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Systemic and joint adipose tissue lipids and their role in osteoarthritis

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ABSTRACT

Osteoarthritis (OA) is a major disease whose prevalence increases with aging, sedentary lifestyles, and obesity. The association between obesity and OA has been well documented, but the precise mechanisms underlying this heightened risk remain unclear. While obesity imposes greater forces on joints, systemic fat-derived factors such as lipids or adipokine may potentially act on the pathophysiology of OA, but the exact role of these factors in weight-bearing and non-weight-bearing joints remains elusive. Intra-articular adipose tissues (IAAT) have gained significant attention for actively participating in OA pathogenesis by interacting with various joint tissues. Lipid content has been proposed as a diagnostic target for early OA detection and a potential source of biomarkers. Moreover, targeting a specific IAAT called infrapatellar fat pad (IFP) and its lipids hold promise for attenuating OA-associated inflammation. Conversely, bone marrow adipose tissue (BMAT), which was long thought to be an inert filling tissue, is now increasingly considered a dynamic tissue whose volume and lipid content regulate bone remodeling in pathological conditions. Given OA's ability to alter adipose tissues, particularly those within the joint (IFP and BMAT), and the influence of adipose tissues on OA pathogenesis, this review examines the lipids produced by OA-associated adipose tissues, shedding light on their potential role in OA pathophysiology and highlighting them as potential therapeutic targets.

Contents

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1. Introduction

Osteoarthritis (OA) is the most common inflammatory and degenerative disease of the joints, affecting nearly 528 million people in 2019. The majority of those affected are over the age of 55, with about 60 % being female. With the increase of risk factors such as an aging population, sedentarity and obesity, OA prevalence is predicted to keep rising (113 % increase since 1990) [1]. OA can impact different types of joints and location, like the knees, hips, and hands. It is a disease with profound societal and psychological repercussions as the physical symptoms (pain, swelling, stiffness) result in decreased mobility and therefore overall well-being. This also leads to an increase in cardiovascular disease and ability to handle daily activities. OA affects all tissues of the joint. Its pathophysiology includes: articular cartilage degradation, subchondral bone sclerosis, osteophyte formation and synovitis [2]. It has long been recognized that excess weight leading to greater forces across the joint cannot be the only driving factor leading to OA in both weight bearing and non-weight bearing joints. This implies the additional involvement of multiple fat-derived systemic factors, such as lipids and adipokines secreted by the different types of adipose tissue (AT) [3].

The role of the intrapatellar AT (IFP) in OA has been largely explored in the last two decades. The IFP actively participates in OA development and progression via its interactions with cartilage, synovium, bone, menisci, ligaments, and nervous tissue [4]. The IFP lipid content has also been suggested as a target for early diagnosis of OA, through both imaging techniques and as a source of biomarkers. Lastly, the IFP and its secreted molecules have been proposed as therapeutic targets, leading to attenuation of the OA inflammatory phenotype [5].

Bone marrow adipose tissue (BMAT) has been almost entirely disregarded in OA research due to large differences in bone marrow adiposity between humans (80–90 % of marrow volume) and mice (2–5% of marrow volume). The BMAT is a dynamic tissue, whose volume and lipid content varies upon the physiological and pathological state of the organism. Remodeling of the BMAT is correlated with an increase in the number of medullary adipocytes in aging [6], osteoporosis (OP), diabetes, anorexia nervosa, as well as therapeutic interventions, including glucocorticoids, radiation and chemotherapy [7,8]. Interestingly, some of them constitute OA risk factors, suggesting that BMAT could regulate bone homeostasis during OA.

Since the lipid profile of AT is modified in OA and an important contribution of AT to OA pathophysiology is done in a paracrine way, herein we review the lipids produced by OA-AT with a special interest in the AT located within the joint, IFP and BMAT.

2. Methodology

A search for original articles published between January 2014 and March 2024 was performed on PubMed. The search terms used for reviews were “adipose tissue AND osteoarthritis” and for original articles were: “lipids AND osteoarthritis, “lipids AND joint health”, “arachidonic acid AND osteoarthritis”, “fatty acids AND osteoarthritis”, “infrapatellar fat pad”, “intra-articular fat pad AND”, “osteoarthritis’, bone marrow adipose tissue AND lipids”, and “intra-articular fat pad AND lipids”. For each term, the number of hits ranged from 12 to 3400. These results were further filtered to match the exact words used, ultimately yielding a mean of 100 hits per term. All articles identified were English-language articles. In addition, relevant references from selected publications and other relevant references were identified.

3. Systemic adipose tissues

3.1. Adipose tissue generalities

There are three main types of AT in the human body: brown (BAT), beige, and white adipose tissue (WAT). BAT is not abundant in the body and is mostly localized in the supraclavicular and in the pericardial area. BAT plays a role in thermoregulation, glucose homeostasis and is more active during cold exposure, exercise, and under certain dietary conditions. BAT is characterized by the presence of small lipid droplets, a large number of mitochondria and the expression of uncoupling protein 1 (UCP-1) (Fig. 1) [9,10]. WAT is characterized by an unilocular lipid droplet. It is able to store and release lipids and acts as a major endocrine organ by secreting adipokines. These include leptin, which influences lipolysis and hepatic glucose production, adiponectin, which contribute to glucose regulation and fatty-acid metabolism, resistin and its contribution to insulin resistance development, and also adipsin, which enhances glucose uptake, boosts triglyceride synthesis, and inhibits lipolysis in WAT (Fig. 1) [11]. In the visceral area, major significant deposits of WAT are localized in the omental, mesenteric, mediastinal, and epicardial tissues. Subcutaneous WAT (SCAT) is present under the skin, and mainly located in the abdominal and gluteal-femoral areas. Beige adipocytes can develop inside WAT in response to stimuli and cold exposure, as they share some properties of BAT (expression of UCP-1 and high mitochondrial density) (Fig. 1) [9,10].

Adipogenesis involves the differentiation of mesenchymal stem cells (MSCs) into mature adipocytes containing lipid droplets. In WAT and BAT, this process is driven by two major transcription factors: peroxisome proliferator-activated receptor-γ (PPARγ) and CCAAT/enhancer-binding proteins (C/EBPs). In WAT, IGF-1 (insulin-like growth factor 1) and insulin are critical regulators of survival, proliferation, and differentiation of pre-adipocytes by activating IGF-1 receptor (IGF1R) in an autocrine or paracrine fashion in neighboring adipocytes. IGF-1 can induce C/EBPα and the adipocyte lipid binding protein (aP2) [12]. In mice, *Gata6* (GATA binding protein 6) was identified as a marker of BAT progenitor cells from E13.5 when using single-cell RNA sequencing, and its deletion led to a drastic reduction or complete loss of interscapular BAT [13]. *Prdm16* (PRD1-BF1-RIZ1 homologous domain containing 16) and *cAMP-binding protein EPAC1* growth are central regulators of proliferation and differentiation of brown and beige adipocytes in juvenile or adult stages [14].

3.2. Systemic adipose tissue dysregulation and OA

AT dysregulation is known to be involved in several diseases. Some of these diseases can influence the development of OA, suggesting a reciprocal role between AT and OA progression. It has

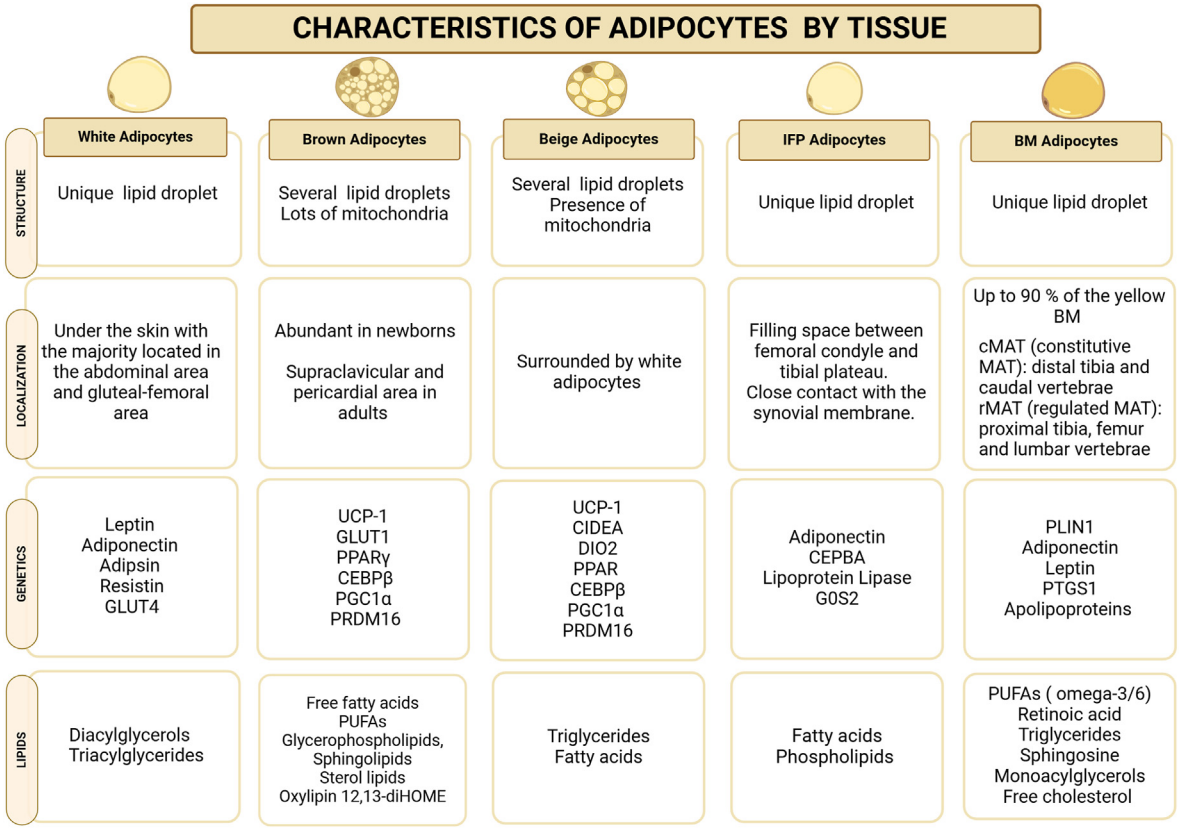

Fig. 1. Characteristics of adipocytes by tissue, in healthy conditions. Under healthy conditions, differences in the localization and function of AT are reflected in the characteristics of adipocytes, which vary their structure, genetic and lipid profiles to perform specific functions.

long been recognized that obesity and OA are associated [3], with obese patients developing OA more severely than non-obese counterparts. Weight excess leads for instance to more wear and tear in the knee but not in the hip [15]. Nowadays, OA is not only a disease drive by an excess of weight due to obesity, secreted factors like leptin are increased in the serum of OA patients, as well as in synovial fluid of obese patients, and has a known deleterious effect on cartilage integrity [16]. Furthermore, obesity will induce a systemic low-grade inflammation with the secretion of pro-inflammatory cytokines. This systemic low-grade inflammation of the synovium, cartilage and bone is involved in inflammatory mechanisms, notably through the activation of the complement in chondrocytes and synovial cells. Moreover, obese patients exhibit elevated levels of free fatty acids (FFA) in the plasma, which lead to increased intracellular lipid accumulation, potentially inducing lipotoxicity. FFA exert a pro-inflammatory effect on bone cells, with elevated levels of IL-6, IL-8, and MCP-1 [17–19].

Several metabolic diseases can amplify OA severity. A study found that patients diagnosed with both Diabetes Mellitus (DM) and OA reported significantly increased severity and frequency of pain, as well as a higher likelihood of requiring knee or hip joint replacement surgery compared to those with OA alone [20]. The risk of DM is correlated with rapid weight gain and obesity, leading to increased insulin resistance and low-grade inflammation with elevated levels of IL-6 and TNF-alpha. Imbalance in adiponectin secretion in DM is linked to increased fat mass, insulin resistance, and inflammation. Furthermore, chronic hyperglycemia and insulin resistance can promote the production of pro-inflammatory cytokines and metalloproteinase leading to cartilage destruction and the development of OA. Additionally, the metabolism of bone can be affected by a hyperglycemic condition [21].

Lipodystrophy, characterized by the selective or total absence of AT, has been studied in relation to bone structure. In humans, although a low BMI is known to be a risk factor for osteoporosis (OP), congenital generalized lipodystrophy type 1 and type 2 (CGL1 and CGL2) show higher bone mineral density [22]. However, CGL1 and CGL2 patients may also exhibit osteosclerosis, and CGL1 patients may present alterations in bone marrow as detected by MRI [23]. To understand the role of AT in OA, Collins et al. created lipodystrophic mice by inducing adipocyte ablation through the expression of diphtheria toxin in adiponectin-expressing cells [24]. Lipodystrophic mice without AT were protected against cartilage degradation. However, when fat was implanted into these mice, cartilage degradation occurred, thereby supporting the implication of AT-derived factors in OA [24].

The effect of systemic AT has been shown to affect OA, while OA modifies AT profile. This relationship shows a pathological loop contributing to disease progression, making AT an interesting therapeutical target for OA.

4. Joint adipose tissues

4.1. Intra articular adipose tissues

i. Infrapatellar fat pad generalities

Intra-articular AT (IAAT) are present in many joints, where they are localized between the synovium and the joint capsule. The Infrapatellar fat pad (IFP) is the most studied IAAT because it is the largest of the IAAT. IFP is localized underneath the patella, between

the patellar tendon, femoral condyle and tibial plateau, filling spaces between these structures. The role of IFP is not yet fully elucidated, but it may facilitate the distribution of synovial fluid and help absorb impulsive actions generated through the joint [25]. Like all AT, IFP is capable of secreting cytokines and adipokines into surrounding tissues, suggesting a role on joint physiology and disease [26]. In addition, IFP could be a source of mesenchymal precursors, with promising regenerative medicine applications for cartilage regeneration [27]. IFP consists of WAT, organized into lobules delimited by thin connective septa, with adipocytes smaller than those of SCAT [28]. Histomorphometric data of IFP revealed predominantly presence of collagen I fibers, with elastic fibers almost absent [29]. The IFP is innervated, meaning that it could play a mechanoreceptor role in regulating knee joint activity, but also be responsible for anterior knee pain in OA (Fig. 2) [28].

ii. IFP and OA

OA has been shown to modify the IFP at different levels. These include adipocyte morphology, transcriptomic profile, cytokines and adipokines secretion, lipid content of the IFP, extracellular matrix composition, vascularization, infiltration by immune cells and MRI signal intensity (Fig. 2) [4,30–34]. Recently, mass spectrometry has revealed 37 protein species exclusively secreted by IFP from OA knee patients, identifying IFP as a significant source of the specific protein composition of OA synovial fluid [35]. Furthermore, a meta-analysis showed that greater IFP volume appears to be associated with the presence and worsening of early OA features [36].

The extracellular matrix of OA patients' IFP shows an increase in type I collagen fibers and decrease in elastic fibers, leading to a more fibrous and thicker connective tissue, with a reduction in the size of adipose lobules. There is also evidence of infiltration of OA IFP by immune cells, specifically pro-inflammatory macrophages. Interestingly, upon treatment with disease-modifying anti-rheumatic drugs, inflammatory cells were primarily located in the IFP, supporting its active role in inflammation [34]. In particular, IFP and synovium form a unique functional unit [34]. Interactions of OA-IFP with the different joint tissues have been extensively reviewed elsewhere [4].

An approach on the use of IFP as a therapeutic target was assessed by Labarre et al. [37]. Patients with knee OA received an infiltration of autologous stromal vascular fraction from abdominal SCAT into their IFP. The number and viability of the cells were measured, and clinical outcome was followed for a year. A correlation between higher cell viability and better clinical outcome was observed, with no major complications or side effects [37]. These results therefore support the use of IFP as a therapeutic target for the treatment of OA.

4.2. Bone marrow adipose tissue

i. Bone marrow adipose tissue generalities

Bone marrow adipose tissue (BMAT) constitutes over 10 % of total adipose mass and 70 % of the bone marrow (BM) volume in young lean healthy human adults. BM adipocytes (BMAds), like WAT adipocytes, are composed of a unique lipid droplet with a small nucleus at the border of the cell. BMAds arise from the bone mesenchymal stromal cells, with the activation of specific pathways [38]. Two populations of pre-adipocytes have been found by scRNAseq in the bone (BMSCs), the *Lepr* and *Cxcl12* populations,

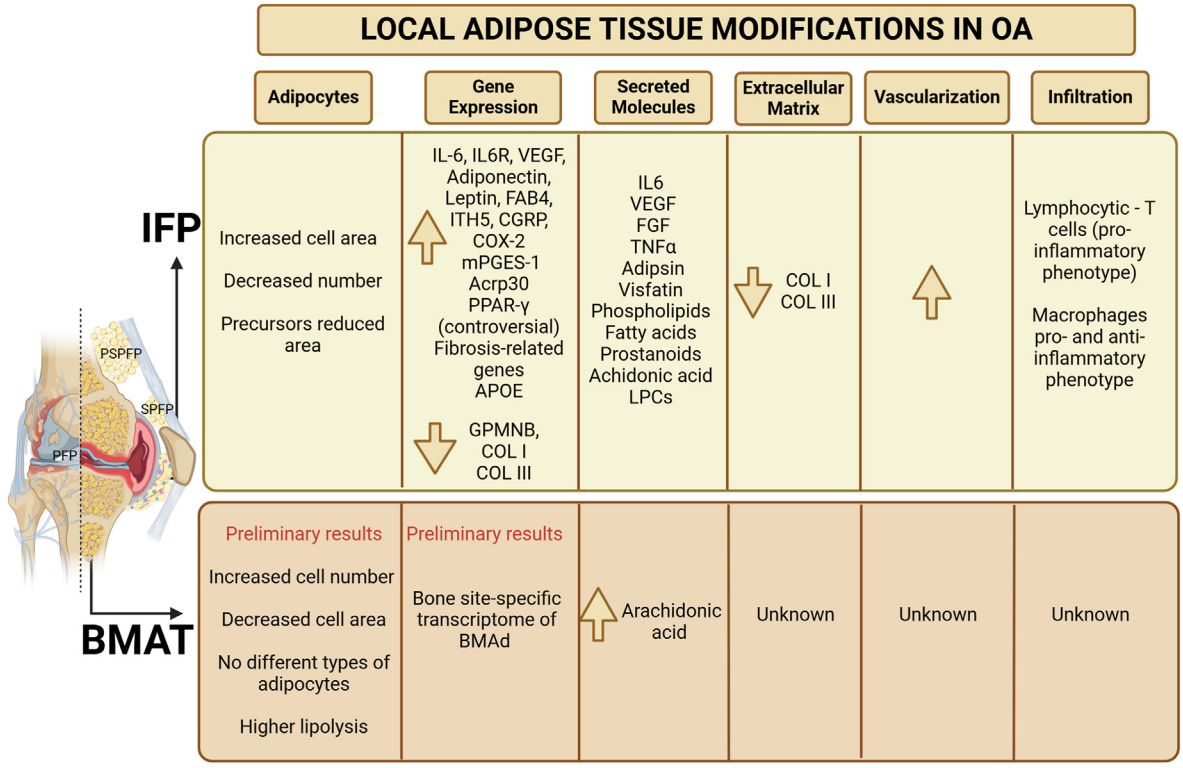

Fig. 2. OA pathophysiology modifies local adipose tissues. OA alters IFP adipocytes morphology, genetic profile, secreted molecules, extracellular matrix, vascularization and infiltration. BMAT responds to pathological conditions and therapeutic strategies. Preliminary results indicate that BMAT can increase due to OA, with higher lipolysis level in sclerotic areas compared to non-sclerotic areas. Innervation in yellow, infrapatellar fat pad (IFP), the suprapatellar fat pad (SPFP), posterior knee fat pad (PFP), posterior suprapatellar fat pad (PSPFP). Innervation of the knee is extensive, with articular nerves originating as single or multiple branches from the femoral, obturator, and sciatic nerves [98]. A schematic of the innervation is shown on the left panel of the figure.

expressing two main adipocyte markers, *Adipoq* and *Pparγ* [39]. There are two types of BMAT, constitutive (cBMAT) and regulated (rBMAT). cBMAT appears early in postnatal development and fills the medullary canal from the tibia-fibular junction into the malleolus, while rBMAT increases upon aging in humans [40]. BMAT accumulation correlates inversely with bone mineral density (BMD) with age, and increased formation of BMAT has been observed in osteoporosis, obesity, type 2 diabetes, chronic kidney disease, and aplastic anemia. rBMAT is increased in animal models of ovariectomy and caloric restriction and also increases in response to glucocorticoids, radiotherapy, or chemotherapy (Fig. 2) [38].

ii. Physiology and pathophysiology of BMAT in bone homeostasis

BMAT can be reconverted to hematopoietic marrow in conditions of chronic anemia and of marrow replacement disorders [41]. In fibrous dysplasia or CGL type I and type II, there is a loss or absence of BMAT, which is replaced by a fibrotic tissue. Interestingly, skeletal abnormalities and bone lesions are observed in patients with fibrous dysplasia and CGL, respectively [23,42,43]. Molecular changes associated with pathological conditions also occur in BMAT. BMAds, positive for performic acid-Schiff staining, disappear in response to experimentally induced hemolysis. A decreased expression of genes linked to BAT was observed in tibiae of aged and diabetic mice despite an increase in the number of BMAds [44]. The content of unsaturated fatty acids (FA) of BMAT from the L3 vertebral body is decreased in OP women [45]. Recent studies have shown that lipids influence bone formation in a sex- and diet-dependent manner [46], with BMAds found to contribute to bone formation in mice [47]. More specifically, the secretion by BMAT of adipokines and cytokines, with a known role in OA, and their crosstalk with osteoblasts has been shown [48].

The specific role of BMAT in OA remains to be explored but is supported by the observed positive correlation between cartilage degradation and the increased BMAd density in an OA mouse model [49]. Due to the proximity between BMAT and joint tissues, functional interactions between them are expected to occur. This crosstalk could possibly affect BMAd and osteoblast precursors, OA bone remodeling, or even participate in the inflammatory phenotype of the disease. Indeed, BMAT of the femoral head of OA patients is enriched in omega-6 PUFA, as compared to osteoporotic patients [50], and OA BMAds from different bone localizations display specific transcriptome [49]. In addition, OA BMAds seem to have a higher lipolysis activity in OA hands [51].

5. Lipids

Adipocytes secrete different types of molecules, including lipids, proteins, and peptides. These molecules exert endocrine, paracrine, and/or autocrine effects, contributing to the regulation of multiple physiological processes such as adipocyte differentiation, energy metabolism, lipid uptake and transport, immune response, inflammation, vasculature and neuron development, as well as extracellular matrix remodeling. Notably, lipids are not solely secreted by adipocytes, but also undergo metabolism, transformation, and synthesis within a cellular context.

5.1. Systemic lipids and OA

The lipid composition of WAT and BAT differs, reflecting their distinct metabolic roles. FFA are more abundant in BAT, whereas diacylglycerols and triacylglycerides (TAG) are more prevalent in WAT. WAT primarily stores energy as TAG [52], where BAT requires FFA for fatty acid oxidation and UCP1 activation, crucial for its role in thermoregulation. Several changes also happen with aging. In BAT, an increase in phosphatidylethanolamine and phosphatidylcholine containing poly unsaturated FA (PUFA) happens, and these tend to undergo oxidative damage [53]. Furthermore, the lipid composition of the plasma changes significantly, including an increase in the levels of glycerophospholipids, sphingolipids, sterol lipids, and FFA (Fig. 1) [54].

Secreted lipids are also dysregulated in OA, even without other comorbidities such as obesity and DM. Patients with early knee OA have been shown to have higher levels of total cholesterol and low-density lipoprotein (LDL), correlating with higher pain intensity and disability [55]. These results are nonetheless controversial, with other publications unraveling a causal relationship between LDL and OA, with a notably a protective effect of LDL [56]. In addition, one study showed a tendency for positive correlation between the risk of developing OA and the lipid accumulation products (LAP) index. LAP index is used to estimate the excessive lipid accumulation in the body considering waist circumference and fasting plasma triglyceride levels [57]. Recently, it has been suggested that imbalances of sphingolipid levels in human plasma and synovial fluids could result in the onset of early OA [58,59]. Specifically, the local inhibition of lipid mediator sphingosine 1-phosphate (S1P) in a mouse model prevented cartilage damage and synovial inflammation, supporting the role of S1P as a possible therapeutic target in OA [60].

AT lipids may affect cartilage integrity in OA exerting a dual effect, either attenuating or initiating cartilage degeneration [24,61]. Specifically, arachidonic acid (ARA) can promote the catabolic process in chondrocytes and enhance the pro-inflammatory response. On the other hand, omega-3 PUFA is known to block cartilage degradation and inflammation by inhibiting the expression of specific genes [62]. To investigate the systemic impact of omega-6 and omega-3 on post-traumatic OA, researchers utilized the Fat-1 mouse model. In this model, mice express the enzyme omega-3 FA desaturase, which can convert omega-6 FA to omega-3 FA. These mice contain elevated serum levels of omega-3 FA. Following post-traumatic OA induction, they displayed a reduction in OA symptoms, less synovitis, and decreased levels of pro-inflammatory cytokines [63]. These promising results suggest that the use of systemic lipids in the treatment of OA should be further investigated [64,65].

5.2. Joint tissue lipids and OA

i. IFP lipids

The lipid profile of IFP from healthy donors showed a similar pattern of FFA and phospholipids as other WAT (Fig. 1) [66]. However, this profile may vary due to pathologic conditions. In particular, an elevated IFP FFA concentration has been described in pancreatic arthritis syndrome [67]. A comparison of FA signatures of synovial fluid and IFP from patients with RA and OA, found that the secretion of ARA from the IFP of OA patients was higher compared to RA patients [68] (Fig. 2). An increased in omega-6/omega-3 PUFA ratio in the IFP of OA was also observed in a rabbit model [69],whereas in human plasma, a high omega-6/omega-3 ratio was associated with greater pain and functional limitations in OA knees [70]. Additionally, in IFP, ARA increases prostaglandin E_2 production [71], alters levels of pro-inflammatory lipid metabolites like lysophosphatidylcholines [72], mobilizes docosahexaenoic acid (DHA) [5] and the release of prostanoids, a family of lipid mediators derived from ARA, whose chemical inhibition has been shown to reduce the inflammatory phenotype of OA [73]. Furthermore, IFP-derived prostaglandins (PG) induce a fibrotic response in synoviocytes [74,75]. Interestingly, IFP adipocytes can

also secrete FA that enhance $CD4^+$ T cell proliferation and production of the pro-inflammatory cytokine IFN-γ [76]. Paradoxically, in the FA signature study, the authors also revealed that the IFP of OA patients had higher levels of DHA compared to RA patients, as well as higher product/precursor ratios of omega-3 PUFA, known to have anti-inflammatory effects and to induce pro-catabolic enzymes in the cartilage [68]. This suggests that IFP induces both protective and aggravating activities in OA. The monounsaturated fatty acid (MUFA) oleic acid was also increased in OA synovial fluid, which is a critical metabolite for distinguishing early from late-stage OA, with levels increasing during disease progression [69]. Although the role of oleic acid in joint diseases is unclear, it has shown anti-destructive effects on chondrocytes and cartilage *in vitro* [77]. Overall, the FA profile of OA IFP reflects both inflammatory and protective biochemical roles. As mentioned, there is growing evidence for a protective role of omega-3 PUFA such as DHA in joint health, but the potential roles of an increased level of omega-6 PUFA and MUFA need further investigation. Lastly, a single-cell analysis of OA IFP adipocytes showed that their high expression of apolipoprotein E is deleterious to articular cartilage *in vitro* [31] (Fig. 2). These studies suggest that alterations in the IFP lipid profile have significant implications for joint diseases, particularly in OA pathophysiology. This highlights the potential of targeting these lipid changes for therapeutic intervention.

ii. BMAT lipids

BMAT lipids, such as PUFA, play important roles in bone health and hematopoiesis, making them essential players in the development and treatment of joint diseases. Treatment of human MSCs with ARA induced adipogenesis at the expense of osteoblastogenesis [78], and BMAT all-trans retinoic acid, a derivative of vitamin A, inhibited stromal cell commitment to adipocytes [79], demonstrating that BMAT lipids can regulate progenitor cells (Fig. 1). RA is not a lipid but an important metabolite for adipocyte commitment. It can activate PPARδ to enhance lipid oxidation and energy dissipation [79].

ARA is the precursor of eicosanoids that include PG and leukotrienes. These molecules have biological signaling functions, notably in the immune response and bone health. For instance, PGE_2 enhances osteoclast differentiation [80]. It has also been observed that lipid droplets of immune cells are particularly enriched in ARA, as ARA is required for the formation of eicosanoids used in the inflammatory response [81]. Glucocorticoid treatment causes rapid senescence of BMAds by inducing a loop that involves PPARγ and oxylipins and spreads senescence to the bone marrow [82]. Enzymes able to convert saturated to monounsaturated FFA are also important in BMAds and AT, such as depletion of stearoyl-CoA Desaturase-1, which leads to vacuole accumulation, cell death and hence BMAT loss [83].

OA chondrocytes are also known to produce excessive PGE_2 and nitric oxide (NO) [84]. As mentioned, they act as mediators of inflammation and hence of OA. In a study in which cultures of OA chondrocyte were supplemented with different FA [85], it was shown that the combination of the omega-6 conjugated linoleic acid (CLA), an isomer of linoleic acid (LA), the precursor of ARA, with eicosapentaenoic acid, an omega-3, resulted in the lowest amount of PGE_2 produced, as well as lower amounts of NO compared with controls. This suggests that CLA may have an impact on the pathogenesis of OA.

Moreover, it has been shown in humans that OA bone samples have higher levels of omega-6 PUFA compared to osteoporotic bone samples [50]. This implies a potential role of omega-6 PUFA in OA. Supplementation with omega-3 PUFA in a high fat diet (HFD + F), specifically DHA and EPA, derived from α-linoleic acid, improved bone parameters, mechanical properties as well as decreased BMAT compared to the HFD group [86]. For instance, primary BMSCs isolated from HFD + F mice showed decreased adipocyte and increased osteoblast differentiation with lower senescent phenotype. This suggests an improved BM microenvironment promoting bone formation in mice. Moreover, omega-3 supplements are given as a treatment option for OA for their anti-inflammatory properties [87,88]. OA Patients who received omega-3 supplements demonstrated reduced knee pain, increased knee stiffness, and improved physical function [89].

Overall, FA and specifically their ratios to one another, seem to be important for inflammation balance in the body, specific compartments, and their pathologies. An additional example is the dihomo-γ-linolenic acid (DGLA), another derivative of LA, which can be metabolized into either pro-inflammatory (from ARA) or anti-inflammatory FA. DGLA increases in various inflammatory conditions such as RA, Crohn's disease, and celiac disease, suggesting that it may be a marker of inflammation [90]. Studies focusing on its effect on OA specifically have not yet been performed.

Beyond its secreted FA with pro- and anti-inflammatory roles, BMAT may also regulate the activity of other cell populations inside and outside the bone, as an energy source and through the secretion of adipokines [91,92]. BMAds have high levels of basal glucose uptake and increased insulin resistance, probably required for *de novo* lipogenesis, which acts as a local energy source to support hematopoiesis and osteogenesis [40].

BMAd lipid metabolism is different from that of SCAT adipocytes, particularly enriched in cholesterol metabolism pathways as opposed to lipolytic pathways [93]. This suggests BMAds act more like a triglyceride reservoir, even during caloric deficit state, and are therefore a preserved source of lipids. Another study revealed the role of cholesterol metabolism in OA cartilage. The LOX1 enzyme (lectin-type oxidized low-density lipoprotein receptor 1), involved in cholesterol uptake, was found to be upregulated in both humans and mice with OA [94,95]. When another cholesterol metabolism factor, cholesterol 25-hydroxylase (CH25H), is overexpressed, features of OA, such as thickening of subchondral bone, are observed in mice [95]. The implication of these cholesterol pathways in other diseases like atherosclerosis suggests that BMAds could play a role in maintaining overall health.

It remains to be shown if BMAT lipolysis is regulated by mechanical loading. However, Reticulocalbin-2 (RCN2), a mechanosensitive lipolytic factor, is involved in lipolysis of the BMAT [47]. This lipolysis provides energy for mechanisms such as lymphopoiesis and osteogenesis, making this factor a promising target for enhancing skeletal health and immune function.

In conclusion, BMAT lipids are implicated in bone health, immune response, BM-related disorders and potentially cartilage degradation making them active players in joint homeostasis and possible targets for OA treatment.

6. Perspectives and conclusion

OA is a major cause of disability worldwide triggering morbidity and constituting a challenge for health systems. To date, no treatment has been approved to prevent, stop, or delay the progression of OA. To meet this need, it is urgent to dissect all the actors involved in the pathophysiology of OA.

There is an accumulation of compelling evidence supporting the role of systemic and local AT-derived lipids in OA diagnosis, onset, and progression. Recent findings on the role of BMAT on the hematopoietic and bone microenvironment, and emerging data on BMAT in the context of OA, support BMAT as a new player involved in the pathophysiology of OA. Lipid crosstalk between BMAT and

other joint tissues like cartilage or synovium need to be addressed, not forgetting a possible systemic impact on low grade inflammation that has been linked to the worsening of OA symptoms. Currently, preclinical approaches are needed to help fill the gaps in knowledge regarding the exact impact of OA on BMAT's extracellular matrix, secreted molecules, immune infiltration and vascularization (Fig. 2). The recent development of more specific animal models [96,97] will make it possible to directly evaluate the functional role of BMAds in the onset and progression of OA, opening up interesting new avenues for basic and applied research.

Currently, high-throughput and non-invasive imaging-based techniques are beginning to be applied at IFP and BMAT. They could lead to the discovery of lipid-related biomarkers and diagnostic strategies for the early detection of OA. This could pave the way for new clinical trials targeting articular AT and its lipids for the prediction of the pathological state of the human joint and the treatment of OA [94]. The transition to the clinic could be as follows: lipids could first be identified and classified as systemic or local depending on their AT of origin. They would then be divided into biomarkers and/or therapeutic targets according to their role in OA. Systemic and marrow lipids could be controlled and/or targeted intravenously or orally, while joint-related lipids would be better managed intra-articularly. We anticipate that in the years to come, articles elucidating the role of lipids in OA will multiply.

In conclusion, there is a complex interplay between joint AT-derived lipids and OA. OA alters the characteristics of joint AT, including their lipid profile, and these lipids may in turn contribute to the disease progression. The treatment of OA requires innovative therapeutic strategies, and targeting IFP and BMAT lipids represents a promising new approach.

CRediT authorship contribution statement

Natalia Zapata-Linares: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Léa Loisay:** Writing – review & editing, Writing – original draft, Visualization, Validation, Formal analysis, Data curation, Conceptualization. **Diego de Haro:** Writing – review & editing, Writing – original draft, Visualization, Validation, Data curation, Conceptualization. **Francis Berenbaum:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Thomas Hügle:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Jeroen Geurts:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Xavier Houard:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

FB reports personal fees from 4P Pharma, 4Moving Biotech, Grunenthal, GSK, Heel, Nordic Bioscience, Novartis, Servier, TRB Chemedica, Viatris outside the submitted work. NZL, LL, DH, TH, JG and XH declare that they have no competing interest.

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