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Metabolic Regulation of Inflammation in Osteoarthritis

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Introduction

Osteoarthritis (OA) has long been considered the unique consequence of a tear and wear process leading to cartilage degradation. Indeed, it is true that an excessive mechanical stress on any joint leads to cartilage loss, with the production of osteophytes being considered a reactive process of the bone to protect and stabilize the altered joint (1). This initial paradigm has been slowly but deeply modified in the past 20 years due to critical discoveries (2). First, the enzymes involved in cartilage degradation have been identified as belonging to metalloproteinases and ADAMTS families, with pro-inflammatory cytokines regulating all of these enzymes. It was the first time that the pathophysiology of OA was associated with a role of soluble mediators better known in the pathophysiology of many other classical inflammatory diseases. Second, later on, whereas synovitis was considered as pathognomonic of RA, some groups demonstrated that a mild to severe synovitis reaction was frequently present in OA, its intensity being correlated to prognosis (3,4). Third, the role of obesity in OA shifted from an exclusive deleterious mechanical effect on load-bearing joints to its capacity to play a role in hand OA too. Indeed, epidemiological studies demonstrated that obese patients have a 2-fold increase in hand OA compared to a non-obese population (5). The interpretation of these unexpected results has been related to a well-

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known systemic release of pro-inflammatory cytokines primarily by abdominal adipose tissue (called adipocytokines or adipokines), which cause a low-grade inflammatory state involved in damage to many peripheral tissues, including joint tissues (2). More recently, the intra-articular fat pads, adipose tissue present inside some joints, have been considered as a new potential source of adipokines (6). All these steps demonstrating the role of inflammation in OA opened the door to a novel and exciting area of research trying to understand the molecular interactions between local articular tissues/cells and distant organs/tissues and how these metabolic processes are disturbed in OA.

Epidemiological and prospective clinical studies linking metabolic syndrome and OA

Puenpatum et al. were the first to suggest that, on top of obesity, the metabolic syndrome (MetS) (defined as the association of components that independently increase the risk of cardiovascular events: abdominal adiposity, diabetes or insulin resistance, high cholesterol, and high blood pressure) could be an independent risk factor for OA (7). They found in the NHANES III cohort that 59% of OA patients had MetS compared to 23% in the general population. Furthermore, they calculated that having OA at 44 years old increases 5.26-fold the risk of having a concomitant MetS, suggesting that the presence of knee OA should inform the practitioner on a need to screen for MetS. Then, other cross-sectional studies confirmed this association (8–12), even if obesity could sometimes be a strong confounding factor longitudinally (13). Nevertheless, the presence of MetS is also associated with hand OA. Taking advantage of an increased prevalence of metabolic syndrome in HIV patients, Tomi et al. looked at the prevalence of hand OA in sex and age-matched HIV patients according to their metabolic status. Interestingly, hand OA prevalence was higher for those with MetS than those without it (64.7% vs 46.3%, $p=0.002$) and the severity was greater (14). In the Netherlands Epidemiology of Obesity population cohort, hand OA was associated with MetS, adjusted for weight (OR 1.46 (95% CI 1.06 to 2.02)) (15).

But a breakthrough in this field comes from the recent publication of several prospective cohorts showing that obese patients with MetS have an increased risk of incidence and severity of knee and hand OA (Table 1) (13,16–21). Based on a sample of 482 women with knee OA, the prevalence of knee OA in obese women with less than 2 cardiometabolic parameters (low levels of high-density lipoprotein cholesterol; elevated levels of low-density lipoprotein cholesterol, triglycerides, blood pressure, C-reactive protein, waist:hip ratio, or glucose; or diabetes mellitus) was 12.8% compared to 23.2% in obese women with more or equal to 2 cardiometabolic parameters (16).

Interestingly, some of these studies show that incidence and severity were positively correlated to the number of cardiometabolic parameters. In a multivariate analysis based on a cohort of 1384 Japanese individuals followed 3 years (ROAD cohort), the incidence of knee OA significantly increased according to the number of MetS components (OR vs no parameters: one parameters, 2.33; two components, 2.82; three parameters, 9.83) (17). Similarly, progression of knee OA significantly increased according to the number of parameters present (OR vs no component: one component, 1.38; two components, 2.29;

three components: 2.80). In a large Australian population cohort followed during 2003–2007 (the Melbourne Collaborative Cohort Study), 660 patients had a total knee replacement (TKR) for OA (18). The accumulation of MetS components was associated with TKR, independently of BMI: one component, OR 2.12 (1.15–3.91); two components, 2.92 (1.60–5.33) and three or more components, 3.09 (1.68–5.69).

However, the weight of each of these factors for increasing OA risk remains largely unknown. Suffering from diabetes mellitus is associated with an independent increase of incident, prevalent and severe OA, although discrepancies exist in the literature (19) (review in (22)). Recent studies have shown an increased risk of knee or hand OA in hypertensive and/or atherosclerotic patients, giving strength to the hypothesis that an abnormal perfusion of the subchondral bone due to atherosclerosis could participate into the OA process (18,21,23). Interestingly, this hypothesis fits with a recent study showing an association of serum cholesterol and triglyceride levels with the incidence of bone marrow lesions on knee MRI at 2 years in an asymptomatic middle-aged women population (20). Moreover, in a population of 809 OA patients, hypercholesterolemia (OR 1.61; 95% CI 1.06–2.47) and high serum cholesterol levels (3rd versus 1st tertile: OR 1.73; 95% CI 1.02–2.92) were independently associated with generalized OA (24). Such an independent association has also been shown in hand OA (25).

Some groups looked at the prognostic value of plasma concentration of adipokines in OA cohorts. An association between leptin levels (but not adiponectin) and knee OA occurrence and progression was demonstrated in a 5-year cohort but this association disappeared after adjustment for BMI (26). In the CHECK cohort, there is a weak association between resistin levels (but not leptin) and disease progression (27). Finally, hand OA patients with high adiponectin levels (but not leptin nor resistin) had a decrease disease progression compared to normal/low levels in a Dutch cohort (28).

Taken together, these epidemiological studies show clear associations between OA, the MetS, and its components, with some of them being clearly independent of the overload effect of obesity (Figure 1). However, there is a high heterogeneity in the design of all these cross-sectional and longitudinal epidemiological studies (definition of the MetS, gender selection, record of medication, etc.), which prevents a definitive conclusion on the real impact of the MetS on knee OA initiation and progression. Recent experimental *in vitro* and animal studies have helped to begin deciphering the potential roles of each of these factors in the initiation and progression of OA.

Perspectives on the role of metabolic inflammation in OA from obese animal models

Beginning in the 1940s, Drs. Martin and Ruth Silberberg studied the role of increased dietary fat on the development of OA in mice. They showed that supplementing rodent chow with lard (30% by weight) increased the incidence of knee OA in C57BL mice by 2-fold (29). Recent studies replicated these early observations in both spontaneous and post-traumatic models of OA (Table 2), focusing primarily on changes in inflammatory cytokines and adipokines as mediators of the increase in OA pathology (30–34). In spontaneous

models, knee OA severity was positively correlated with total body fat, and numerous cytokines and adipokines were also elevated with the percentage of body fat (30–32). Statistically adjusting for adiposity using multivariable modeling negated most of the associations between systemic inflammatory mediators and knee OA, except for leptin and adiponectin (30,31).

These findings are notable since both leptin and adiponectin are implicated in OA pathogenesis (26,28). They are also of interest because mice with loss of function mutations in the leptin gene or the leptin receptor gene are protected from developing knee OA despite an extreme obesity phenotype, with body weights in excess of 80 grams and body fat levels >50% (35). Mice with impaired leptin signaling become obese primarily by hyperphagia, and in the study by Griffin and colleagues (35), leptin deficient mice were fed a normal chow-based diet. Increasing body weight by chemically inducing hyperphagia in mice fed a normal chow diet also does not increase knee OA [reviewed in (36)]. This finding may be explained by the anti-inflammatory and anti-oxidative actions of aurothioglucose, the chemical agent used to induce hyperphagia. However, it also raises the possibility that an increase in dietary fat or the composition of fat itself contribute to OA pathogenesis.

Mice fed high-fat lard diets supplemented with polyunsaturated fatty acids (PUFAs) or diets composed of vegetable oils (e.g., cottonseed oil) develop less severe knee OA (36). Fatty acids are well known to modulate inflammation positively or negatively, and recent studies have tested the effect of different types of dietary fatty acids on inflammation in rodent models of idiopathic and post-traumatic OA. Two central classes of lipid mediators of inflammation are omega-6 (n-6) and omega-3 (n-3) PUFAs. n-6 PUFAs, such as arachidonic acid, are precursors of pro-inflammatory eicosanoids, including prostaglandins, thromboxanes, and leukotrienes. Conversely, n-3 PUFAs, such as eicosapentaenoic and docosahexaenoic acids, inhibit inflammation and accelerate its resolution. Obesogenic diets of middle and high-income countries, commonly referred to as Western Diets, contain a high ratio of n-6:n-3 PUFAs.

Two recent studies in mice have shown that decreasing the ratio of n-6:n-3 PUFAs, either by diet or genetically through the introduction of the *fat-1* transgene that endogenously converts n-6 to n-3 PUFAs, reduces the development of post-traumatic knee OA (37,38). This reduction was associated with a decrease in serum pro-inflammatory cytokines and adipokines (e.g., IL-1 β , TNF, leptin, and resistin), joint synovitis, synovial macrophage infiltration, and heterotrophic joint ossifications. Intriguingly, wound healing in an ear-punch model was also improved by reducing the ratio of n-6:n-3 PUFAs (38). In contrast, the development of early-stage idiopathic knee OA in 1 year-old *fat-1* transgenic mice was not reduced compared to control littermates despite lower serum IL-6 and TNF levels (39). These studies suggest that the ratio of n-6:n-3 PUFAs has the greatest impact on OA progression under conditions of more acute activation of cellular and humoral immune responses, such as following tissue damage or joint trauma. It is not yet clear how n-6 and n-3 PUFAs regulate joint inflammation and repair. There is evidence that the ratio of n-6:n-3 PUFAs directly modulate cytokine-induced catabolic responses in joint connective tissues, such as cartilage (40); however, the effect likely involves heterogeneous cell populations involved in the regulation of wound healing and resolution of inflammation. A recent

randomized clinical trial of fish oil supplementation in knee OA patients showed improvement in OA-related pain and function at 2 years, albeit without altering cartilage loss (41), suggesting that n-3 PUFAs may also reduce inflammation by improving physiologic joint use and function.

Another way in which high-fat diets may stimulate joint inflammation and OA is through activation of innate immune pathways. Obesogenic high-fat diets and alcohol consumption impair the gut mucosal barrier, resulting in increased intestinal permeability and elevated circulating levels of lipopolysaccharide. In addition, long-chain saturated fatty acids have also been implicated in promoting low-grade inflammation through activation of the Toll-like receptor (TLR) pathway, specifically TLR4. Mice lacking functional lipopolysaccharide receptor CD14 and TLR4 are partially protected from high-fat diet induced inflammation and related metabolic impairments, such as insulin resistance. Two recent animal studies support a model of systemic lipopolysaccharide inflammation in OA (42,43). However, this work is at an early stage, and there are many questions about how TLR4 or lipopolysaccharide may mediate inflammation in OA (44).

A growing body of work has implicated dyslipidemia in innate immune pathway activation and OA pathophysiology. Activated synovial macrophages are present in OA joints, especially in diabetic patients (34). One potential mediator of macrophage activation is low-density lipoprotein (LDL) cholesterol. LDL is elevated with obesity and when oxidized stimulates the production of pro-inflammatory mediators, matrix degrading proteinases, and growth factors involved in OA pathogenesis (45). Furthermore, obesity and MetS also suppress the production of high-density lipoprotein (HDL) cholesterol, which exerts anti-inflammatory effects on macrophages through down-regulation of TLR-induced pro-inflammatory cytokines. Mouse models of dietary and genetic-induced hypercholesterolemia increase knee OA pathology, even without increasing body weight (46–50). Moreover, statin treatment diminished OA severity in these models, supporting a direct role for cholesterol homeostasis in OA pathogenesis [reviewed in (45)]. Recent evidence also shows a role for cholesterol homeostasis in chondrocyte hypertrophy through regulation of hedgehog signaling (51), indicating multiple potential pathways linking dyslipidemia and OA pathophysiology.

Infrapatellar fat pad as a local regulator of knee joint inflammation

Abdominal adipose tissue inflammation is a central feature of dysregulated metabolism that occurs with obesity. This finding has piqued interest in the infrapatellar fat pad (IFP) as a local paracrine mediator of knee joint inflammation and OA pathogenesis. Indeed, the IFP is a source of numerous soluble factors, including cytokines (eg, IL-1, IL-4, IL-5, IL-6, IL-8, IL-13, IFN γ , TNF), chemokines (eg, CCL2), adipokines (eg, leptin, adiponectin, adipisin, resistin, and visfatin/eNAMPT), growth factors (eg, basic fibroblast growth factor and vascular endothelial growth factor), free fatty acids, and lipid derivatives (eg, arachidonic acid and prostaglandin E₂) [reviewed in (6)]. These factors are derived from adipocytes as well as stromal cells, including resident and infiltrating macrophages and T cells present within the IFP.

The role of IFP-derived soluble factors in OA initiation and progression is unclear because the majority of studies have evaluated IFP cell populations and secreted factors in tissue harvested from joints with end-stage OA during joint replacement surgery. At this late stage of disease, the IFP contains more anti-inflammatory M2/CD206+ macrophages than pro-inflammatory M1/CD86+ macrophages and exerts an anti-catabolic effect on cartilage *in vitro* using IFP-conditioned medium (52). It is not known if these findings are unique to IFP tissue from end-stage OA joints or if these are general characteristics of IFP tissue.

Clinically, alterations in IFP magnetic resonance imaging signal intensity are significantly and positively associated with knee pain in cross-sectional and longitudinal analyses (53,54). Peripatellar synovitis scores are positively associated with synovial neovascularization, hyperplasia, and villi (55), and IFP-conditioned medium stimulates the expression of pro-inflammatory mediators and matrix metalloproteinases in autologous fibroblast-like synoviocytes, suggesting a role for the IFP in synovial inflammation (56). Surprisingly, though, IFP size is negatively associated with knee OA prevalence and risk of progression (57). These findings imply that a larger healthy IFP protects against OA, possibly by helping to better distribute joint biomechanical stresses (57). Alternatively, IFP size could be indirectly associated with knee OA risk.

In a recent analysis of the IFP in an aging rodent model of adult-onset obesity and knee OA (58), IFP mass significantly decreased with age despite increasing total body mass. This decrease occurred independent of changes in adipocyte size, suggesting that the reduction in fat pad size with age is due to an imbalance in the rates of adipogenesis and cell death. Although the basal expression of markers for adipogenesis did not change with age, they were significantly reduced with aging following IL-1 β stimulation, suggesting that inflammation negatively regulates IFP adipogenesis and potentially IFP size. In this model, aging increased the production of TNF and IL-13 and decreased the expression of anti-inflammatory M2 macrophage markers. Thus, joint inflammation may mediate the negative association between IFP size and OA risk. Intriguingly, IL-1 β inhibited leptin production in an age-dependent manner. This suggests that aging may protect against OA when joint inflammation is elevated (eg, post injury) by downregulating IFP adipogenesis and adipocyte-derived inflammatory mediators such as leptin.

Although the clinical evidence is growing that links alterations in IFP size or quality to OA risk and pain, the mechanistic understanding of these relationships is poor. Additional studies are needed at the early stages of disease to better evaluate the cause-effect relationship between IFP inflammation, size, and OA pathogenesis. Testing in multiple pre-clinical models of OA (eg, post-traumatic, diet-induced obesity, aging, genetic) will help to identify shared and unique mediators of IFP remodeling and inflammation by OA sub-type. Furthermore, the IFP is highly innervated with nociceptive fibers, and little is known about how changes in IFP remodeling and inflammation regulate OA pain and joint function.

Energy and nutrient sensors, metabolic syndrome, and OA

Evolutionarily conserved cellular energy and nutrient sensors, such as AMP-activated protein kinase (AMPK), sirtuins (SIRT6), and mammalian target of rapamycin (mTOR),

determine how cells respond to excess or insufficient nutrients and changes in cellular energy balance. With the development of obesity or MetS—conditions of chronic excess nutrients—these sensors become impaired and further contribute to MetS, including abdominal adiposity, diabetes, and dyslipidemia (59–62). These changes include a decrease in AMPK and sirtuin activities and an increase in mTOR activity. Understanding how obesity and conditions that contribute to MetS also lead to aberrant AMPK, SIRT, and mTOR function provide potential clues into how metabolic derangements increase OA.

AMPK is a serine/threonine protein kinase that exists as a heterotrimeric complex consisting of a catalytic α -subunit and two regulatory β - and γ -subunits (59). Phosphorylation of a conserved threonine residue within the activation loop of the kinase domain (Thr172) is required for the kinase activity of AMPK (59). AMPK is activated in response to decreases in cellular energy state by stimulating processes that generate ATP (e.g., fatty acid oxidation and glucose transport), and inhibiting others that consume ATP (e.g., fatty acid and protein synthesis) (59). In this manner, AMPK allows cells to adjust to changes in energy demand. Sirtuins, a conserved family composed of seven members (SIRT1–7), possess nicotinamide adenine dinucleotide (NAD⁺)-dependent protein deacetylase, deacylase, and ADP-ribosyltransferase activities (63). They guard against cellular metabolic stress by modifying the activity of metabolic enzymes and gene transcription to balance nutrient supply and demand (63). mTOR is a serine-threonine kinase that serves as a converging point for signals controlling cellular growth, energy metabolism, nutrient availability, and stress. The mTOR signaling pathway is frequently activated in various tissues during conditions of excessive nutrient intake (63). Chronic activation of mTOR signaling can lead to the development insulin resistance (63). These energy and nutrient sensors become dysfunctional when cells are exposed to obesity-associated metabolic derangements, such as high concentrations of blood glucose and fatty acids (e.g., palmitate), low-grade metabolic inflammatory mediators (e.g., TNF), and low concentrations of adiponectin (60,64).

Recent studies have implicated dysfunctional AMPK, sirtuin and mTOR activity in OA development and progression. Phosphorylation of AMPK α Thr172 is decreased in human knee OA chondrocytes/cartilage (65) and in mouse knee OA cartilage, compared with their respective normal counterparts (66). In addition, mouse knee cartilage exhibits an aging-associated reduction in phosphorylation of AMPK α (66). Moreover, *in vitro* studies demonstrate that the inflammatory cytokines IL-1 β and TNF α , as well as biomechanical injury, can cause de-phosphorylation of AMPK α in normal articular chondrocytes. This is correlated with increased catabolic responses (e.g. increased MMP-3 and MMP-13 release). All of these effects can be inhibited by AMPK pharmacological activators (65,66). Furthermore, recent *in vivo* studies show that activation of AMPK by berberine, a natural plant product that is known to activate AMPK, limits both surgical knee instability-induced and aging-related OA in mice (67). Collectively, sustained AMPK activity in articular chondrocytes appears to be chondroprotective.

Three members of sirtuins (SIRT1, SIRT3 and SIRT6) have been studied in articular chondrocytes. Among them, SIRT1 is best characterized so far. Similar to AMPK α phosphorylation, SIRT1 expression is decreased in both human and mouse knee OA cartilage and in aged mouse knee cartilage (68–70). Consequently, adult heterozygous *Sirt1*

mice and mice with a *Sirt1* point mutation lacking SIRT1 enzyme activity exhibit increased OA progression (71,72). Moreover, cartilage-specific *Sirt1* knockout (KO) mice develop accelerated OA progression (70). Sustained SIRT1 expression and activity in articular chondrocytes also appears to be important for cartilage homeostasis. Indeed, SIRT1 promotes cartilage-specific gene expression (73), and activation of SIRT1 in a mouse OA model using an intra-articular injection of resveratrol significantly reduced cartilage destruction (74). Cartilage SIRT3 expression was recently shown to also decrease with age, and SIRT3 deficiency increases acetylation of the antioxidant enzyme SOD2 resulting in impaired SOD2 activity in chondrocytes (75). In addition, whole-body deletion of SIRT3 accelerates the development of knee OA (75). Expression of SIRT6 is significantly decreased in human OA chondrocytes as well (76). Depletion of SIRT6 in human chondrocytes causes increased DNA damage, telomere dysfunction, and premature senescence, which are processes implicated in cartilage degeneration in OA (77).

Activation of AMPK stimulates the expression and activity of SIRT1 in articular chondrocytes (78). Activated AMPK-SIRT1 signaling increases cellular stress resistance through downstream targets peroxisome proliferator-activated receptor γ co-activator 1 α (PGC-1 α , a master regulator of mitochondrial biogenesis and function) and forkhead box O 3a (FOXO3a, a transcription factor that regulates oxidative stress response). In this context, mitochondrial function is preserved and excessive oxidative stress and inflammation-mediated matrix catabolism are inhibited (79,80). Activated AMPK also protects housekeeping cellular quality control in articular chondrocytes by limiting endoplasmic reticulum (ER) stress (81) and maintains autophagy capacity (82). Activation of AMPK can promote SIRT3 expression in articular chondrocytes as well (unpublished observation). Age-related loss of SIRT3 expression in cartilage may be a consequence of loss of AMPK activity. Loss of mitochondrial function is a hallmark of aging and age-related diseases, which is associated with reduced activity of AMPK and sirtuins (60,63). Since loss of SIRT3 activity results in profound aberrations in mitochondrial function (63), AMPK-SIRT3 signaling could play an important role in maintaining normal mitochondrial function in chondrocytes.

mTOR is a potent inhibitor of autophagy, which is a cellular degradative process that maintains fundamental biological activities during cellular stresses, especially nutrient starvation (60). Activation of AMPK and SIRT1 promotes autophagy by inhibiting activity of mTOR complex (e.g. mTORC1) and enhancing the later steps in autophagosome formation through deacetylation of several autophagy-related proteins, respectively (60). Chondrocyte autophagy is reduced with a linked increase in apoptosis in human knee OA, mouse knee OA, and aged mouse knee cartilage (83). In mice, cartilage-specific genetic deletion of mTOR (84) and pharmacologic inhibition of mTOR signaling by rapamycin (85) upregulate autophagy, which reduces the severity of post-traumatic OA.

Cellular energy and nutrient sensors, in particular AMPK and sirtuins (SIRTs), are potential mediators of the systemic (plasma) and local (synovial fluid) effects of adipokines on cartilage degeneration, osteophyte formation and synovial inflammation (86,87). AMPK and sirtuins regulate inflammatory responses, cartilage homeostasis, and bone metabolism [reviewed in (88)]. Since dysregulation of AMPK and sirtuins are seen in experimental

animal models of obesity and MetS, AMPK and sirtuins could be critical mediators in the cross talk between dysregulated metabolic tissues, such as adipose tissue, and joint tissues. A recent study showed significantly increased mRNA expression of inflammatory cytokines and adipokines, including TNF α , IL-6 and leptin, in the IFP of SIRT6 haploinsufficient (SIRT6^{+/-}) mice compared to WT mice (89). Following high-fat diet feeding, mRNA expression levels of all these cytokines were enhanced in WT and SIRT6^{+/-} mice, with IL-6 mRNA expression further enhanced in SIRT6^{+/-} mice (89). Moreover, SIRT6^{+/-} mice exhibited accelerated cartilage degradation when fed a normal diet, and they displayed greater osteophyte formation and synovial inflammation when fed a high-fat diet (89). These results suggest that impaired SIRT6 links metabolic dysfunction with multiple aspects of OA, including cartilage degradation, synovial inflammation, and bone remodeling. Further study is warranted to investigate how energy sensors in joint tissues become dysregulated in response to abnormal systemic and/or local metabolism associated with MetS.

AMPK, sirtuins and mTOR as therapeutic targets for OA

The pathways of AMPK, sirtuins and mTOR are tightly cross-linked and share many downstream targets that regulate cell processes involved in aging, including mitochondrial biogenesis, cellular metabolism, autophagy, and DNA repair (59). Increasing evidence indicates that aging, joint injury, low-grade inflammation, and possibly nutritional overload, obesity and MetS impair normal function of energy and nutrient sensors in articular cartilage. Reduced activities of AMPK and sirtuins and increased mTOR activity in articular chondrocytes trigger significant metabolic stress, manifested as mitochondrial dysfunction, oxidative stress, and inflammation. As a result, cell survival and tissue integrity and function are compromised, ultimately leading to OA development and progression (Figure 2). Interestingly, activation of AMPK and sirtuins and inhibition mTOR signaling are implicated in the beneficial effects of dietary restriction (90). In addition, some drugs already in the clinic (e.g. metformin for type 2 diabetes and methotrexate for rheumatoid arthritis), and some natural plant products used as dietary supplements (e.g. berberine, resveratrol) activate the AMPK/SIRT1 and/or AMPK/mTOR signaling pathways. As such, AMPK, sirtuins, and mTOR are potentially attractive and achievable therapeutic targets for OA. A systemic treatment (e.g. activation of AMPK) may be an effective means to combat both metabolic diseases and OA.

Conclusions

Exciting new discoveries are revealing a vast network of inter-connected pathways that regulate metabolism and inflammation. These pathways exist at the molecular level in the form of cellular energy sensors (e.g. AMPK, sirtuins, mTOR) that regulate enzyme activity, gene transcription, and proteostasis to coordinate cell survival mechanisms. They also exist at the cellular level, where changes in energy metabolism and nutrient utilization impact the activation and resolution of inflammation via effects on both immune and non-immune cells. At the organismal level, excess caloric intake, increased saturated and n-6 dietary fat, and insufficient metabolic energy expenditure can impair organ and tissue function, resulting in systems-level dysfunction (e.g. diabetes) and pathologic paracrine or endocrine pro-inflammatory signaling (e.g. intestinal or adipose-tissue derived inflammatory mediators).

The increasingly recognized role of inflammation in OA, together with the high comorbidity of obesity and OA, set an exciting new path for trying to understand how disrupted metabolic signaling in distant organs or in local articular tissues contribute to an increase in OA risk.

Current prospective epidemiological studies show clear associations between OA, the MetS, and its components, even when controlling for obesity in some studies. Animal models that recapitulate some aspects of the MetS also support a role for disrupted metabolic and inflammatory signaling in OA risk independent of obesity itself. Many questions remain, however, about the nature of these interactions. Despite a growing body of clinical evidence on sex-specific associations between components of the MetS and OA, few animal studies have tested sex-dependent outcomes in obese OA models. Additional questions remain about the relative role of systemic versus local factors in regulating articular joint tissue inflammation and metabolism. Therefore, we propose the following research agenda to address these questions and additional unmet needs to better understand how metabolic dysfunction mediates joint inflammation and the pathophysiology of OA.

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Research Agenda

- To design an epidemiological prospective study looking at the risk of hand OA in presence of MetS
- To design an epidemiological prospective study looking at the risk of knee/hip/hand OA in presence of hypertension
- To design studies and develop model systems evaluating sex-dependent differences in OA risk in the presence of MetS and its underlying components
- To design studies and develop model systems that isolate the effects of body weight, MetS components, and aging on tissue-specific cellular and molecular mediators of articular joint inflammation and metabolism
- To develop methods and model systems to evaluate *in vivo* cellular energy metabolism and metabolic signaling networks within and between articular joint tissues under physiologic and pathophysiologic conditions
- To design clinical and preclinical studies that test the efficacy of metabolic-based therapies (e.g., dietary, natural products, pharmaceutical) on OA risk in the presence of obesity and MetS

Figure 1. Cardiometabolic factors and associated mediators of increased OA pathophysiology

The clustering of cardiometabolic conditions that collectively increase the risk of heart disease, diabetes, and stroke are referred to as the Metabolic Syndrome (MetS). Emerging data indicate that the MetS also increases OA risk by impairing the regulation of numerous metabolic and inflammatory pathways, including adipose tissue inflammation, blood glucose and lipid homeostasis, and vascular inflammation. Dysregulation of these signaling pathways impact multiple articular joint tissues either directly or indirectly through disrupted tissue paracrine signaling and/or biomechanical function. The net result is an increase in synovial and intra-articular fat inflammation, impaired bone remodeling, and the suppression of cartilage anabolic activity in favor of catabolism.

Figure 2. AMPK and sirtuins as potential therapeutic targets for OA

Aging, joint injury, low-grade inflammation, and possibly altered metabolism resulted from nutritional overload, obesity or MetS impair activities energy sensors AMPK and sirtuins in articular cartilage. In turn, the dysregulated signaling of AMPK and/or sirtuins triggers significant chondrocyte stress by inducing mitochondrial dysfunction, oxidative stress, and inflammation and weakening cellular quality control that compromise cell survival and cartilage tissue integrity, ultimately leading to OA development and progression. However, targeted activation of AMPK and sirtuins potentially by dietary restriction, natural plant products used as dietary supplements (e.g. berberine, resveratrol), and drugs already in the clinic (e.g. metformin for type 2 diabetes, methotrexate for rheumatoid arthritis) could be an attractive therapeutic strategy for OA, particularly for those OA patients who also have MetS. Note: *predicted pathways.

Table 1
Prospective studies on the risk association of OA with metabolic syndrome and/or its components

	Participants	M/F	OA	follow-up (year)	Overweight	Diabetes	Hypertension	Dyslipidemia	Atherosclerosis	Results
Sowers (16)	482	0/482	K	10	Waist:hip ratio >0.81 cm	Self-reported DM OR medications OR glucose level >126mg/dL	SBP> 130mmHg Or DBP>85mmHg OR medication	HDL-C 45 mg/dl OR LDL-C> 160 mg/dl	ND	Prevalence: Nonobese women without cardiometabolic clustering (at least 2 metabolic parameters including CRP 2mg/dL) 4.7%, compared with 12.8% in obese women without cardiometabolic clustering and 23.2% in obese women with cardiometabolic clustering
Yoshimura (17)	1384	466/918	K	3	BMI > 25 kg/m ²	HbA1C> 5.5% Or medication	SBP 130mm Hg Or DBP 85mm Hg OR medication	HDL-C <40 mg/dL OR medication	ND	Occurrence: OR vs no component: one component, 2.33; two, 2.82; three, 9.83 Progression: OR vs no component: one component, 1.38; two, 2.29; three: 2.80).
Monira-Hussain (18)	1222	413/809	K H	6.8 SD=1.5	Waist circumference: Men: 94 cm Women: 80cm	Fasting glucose 5.6mmol/L OR history of type 2 diabetes	SBP 130mmHg Or DBP 85mmHg OR medication	Trigly 1.7mmol/L AND/OR Men: HDL-C <1.03 Women: <1.29mmol/L OR medication	ND	Central obesity (HR 1.59, 95% CI 1.25– 2.01) and hypertension (1.24, 1.05–1.48) associated with increased risk of knee OA. Risk of knee OA with accumulation of MetS components, independent of BMI: one component, 2.12 (1.15–3.91); two, 2.92 (1.60–5.33) and three or more,

	Participants	M/F	OA	follow-up (year)	Overweight	Diabetes	Hypertension	Dyslipidemia	Atherosclerosis	Results
										3.09 (1.68–5.69). No statistically significant associations for hip OA.
Schett (19)	927	431/427	K H	20 years Follow-up	ND	Fasting glucose 7 mmol/L Or medication	ND	ND	ND	Risk for arthroplasty with type 2 diabetes : HR (95%CI), 2.1 (1.1–3.8) after adjustment for age, BMI, and other risk factors for OA
Davies-Tuck (20)	148	0/176	K	2.2 SD=0.12	ND	ND	ND	ND	ND	Risk for incident BML associated with higher levels of total cholesterol (OR 1.84, 95% CI 1.01–3.36) and triglycerides (OR 8.4, 95% CI 1.63–43.43), but not HDL, LDL or total cholesterol/HDL ratio.
Hoeven (21)	3465	1501/1964	K	4.5 SD =0.5	ND	ND	SBP 140mmHg Or DBP 90mmHg Or medication	ND	CD40L, VCAM-1, VEGF, CAC	CD40L and VCAM-1 higher in women with knee OA compared with those without knee OA.
Engstrom (13)	209	70/139	K H	12.4	Waist circumference: Men: 102 cm Women: 88cm	Fasting glucose 5.6 mmol/L	SBP> 130mm Hg Or DBP>85mm Hg Or medication	Trigly 1.7 mmol/L Or medication	ND	MetS associated with increased risk of knee OA (RR: 2.1, 95% CI 1.3–3.3) After adjustment for age, sex, smoking, physical activity and CRP but non-significant after adjustment for BMI (RR: 1.1, 95% CI 0.7–1.8). MetS not associated with incidence of hip OA. In women, CRP associated with knee OA in the age-adjusted analysis

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	Participants	M/F	OA	follow-up (year)	Overweight	Diabetes	Hypertension	Dyslipidemia	Atherosclerosis	Results
										but no significant relationship between CRP and incidence of knee or hip OA after risk factor adjustments

OA: osteoarthritis; BMI: Body Mass Index; DM: diabetes mellitus; SBP: systolic blood pressure; DBP: diastolic blood pressure; trigly: triglycerides; HDL-C: HDL cholesterol; LDL-C: LDL cholesterol; CAC: coronary artery calcification; BML: bone marrow lesions; OR: odds ratio; HR: hazard ratio; CI: confidence interval; MetS: metabolic syndrome; RR: relative risk; SD: standard deviation;

Table 2
Obese rodent models of spontaneous and induced OA and Metabolic Syndrome-related outcomes

Species (Sex)	Obesity-related manipulation	OA model	OA phenotype(s)	OA & MetS-related outcomes	Ref.
Rat (M)	Dietary (high fat, sucrose) Fat source: Soybean oil, lard	Spontaneous	Cartilage pathology, synovial fluid inflammation	Body fat; serum cytokines and adipokines	(42)
Rat (M)	Spontaneous (adult-onset) Fat source: Soybean oil, fish meal	Spontaneous	Cartilage and meniscus pathology, synovial thickening	Infra-patellar fat pad cytokines and adipokines	(75)
Mouse (F)	Dietary (high fat) Fat source: Soybean oil, lard	Spontaneous	Cartilage pathology	Body fat; serum cytokines and adipokines	(30)
Mouse (M)	Dietary (high fat, sucrose) Fat source: Safflower oil, beef tallow	Spontaneous	Cartilage pathology, osteophytes, synovial thickening	Infra-patellar fat pad cytokines; xanthine oxidoreductase inhibition	(91)
Mouse (M)	Dietary (very high fat) Fat source: Soybean oil, lard	Spontaneous	Cartilage pathology, subchondral bone thickness	Glucose intolerance; serum cytokines and adipokines	(31)
Mouse (M)	Dietary (very high fat) Fat source: Soybean oil, lard	Spontaneous	Osteophytes, synovial inflammation	Glucose intolerance; systemic and synovial TNF	(34)
Mouse (M/F)	Genetic (<i>H-CRP</i>) and dietary (high fat, sucrose) Fat source: Soybean oil, lard	Spontaneous	Cartilage pathology (male only)	Serum CRP, statin treatment (protective)	(46)
Mouse (M)	Genetic (<i>Lcat^{-/-}</i> , <i>ApoA-I^{-/-}</i>) and dietary (high fat, sucrose) Fat source: Milk fat	Spontaneous	Cartilage pathology	Serum dyslipidemia	(47)
Mouse (F)	Genetic (<i>APOE*3Leiden.CETP</i>) and dietary (cholesterol supp.)	Spontaneous	Cartilage pathology	Serum dyslipidemia, serum E-selectin, statin treatment (protective)	(49)
Mouse (M)	Dietary (very high fat) Fat source: Soybean oil, lard	PTOA (Intra-articular fracture)	Cartilage pathology, synovial inflammation, reduced cancellous bone fraction	Body fat; serum cytokines and adipokines	(33)
Mouse (M)	Dietary (very high fat) Fat source: Soybean oil, lard	PTOA (Meniscus- ligament injury)	Cartilage pathology, osteophytes	Glucose intolerance	(92)
Mouse (M)	Dietary (very high fat, varied type) Fat source: varied (Soybean, safflower, olive, coconut, menhaden, and lard)	PTOA (Medial meniscus destabilization)	Cartilage pathology, synovial inflammation, heterotopic ossification, altered cancellous bone fraction	Body fat; dietary fatty acid composition (saturated and ω -6 fatty acids); serum adipokines; hyperinsulinemia	(38)
Mouse (F)	Genetic (<i>Ldlr^{-/-}</i>) and dietary (cholesterol supp.)	Intra-articular collagenase	Osteophytes, heterotopic ossification, synovial inflammation	Serum dyslipidemia	(48)
Mouse (F)	Genetic (<i>ApoE^{-/-}</i> , <i>S100a9^{-/-}</i>) and dietary (cholesterol supp.)	Intra-articular collagenase	Osteophytes, heterotopic ossification, synovial inflammation	Serum dyslipidemia	(50)

M = male; F = female; PTOA = Post-traumatic osteoarthritis; MetS = Metabolic Syndrome; supp. = supplement.