant natural killer T cells (iNKT cells), visceral AT-resident NK cells and visceral adipose T regulatory (Treg) cells, characterized by high metabolic flexibility and adaptation to AT microenvironment, contribute to AT homeostasis and M-2 macrophage polarization. Rectangle inserts: immune cell activation (naïve > effector) correlates with metabolic shift towards glycolysis,which provides fast energy for high rates of proliferation or acute response, while further generation of memory cells is characterized by metabolic shift towards FA oxidation and OXPHOS. In macrophages, the metabolic shift in fuel partitioning is under the control by AMPK. WAT-adapted immune cells are able to process the high load of FA (i.e. through FA oxidation) and exert their specific programs, but low grade inflammation impairs the metabolic flexibility of all cells in WAT and prevents immune homeostasis. See the main text for all the details. Scheme adapted from (Carvalheira et al., 2013).

derived from DHA in WAT. 13-DHAHLA exerted anti-inflammatory and pro-resolving properties while reducing macrophage activation by lipopolysaccharide and enhancing the phagocytosis of zymosan particles. Our results thus documented the existence of novel lipid mediators, which are involved in the beneficial anti-inflammatory effects attributed to omega-3 PUFA, in both mice and humans (Kuda et al., 2016a).

Both EPA and DHA trigger signaling through FFAR4/GPR120 (Mobraten et al., 2013; Oh da et al., 2014; Oh et al., 2010), while dysfunction of FFAR4 leads to obesity in both mice and humans (Ichimura et al., 2012). Experiments with human adipocytes differentiated in cell culture indicated a marked reduction of FFAR4/GPR120 expression in response to pro-inflammatory cytokines (Muredda et al., 2017), suggesting that the lack of omega-3 PUFA on insulin sensitivity in T2DM subjects (see Section 3.2.) might reflect down-regulation of FFAR4/GPR120 in inflamed WAT of these patients. However, this hypothesis is not supported by other recent studies showing that FFAR4 is not required for the anti-inflammatory and insulin sensitizing effects of omega-3 PUFA (Bjursell et al., 2014; Paerregaard et al., 2016; Shewale et al., 2017), thereby suggesting the existence of additional omega-3 PUFA receptors (reviewed by Olefsky J. in this issue). In accordance with the concept of immunometabolism ((Kohlgruber et al., 2016; Mathis, 2013; Mathis and Shoelson, 2011); see Section 2.3.4.), the beneficial effects of omega-3 PUFA on obesity-associated metabolic disorders (see Section 3.2.) could be explained largely by amelioration of low-grade inflammation in various tissues including WAT, liver, brain (i.e. neuroinflammation) as well as in other tissues, while normalizing their metabolic properties. In WAT, it results in the preservation of the “healthy adipocyte” phenotype (see Section 4.4.). Low-grade AT inflammation, characterized by high levels of pro-inflammatory cytokines, FA, and pro-inflammatory M1 macrophages, could be resolved by omega-3 PUFA-derived lipid mediators such as resolvins, maresins and FAHFAs, which have been reported to decrease AT macrophage accumulation and the expression of pro-inflammatory adipokines, and to promote macrophage re-polarization towards the M2 form and inhibit the NLR Family Pyrin Domain Containing 3 (**NLRP3**) inflammasome activation in obese mice (Claria et al., 2012; Hellmann et al., 2011; Titos and Claria, 2013; Titos et al., 2011; Yan et al., 2013). AT has its unique immune cell repertoire and AT-resident immune cells have been involved in the production of omega-3 PUFA-derived anti-inflammatory lipid mediators (Kuda et al., 2016b), and a wide range of these compounds including resolvins (e.g. **RvD1**, **RvD2**),

protectins (**PD1**) and FAHFAs (**13-DHAHLA**) has been also identified in human subcutaneous AT (Claria et al., 2013; Kuda et al., 2016a). Thus, the interaction of immune cells in AT with omega-3 PUFA supplemented by a diet seems to be crucial for the amelioration of low-grade inflammation in AT.

Resolution of inflammation by omega-3 PUFA is also linked to improved insulin sensitivity and increased adiponectin expression in diet-induced obese mice (Claria et al., 2012; Flachs et al., 2006; Martinez-Fernandez et al., 2017). The induction of adiponectin in mice (Flachs et al., 2006; Neschen et al., 2006) has been verified in humans and is supported by the meta-analysis of randomized controlled trials (Wu et al., 2013). Adiponectin exerts its beneficial metabolic effects (e.g. increased FA oxidation and glucose uptake) in part by stimulating 5′ AMP-activated protein kinase activity (**AMPK**), which is likely the mechanism that contributes to the insulin-sensitizing effects of omega-3 PUFA (Jelenik et al., 2010). Accordingly, activation of AMPK in macrophages and the resulting switch of metabolism of these cells from oxidative phosphorylation to glycolysis contributes to resolution of inflammation, reflecting the enhancement of macrophage chemokinesis and the capacity for clearence of dying cell (**efferocytosis**, ref. (Jiang et al., 2013)). Contribution of AT to circulating levels of anti-inflammatory cytokines (adipokines) and lipid mediators extends the beneficial effects of omega-3 PUFA on AT also to the systemic level. In severely obese non-diabetic patients undergoing elective bariatric surgery, omega-3 PUFA supplementation reduced both AT and systemic inflammation through reduction of plasma TAG and interleukin-6 levels, while inducing anti-inflammatory omega-3 PUFA-derived lipid mediators (Itariu et al., 2012, 2013). Therefore, multiple mechanisms involved in the omega-3 PUFA's action could be responsible for affecting AT low-grade inflammation and improvement of AT metabolism (see Section 2.3.3. and Section 4.4.).

Still largely unexplored is the effect of omega-3 PUFA on the endocannabinoid system, which regulates food intake, energy balance, as well as lipid and glucose metabolism and inflammation; both central and peripheral effects are involved (reviewed in (Silvestri and Di Marzo, 2013)). The whole system is comprised of endocannabinoids such as N-arachidonoylethanolamide (anandamide; **AEA**) and 2-arachidonoylglycerol (**2-AG**), the enzymes that regulate the production and degradation of endocannabinoids, and cannabinoid receptors 1 and 2 (**CB1** and **CB2**). In obesity and T2DM, the endocannabinnoid system becomes dysregulated, including its major alteration in WAT (Bluher et al., 2006; Engeli et al., 2005; Starowicz et al., 2008; Tam et al., 2012; Tedesco et al., 2010); this was observed in both mice (Starowicz et al., 2008; Tam et al., 2012; Tedesco et al., 2010) and humans (Bluher et al., 2006; Engeli et al., 2005). Omega-3 PUFA limit the availability of biosynthetic precursors for endocannabinoids, i.e. they reduce the content of arachidonic acid in membrane phospholipids, and, therefore, suppress the levels of endocannabinoids in peripheral tissues (reviewed in (Banni and Di Marzo, 2010; Kim et al., 2013)), see also Section 4.4.

3.2. Metabolic and health effects

Omega-3 PUFA exert multiple beneficial effects on health that are underlined by the molecular mechanisms described above (see Section 3.1.). In this review, we focus mainly on those effects, which reflect the interactions of omega-3 PUFA with AT, that serves as a hub in energy homeostasis and represents one of the key targets in the treatment of major diseases linked to aberrant accumulation of body fat, systemic low-grade inflammation, dyslipidemia and insulin resistance.

In humans, omega-3 PUFA attenuate systemic inflammatory processes (Hung et al., 2015), ameliorate non-alcoholic fatty liver disease (Scorletti et al., 2014), and protect against cardiovascular disease (Mozaffarian et al., 2013). Therefore, several national health associations and international health authorities have recommended dietary omega-3 PUFA intake to be between 0.2 g and 2.0 g per day (Mozaffarian and Wu, 2012), and omega-3 PUFA supplementation is advised as part of the secondary prevention of coronary heart disease (Siscovick et al., 2017). However, the chemical form of omega-3 PUFA is not always specified (see below).

In both dietary obese rodents (Pavlisova et al., 2016; Ruzickova et al., 2004) and human subjects (Lopez-Huertas, 2012), dietary intake of omega-3 PUFA leads to reduced circulating levels of lipid metabolites, primarily TAG. In contrast, beneficial effects of omega-3 PUFA on insulin sensitivity (reviewed in (Flachs et al., 2014; Kris-Etherton et al., 2003)), observed frequently in obese rodents fed a high-fat diet (Flachs et al., 2006; Jelenik et al., 2010; Kuda et al., 2009; Storlien et al., 1987), are not reproduced in human subjects. Although omega-3 PUFA cannot reverse T2DM (Veleba et al., 2015), and their impact on insulin sensitivity in obese human subjects is controversial (Flachs et al., 2011; Lalia et al., 2015; Spencer et al., 2013; Veleba et al., 2015), they can still exert anti-inflammatory effects even in WAT of insulin-resistant subjects (Itariu et al., 2012; Spencer et al., 2013). Modulation of adiposity and AT features by omega-3 PUFA is described in details in the following Sections.

The dose-response relationship might help to explain some of the differential effects of omega-3 PUFA in obese rodents and humans. For instance, in our mouse studies using DHA-enriched, TAG-based omega-3 PUFA concentrate (Flachs et al., 2006; Jelenik et al., 2010; Kuda et al., 2009), the dose of EPA+DHA was ~2 g/kg body weight, while in our clinical study on T2DM subjects receiving omega-3 PUFA for 6 months (Veleba et al., 2015) the EPA+DHA dose was ~30 mg/kg body weight, using the same omega-3 PUFA concentrate as above. This resulted in a ~6.0- and 1.6-fold increase in the relative EPA+DHA concentration measured in total plasma lipids of mice (assessed after 9 weeks of omega-3 PUFA feeding; ref. (Rossmeisl et al., 2012)) and in total plasma phospholipids of T2DM patients (Veleba et al., 2015), respectively.

3.3. Forms of omega-3, bioavailability

Both bioavailability and metabolic efficacy of omega-3 PUFA depend in part on their chemical binding form (reviewed in (Burri et al., 2012; Masoodi et al., 2015; Schuchardt and Hahn, 2013)). Omega-3 PUFA can be part of TAG, diacylglycerols, phospholipids (**PL**), wax esters, or exist as free FA, while being administered in the form of fish, Krill oil, Calanus oil or meat; in contrast, food supplements contain usually emulsions or oils modified by transesterification to increase DHA and EPA content. Thus, it is difficult to compare the bioavailability or even biological effects of various forms of omega-3 PUFA, because most human and animal studies did not correct for the molecular weights of the different forms of omega-3 PUFA used (balanced number of moles per gram of diet) (Ghasemifard et al., 2014; Schuchardt and Hahn, 2013), but PL seem to be superior to TAG in preserving a healthy metabolic profile of WAT under obesogenic conditions ((Awada et al., 2013; Rossmeisl et al., 2012); see also Section 4.2.). Moreover, yet unknown biologically active components besides omega-3 PUFA could contribute to the differences in the metabolic efficacy and effects of various naturally occuring marine-derived lipids (Yamada et al., 2014). The therapeutic potential of omega-3 PUFA supplementation might be compromised by inappropriate doses of different omega-3 PUFA forms, missing adjustments for body weight and gender of obese subjects, by oxidized content of food supplements, or by selection of unsuitable biomarker(s) of omega-3 PUFA bioavailability (Albert et al., 2015; Lohner et al., 2013; Mason and

Sherratt, 2017; Schuchardt and Hahn, 2013). With regard to bioavailability of EPA and DHA, mice fed a high-fat diet containing marine PL had a higher increase in plasma levels of DHA and especially EPA than animals fed omega-3 PUFA as TAG (Rossmeisl et al., 2012), similarly to situation in overweight/obese subjects (Maki et al., 2009). More comparative studies in obese rodents and humans are needed to examine the bioavailability of EPA and DHA using omega-3 PUFA concentrates based on different chemical forms.

As compared to omega-3 PUFA as TAG, a more pronounced reduction in WAT levels of classical endocannabinoids, especially 2-AG, was observed in mice fed a high-fat diet in response to supplementation with herring-derived PL (Rossmeisl et al., 2012). Similar data were obtained in obese rodents (Batetta et al., 2009; Piscitelli et al., 2011) and obese men (Berge et al., 2013) using marine PL as Krill oil. Marine PL also had improved efficacy regarding alleviation of hepatic steatosis (Batetta et al., 2009; Ferramosca et al., 2012; Rossmeisl et al., 2012, 2014; Tandy et al., 2009) and glucose intolerance (Rossmeisl et al., 2012). A recent randomized controlled trial (Lobraico et al., 2015) using a 4-week-intervention in T2DM subjects reported improvements in insulin sensitivity in response to Krill oil supplementation. Also omega-3 PUFA as wax esters (Calanus oil) showed greater beneficial effects on glucose metabolism in dietary obese mice when compared to their ethyl ester form (Hoper et al., 2013, 2014).

4. Modulation of adipose tissue features by omega-3 PUFA

4.1. Storage capacity of WAT for omega-3 PUFA

It can be assumed that biological responses induced by dietary omega-3 PUFA supplementation depend on the relative increases in EPA and DHA accumulation in WAT and other places in the body (reviewed in (Kopecky et al., 2009; Todorcevic and Hodson, 2015)). Thus, in experiments on obese mice fed a high-fat diet supplemented with omega-3 PUFA (Kopecky et al., 2009), we investigated the bioavailability of EPA and DHA, i.e. dietary omega-3 PUFA-induced incorporation of EPA and DHA into various tissue compartments. In case of WAT, a 4- to 5-fold lower concentration of EPA and DHA in total tissue lipids (i.e. mostly TAG) was observed when compared to the liver TAG fraction (Kopecky et al., 2009), similarly to the situation in humans (Arterburn et al., 2006). Accordingly, EPA and DHA incorporation into WAT lipids is characterized by an extended period of time before reaching its maximum (Browning et al., 2012; Kopecky et al., 2009). In spite of a relatively low specific content of EPA and DHA in WAT, the total amount of omega-3 PUFA stored in this tissue can be significant due to a high tissue expandability and storage capacity for lipids in general. This fact is also supported by a study in lactating women (Fidler et al., 2000), showing that only ~20% of dietary DHA was secreted into breast milk while the remaining part came from body stores, presumably WAT; this is likely to prevent large fluctuations in the omega-3 PUFA levels in human milk. Furthermore, this high storage capacity of WAT for omega-3 PUFA may also underlie the importance of this tissue as a source of various types of omega-3 PUFA-derived lipid mediators that are found both in circulation and in the breast milk. Breast milk contains high levels of maresins, resolvins and FAHFA, which indicate the role of omega-3 PUFA in neonatal immunity (Arnardottir et al., 2016; Brezinova et al., 2017; Weiss et al., 2013).

It is well established that in WAT individual FA are differentially mobilized from TAG during stimulated lipolysis, i.e. they are more readily mobilized when they are short and unsaturated, and when their double bonds are closer to the CH_3-end of the carbon chain (Raclot and Groscolas, 1993). However, it is the location of EPA and DHA primarily in membrane phospholipids of adipose cells, which is important for the generation of biologically active EPA- and DHA-derived lipid mediators in WAT (reviewed in (Banni and Di Marzo, 2010; Kuda, 2017; Masoodi et al., 2015)). Thus, FA composition of the membrane PL, namely the ratio between arachidonic acid, i.e. the precursor of lipid mediators exerting primarily pro-inflammatory properties, and DHA, is an important factor determining the susceptibility of WAT to inflammation ((Pietilainen et al., 2011); see also Section 4.4.).

4.2. Modulation adiposity

In accordance with other studies in animals (for review, see (Ruzickova et al., 2004; Todorcevic and Hodson, 2015)), our experiments using C57BL/6 mice have demonstrated that substituting 15% (w/w) of lipids in the corn oil-based high-fat diet (lipids ~ 35% w/w) by a TAG-based omega-3 PUFA concentrate (Epax 1050 TG; containing ~60% of EPA+DHA) prevented fat accumulation, usually with a greater reduction in abdominal (epididymal) fat depot (Flachs et al., 2005; Jelenik et al., 2010; Pavlisova et al., 2016; Ruzickova et al., 2004); reversal of obesity using omega-3 PUFA supplementation was also observed in our experiments (Kuda et al., 2009; Rossmeisl et al., 2009, 2012). The differential effects of omega-3 PUFA on fat depots is associated with changes in the expression of genes engaged especially in lipid metabolism in adipocytes (e.g. (Azain, 2004; Flachs et al., 2005; Hun et al., 1999; Pavlisova et al., 2016; Ruzickova et al., 2004)). Dietary omega-3 PUFA could affect body weight gain and adiposity in relation to the chemical form in which they are administered into the organism; for example, marine PL as Krill oil could preferentially reduce the accumulation of mesenteric WAT (M. Rossmeisl, unpublished observation), while wax esters in Calanus oil preferentially reduced perirenal WAT (Hoper et al., 2013, 2014). Importantly, omega-3 PUFA intake was also shown to reverse already established obesity in mice (Kuda et al., 2009; Rossmeisl et al., 2009, 2012). In general, the anti-obesity effects of dietary omega-3 PUFA could involve modulation of intestinal metabolism (Mori et al., 2007; van Schothorst et al., 2009), but they could also reflect a subtle tendency for decreased food intake observed in some experiments (Kuda et al., 2009; Pavlisova et al., 2016; Rossmeisl et al., 2012). Furthermore, it seems that the anti-obesity effect of omega-3 PUFA in mice fed a high-fat diet is independent of cold-induced thermogenesis (Janovska et al., 2013). Dysfunction of FFAR4/GPR120, which is a putative receptor/sensor for omega-3 PUFA (see ref. (Oh et al., 2010) and Sections 2.3.3 and 3.1.), was previously reported to be associated with obesity in both mice and humans (Ichimura et al., 2012).

In a sharp contrast to the animal studies, none or only very subtle weight reduction was observed following omega-3 PUFA intake in obese humans (reviewed in (Lorente-Cebrian et al., 2013)). On the other hand, an additive weight-reducing effect was found when omega-3 PUFA were combined either with physical exercise (Hill et al., 2007; Warner et al., 1989) or reduced calorie intake (Krebs et al., 2006; Kunesova et al., 2006; Mori et al., 1999; Thorsdottir et al., 2007). These results are in accordance with our study in mice fed a high-fat diet, showing an effective prevention of weight gain when calorie restriction (by ~10%) was combined with omega-3 PUFA intake (see ref. (Flachs et al., 2011) and above). Interestingly, several association studies in humans also document a negative correlation between the omega-3 PUFA content in WAT (Pietilainen et al., 2007) or plasma lipids (Micallef et al., 2009) and obesity. Thus, while dietary omega-3 PUFA supplementation is frequently associated with reduced body weight and/or the weight of different WAT depots in experimental animals, they are less effective in obese, insulin resistant patients and can only potentiate

the effect of other weight-reducing therapies such as exercise or calorie restriction. This, however, does not preclude their beneficial effects in terms of stimulating the synthesis of anti-inflammatory lipid mediators in obese WAT (see refs. (Itariu et al., 2012; Kuda et al., 2016a; Spencer et al., 2013) and Section 3.1.).

4.3. Decrease of WAT cellularity

Fat cell turnover is involved in the control of AT mass (Spalding et al., 2008). As revealed for the first time by our experiments in mice, the reduction in WAT growth on obesogenic diets in response to omega-3 PUFA supplementation probably results in part from decreased cellularity of the tissue (Ruzickova et al., 2004). Moreover, using a mouse transgenic model of inducible and reversible lipoatrophy, in which death of mature brown and white adipocytes is achieved by selective ablation of peroxisome proliferator-activated receptor gamma (**PPARγ**), we have demonstrated that omega-3 PUFA slow down compensatory WAT growth and adipocyte proliferation assessed 3 weeks after the induction of transient lipoatrophy (Hensler et al., 2011). The mechanism of omega-3 PUFA's effects on WAT cellularity remains poorly characterized, but inhibition of fat cell proliferation and/or induction of apoptosis could be involved (reviewed in (Todorcevic and Hodson, 2015)). The clearence of dying cell by phagocytes (efferocytosis) may depend on activation of AMPK and the shift in tissue macrophages metabolism (Jiang et al., 2013), see Section 3.1., Thus, *in vitro*, DHA inhibits adipocyte differentiation and induces apoptosis in post-confluent preadipocytes (Kim et al., 2006). DHA also induces apoptosis in several models of cancer (Stillwell et al., 2005). The mechanism may reflect modulation of *in situ* eicosanoid production (Darimont et al., 1994; Gregoire et al., 1998; Okuno et al., 1997), specifically of the epoxy DHA metabolites that inhibit angiogenesis, tumor growth, and metastasis (Zhang et al., 2013). Alternatively, also the interaction of omega-3 PUFA with the endocannabinoid system in WAT may be involved (see Sections 3.1 and 3.3.), since CB1 modulates adipocyte proliferation and differentiation (Gary-Bobo et al., 2006). Accordingly, a decrease in WAT cellularity may be also involved in the reduction of adiposity of pups born to rat or mouse dams fed diets supplemented with omega-3 PUFA (Korotkova et al., 2002) or α-linolenic acid (**ALA**; 18:3 ω −3; ref. (Massiera et al., 2003)) during gestation and suckling, and even in the anti-obesity (Arenz et al., 2004) and anti-diabetic effects (Knip and Akerblom, 2005) of breast-feeding.

4.4. Induction of "healthy adipocyte" metabolism

Modulation of the intrinsic immunometabolic properties of WAT is crucial for the whole-body beneficial effects of omega-3 PUFA in the context of obesity-associated metabolic disorders. In accordance with the concept of immunometabolism, i.e. the mutual links between the immune and metabolic systems (see Section 2.3.4.), the anti-inflammatory effects of omega-3 PUFA in WAT promote the "healthy adipocyte" metabolic phenotype. These effects of omega-3 PUFA were described using dietary interventions in both obese humans and obese rodents (see below). Moreover, even the study performed in monozygotic twins discordant for obesity, and in the absence of any omega-3 PUFA supplementation, revealed the role of FA composition of membrane phospholipids in WAT in the adaptation to adipocyte hypertrophy (Pietilainen et al., 2011). These results have demonstrated lipidome remodeling in obesity due to a relative decrease of DHA and DPA as compared to arachidonic acid, leading to an increase of arachidonic acid content relative to DHA. Arachidonic acid was targeted to ethanolamine plasmalogens. These changes allowed for adipocyte cellular membranes expansion while the physical properties of the membranes were preserved. However, the change in FA composition of membrane PL promoted formation of pro-inflammatory lipid mediators derived from arachidonic acid (Pietilainen et al., 2011). These findings help to explain the origins of low-grade inflammation in obesity and call for omega-3 PUFA supplementation in obese individuals.

The anti-inflammatory effect of omega-3 PUFA in WAT is underlined by complex changes in tissue levels of various lipid mediators (see Section 3.1.), including the formation of anti-inflammatory mediators like 13-DHAHLA (Kuda et al., 2016a). Dietary omega-3 PUFA had a sustained suppressive effect on the levels of 2-AG and AEA in WAT of obese mice. In contrast, WAT levels of both 2-AG and AEA remained unaffected in response to omega-3 PUFA supplementation in patients with T2DM. However, WAT levels of endocannabinoid-related anti-inflammatory molecules N-eicosapentaenoyl ethanolamine and N-docosahexaenoyl ethanolamine increased in response to omega-3 PUFA in both obese mice and patients (our unpublished observation). These effects on WAT endocannabinoid system could be related to the species-specific effect of omega-3 PUFA on insulin sensitivity (see Section 3.2.) and to the fact that omega-3 PUFA exert anti-inflammatory effects even in WAT of human subjects with insulin resistance (Itariu et al., 2012; Spencer et al., 2013).

Regarding cell metabolism, modulation of lipid flux towards higher FA oxidation and TAG/FA cycle (Flachs et al., 2011; Mottillo et al., 2014) by omega-3 PUFA was also observed in porcine adipocytes (Huang et al., 2017). Omega-3 PUFA could partially improve the negative effects of excess lipids on macrophages and increase the rate of FA re-esterification and oxidation (Rombaldova et al., 2017). Such beneficial metabolic effects (e.g. increased FA oxidation and glucose uptake for DNL, production of anti-inflammatory lipid mediators) ultimately affect the metabolic flexibility and phenotype of immune cells within WAT, and, via locally-acting lipid mediators, also the function of adipocytes (see Section 3.1.)

With respect to the induction of "healthy adipocytes" *in vivo*, all their key features (see Section 2.3.3.) were revealed, especially in epididymal WAT in the abdomen, in response to dietary intervention with omega-3 PUFA in mice fed obesogenic high-fat diet. Thus, in this fat depot, the size of adipocytes was decreased (Kuda et al., 2009) and mitochondrial biogenesis was induced (Flachs et al., 2005), while FA oxidation, TAG turnover, DNL and mitochondrial ATP production were stimulated, namely when the combined intervention with omega-3 PUFA and mild calorie restriction was used (Flachs et al., 2011). Stimulation of TAG turnover by omega-3 PUFA was independent of cold-induced thermogenesis (Janovska et al., 2013) and occurred in the absence of UCP1 induction (Flachs et al., 2011). The synergistic induction of lipid metabolism in WAT by omega-3 PUFA and calorie restriction, which was associated with the suppression of tissue inflammation, was reflected in the improvements of systemic meta-inflammation, lipid metabolism and glucose homeostasis, as well as in a decrease of adiposity and liver fat accumulation (Flachs et al., 2011). All these changes thus represent the beneficial systemic effects of the induction of "healthy adipocytes" in WAT.

Regarding the effects of omega-3 PUFA on immunometabolism of WAT in humans, the anti-inflammatory effects of these lipids were demonstrated even in WAT of human subjects with insulin resistance and were linked to *in situ* formation of anti-inflammatory lipid mediators (see above). Moreover, omega-3 PUFA could decrease the size of fat cells in human subjects with diabetes (Skurnick-Minot et al., 2004), and supplementation with omega-3 PUFA in healthy individuals modulates the adipose tissue transcriptomic response during inflammatory stress (Ferguson et al., 2016). However, the effects of omega-3 PUFA on WAT

metabolism in humans remain poorly characterized.

4.5. BAT and brite/beige fat

Many studies were performed to reveal whether the beneficial metabolic effects of omega-3 PUFA, and especially their anti-obesity effects frequently observed in laboratory rodents (see Section 4.2.), could be attributed to the induction of UCP1-mediated thermogenesis in BAT and/or brite/beige fat. As mentioned in Section 2.2., classical BAT is the main site of adaptable thermogenesis, which contributes significantly to total energy balance. Brite/beige adipocytes interspersed in some WAT depots have much lower total thermogenic capacity compared with BAT, in spite of highly inducible UCP1 expression in these cells.

Studies *in vitro* demonstrated the induction of UCP1 in response to omega-3 PUFA in human preadipocytes (Fleckenstein-Elsen et al., 2016) and murine brown preadipocytes (Kim et al., 2016; Pahlavani et al., 2017; Quesada-Lopez et al., 2016). The *in vitro* studies also suggested involvement of FFAR4/GPR120 that binds long-chain PUFA and is strongly up-regulated in both BAT and brite/beige fat by cold exposure (Quesada-Lopez et al., 2016), and thus may be necessary for the anti-obesity effects of omega-3 PUFA in mice (see Section 3.3.); the FFAR4/GPR120-mediated induction of the UCP1-thermogenic program *in vitro* involves the induction of FGF21, a hormonal factor released by brown and brite/beige adipocytes, with multiple beneficial metabolic effects (reviewed in (Quesada-Lopez et al., 2016; Villarroya et al., 2017)). Accordingly, several experiments *in vivo*, in both rats (Oudart et al., 1997) and mice (Bargut et al., 2016; Kim et al., 2015, 2016; Pahlavani et al., 2017) fed obesogenic high-fat diets, revealed the induction of UCP1 in both BAT (Bargut et al., 2016; Kim et al., 2015; Oudart et al., 1997; Pahlavani et al., 2017) and WAT depots (i.e. the brite/beige fat; ref. (Kim et al., 2015)) in response to omega-3 PUFA supplementation. Induction of UCP1 in AT was associated with the prevention of dietary obesity (Bargut et al., 2016; Kim et al., 2015, 2016; Oudart et al., 1997; Pahlavani et al., 2017) while it increased energy expenditure and cold tolerance of the mice (Kim et al., 2015, 2016). Therefore, these *in vivo* observations were in favor of the involvement of UCP1-mediated thermogenesis in the anti-obesity effects of omega-3 PUFA in rodents, also in accordance with the stimulation of the sympathetic nervous system observed under these conditions (Kim et al., 2015).

Also in our studies using C57BL/6 mice fed an obesogenic corn oil-based high-fat diet omega-3 PUFA supplementation prevented and/or reversed diet-induced obesity (see Section 4.2.); however, in contrast with the above animal studies (Bargut et al., 2016; Kim et al., 2015, 2016; Oudart et al., 1997; Pahlavani et al., 2017), no induction of UCP1 (and/or FGF21) in BAT could be observed even at a 3-fold higher dose of omega-3 PUFA than required for the anti-obesity effect (i.e. the substitution of 44 vs. 15%, w/w, of dietary lipids by the 60% TAG-based omega-3 PUFA concentrate; compare refs. (Flachs et al., 2011; Villarroya et al., 2014)). Moreover, in epididymal but not subcutaneous WAT, omega-3 PUFA stimulated the formation of "healthy adipocytes" (see Section 4.4.), marked by a high mitochondrial content, enhanced β-oxidation, and high activity of oxidative phosphorylation, rather than UCP1-mediated thermogenesis (Flachs et al., 2005). The contrasting effects of omega-3 PUFA on UCP1 content in BAT in various rodent studies could reflect many variables and remain to be explained. However, it is apparent that the anti-obesity effect of omega-3 PUFA in mice could occur independently of UCP1-mediated energy dissipation in BAT, the major site of cold-induced non-shivering thermogenesis (see Section 2.2.). Whether BAT activation is involved in a situation when the obesity/adiposity-reducing effect of omega-3 PUFA is augmented by the combined intervention using either calorie restriction (Flachs et al., 2011) or thiazolidinediones (Horakova et al., 2012; Kuda et al., 2009) remains to be tested. Also the involvement of brite/beige adipocytes in the whole-body effects of omega-3 PUFA remains uncertain at best.

5. Summary and future perspectives

Our review provides evidence that immunometabolism of AT, namely of WAT, represents one of the key components in the integrated control of whole-body energy homeostasis and insulin sensitivity. A unique immune cell repertoire in WAT, which is adapted to local microenvironment, suggests that the immune cell populations are significantly involved in the control of mature adipocyte metabolism. Detrimental changes of WAT immunometabolism, which are frequently associated with obesity, namely low-grade inflammation and disturbed lipid and glucose metabolism, result in ectopic accumulation of lipids and lipotoxic damage of insulin signaling in extra-adipose tissues, dyslipidemia and release of pro-inflammatory molecules from WAT into circulation. In murine obesity models, these adverse effects could be counteracted by various interventions, including omega-3 PUFA, which affect intrinsic immunometabolic features of WAT, namely by promoting the formation of "healthy adipocytes" with specific and flexibly regulated metabolic properties. These cells are characterized by a high capacity for oxidative phosphorylation, TAG/FA cycling and DNL. Efficacy of omega-3 PUFA in terms of promoting the "healthy adipocytes" phenotype depends in part on the chemical binding form of EPA and DHA, which can affect both their bioavailability and metabolic effects, and could be augmented by combined interventions using, for example, calorie restriction or some anti-diabetic drugs. Therefore, immunometabolic properties of WAT represent an outstanding target for new treatment strategies aimed for diseases linked to obesity and other systemic inflammatory conditions. Especially the induction of DNL in WAT could be instrumental, since this biochemical pathway is critically involved in the formation of lipid mediators exerting anti-inflammatory, insulin-sensitizing and pro-resolving properties, with some of these mediators derived directly from DHA. Similarly to the situation in mice, also in humans the intrinsic immunometabolic features of WAT have a major impact on energy homeostasis and insulin sensitivity. However, the potential of omega-3 PUFA with regard to induction of "healthy adipocytes" in human WAT, particularly in the context of obesity, remains to be determined.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.mam.2018.01.004.

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