The role of metabolism in the pathogenesis of osteoarthritis

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Abstract | Metabolism is important for cartilage and synovial joint function. Under adverse microenvironmental conditions, mammalian cells undergo a switch in cell metabolism from a resting regulatory state to a highly metabolically activate state to maintain energy homeostasis. This phenomenon also leads to an increase in metabolic intermediates for the biosynthesis of inflammatory and degradative proteins, which in turn activate key transcription factors and inflammatory signalling pathways involved in catabolic processes, and the persistent perpetuation of drivers of pathogenesis. In the past few years, several studies have demonstrated that metabolism has a key role in inflammatory joint diseases. In particular, metabolism is drastically altered in osteoarthritis (OA) and aberrant immunometabolism may be a key feature of many phenotypes of OA. This Review focuses on aberrant metabolism in the pathogenesis of OA, summarizing the current state of knowledge on the role of impaired metabolism in the cells of the osteoarthritic joint. We also highlight areas for future research, such as the potential to target metabolic pathways and mediators therapeutically.

Immunometabolism is an emerging field at the interface of immunology and metabolism, which, historically, have been considered distinct disciplines[1,2]. Focusing on changes in the intracellular metabolic pathways of immune cells, and how these alterations modulate cellular function[3], immunometabolism highlights the key role of metabolic reprogramming within the immune system in the pathogenesis and progression of chronic inflammatory diseases. Evidence suggests that six major metabolic pathways are involved in immunometabolism, including glycolysis, the tricarboxylic acid (TCA) cycle, the pentose phosphate pathway (PPP), fatty acid oxidation, fatty acid synthesis and amino acid metabolism[3]. Changes in the levels of metabolites in these pathways act as important metabolic switches with the capacity to shape the ways in which immune cells respond to their environment.

Interest in this new field of research is steadily gaining momentum owing to the discovery that underlying metabolic disturbances in obesity-induced inflammation, insulin resistance and type 2 diabetes mellitus have the potential to promote a variety of chronic diseases and comorbidities[1,4]. Inflammatory diseases, including osteoarthritis (OA) (which is now appreciated to involve low-grade inflammation), are associated with a sedentary lifestyle, physical inactivity, obesity and inflammaging; in OA, poor diet, obesity and physical inactivity directly contribute to metabolic changes that promote inflammaging and cellular senescence[5,6] (FIG. 1). According to the immunometabolic hypothesis, aberrant metabolism, inflammatory mediators and disturbed circadian rhythms and biological clocks are intimately involved in many inflammatory responses[7]. The ability to control and manipulate cellular metabolism could, therefore, lead to new approaches for treating inflammatory diseases.

Evidence is emerging for a key role for metabolism in the regulation of inflammatory responses and immune cell function, with different immune cells showing distinct metabolic signatures that regulate their biological responses[8]. However, the same principle can also be applied to many non-immune cell types. Under adverse conditions, most mammalian cells undergo a shift in energy metabolism from a resting regulatory state to a highly metabolically active state to maintain energy homeostasis and promote cell survival[9]. This metabolic shift normally occurs when oxygen levels are low, limiting the metabolism of pyruvate by the tricarboxylic acid cycle in mitochondria during oxidative phosphorylation. However, in some instances this shift can occur under aerobic conditions (known as the Warburg effect), as in cancer and many degenerative and inflammatory conditions, and represents a potential threat to cell function and survival. Such a metabolic shift is now believed to occur in the articular cartilage, subchondral bone and synovium of the joints of patients with OA, influencing

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Key points

- Metabolism has a key role in the physiological turnover of synovial joint tissues, including articular cartilage
- In osteoarthritis (OA), chondrocytes and cells in joint tissues other than cartilage undergo metabolic alterations and shift from a resting regulatory state to a highly metabolically active state
- Inflammatory mediators, metabolic intermediates and immune cells influence cellular responses in the pathophysiology of OA
- Key metabolic pathways and mediators might be targets of future therapies for OA

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the metabolic behaviour of chondrocytes, synoviocytes and bone cells, as well as their interactions with the immune system through synovial macrophages[10]. There is also increasing and overwhelming evidence to suggest that OA is a metabolic disorder[11–13]. In this Review, we focus on aberrant metabolism in OA, summarizing the current state of knowledge in this area by focusing on metabolic aspects of synovial joint tissue and cell function, and examining the evidence for deregulated metabolism in chondrocytes and synoviocytes in OA. We also propose priority areas for future research, in particular metabolic pathways in synovial fibroblasts and activated macrophages, about which little is currently known.

OA as a metabolic disorder

OA, an age-related low-grade inflammatory disease of the synovial joints[14,15], is one of the most costly and disabling forms of arthritis, being more prevalent than rheumatoid arthritis (RA) or other arthritic diseases and representing a major public health burden[16]. OA is characterized by the progressive deterioration of articular cartilage and structural changes to the entire synovial joint, including the synovium[17], meniscus (in the knee)[18], periarticular ligaments[19], adipose tissue (for example, the infrapatellar fat pad in the knee)[20] and subchondral bone[21]. These deleterious structural changes in articular tissues impair the functional integrity of the synovial joint[22], adversely affecting its biomechanics and attenuating its already limited inherent capacity for repair and regeneration[23]. Although OA was historically viewed as a 'wear and tear' disease, it is now generally accepted to be a low-grade inflammatory disease[24,25] affecting the whole joint[11,15,26,27]. The pathogenesis and progression of OA seem to be the result of the complex and dynamic interplay of mechanical, cellular and systemic molecular factors[26]. Many of the biochemical mediators involved in OA have important systemic and immunoregulatory roles[28], including several complement proteins that are implicated in low-grade inflammation[25], providing new evidence for key molecular and metabolic factors as drivers of OA.

Notably, OA is not a homogeneous disease but is in fact highly heterogeneous, characterized by a number of different phenotypes (including a distinct metabolic phenotype), each of which is thought to have different drivers (FIG. 2). The various phenotypes of OA have important differences, but are likely to share key elements such as ageing, biomechanical factors and metabolic alterations. Although this idea complicates traditional approaches for developing new treatments, it also presents opportunities for developing therapies targeted to each phenotype.

Preclinical research in animal models of OA and clinical studies in patients with OA have shown that age[14], obesity[29] and metabolic syndrome[30] are major risk factors for the development of OA[11,31]. Obesity is the strongest risk factor for disease onset in the knee[32], and mechanical factors (such as ambulatory load) dominate the risk for disease progression[26,33]. However, the fact that obese individuals have an increased risk of developing OA in non-weight-bearing joints such as the hands and wrists[34] suggests that factors produced by white adipose tissue (WAT) might have a role in the onset and/or progression of OA. Increased adiposity and dysfunction of WAT is closely related to the chronic low-grade inflammatory status that is a systemic feature of both obesity and OA[35–37]. A consequence of this dysfunction is that WAT adopts an atherogenic, diabetogenic and inflammatory profile, producing proinflammatory factors (known as adipokines) that promote inflammation and the degradation of cartilage and thus affect the whole joint microenvironment[38], including the activity of immune cells in patients with OA[39]. Accumulating evidence also points to the infrapatellar fat pad as another potential source of proinflammatory adipokines in the joint[20]. Chondrocytes, synoviocytes, adipocytes, macrophages and other types of cell in the fat pad are likely to collectively contribute to the production of proinflammatory cytokines and chemokines. Therefore, tackling obesity[29] and the underlying causes of metabolic syndrome[30] through lifestyle changes (such as improved diet, increased physical activity and weight loss) has been proposed as a realistic and achievable approach for preventing OA and thus reducing its burden on society. However, a greater understanding of the important roles of biomechanical factors, joint injury, obesity and metabolic syndrome in the pathogenesis of OA is required to reduce the effect of this disease on public health.

Glycolysis
An oxygen-independent metabolic pathway that generates two molecules of pyruvate, ATP and NADH from every one molecule of glucose, supporting the tricarboxylic acid cycle and providing intermediates for the pentose phosphate pathway, glycosylation reactions and the synthesis of biomolecules (including serine, glycine, alanine and acetyl-CoA).

Tricarboxylic acid (TCA) cycle
(Also known as the Krebs cycle) A set of connected pathways in the mitochondrial matrix, which metabolize acetyl-CoA derived from glycolysis or fatty acid oxidation, producing NADH and $FADH_2$ for the electron transport chain and precursors for amino acid and fatty acid synthesis.

Metabolism in articular cartilage

Articular cartilage is hypocellular, avascular, aneural and alymphatic[40]. Despite its hypocellularity, cartilage is a metabolically active connective tissue with reduced access to oxygen and glucose compared with synovial fluid and plasma[41], producing an environment that presents its few resident cells with a number of metabolic challenges. Consequently, the turnover of extracellular matrix (ECM) molecules in mature skeletal cartilage is extremely slow. For example, the turnover of proteoglycans (such as aggrecan) can take up to 25 years[42] and the half-life of type II collagen, the major fibrillary collagen in cartilage, is between 100 and 400 years[43,44]. Therefore, healthy cartilage with optimal ECM function requires the maintenance of a delicate balance between anabolic and catabolic activities, which is critical for long-term tissue integrity and the capacity for cartilage to repair itself[45].

Glucose is an important metabolic fuel and structural precursor in cartilage, being vital for ECM synthesis and degradation[46]. It serves as a major energy substrate as well as being the main precursor for the synthesis of glycosaminoglycans in chondrocytes[47] (FIG. 3). Facilitated glucose transport therefore represents the first rate-limiting step of glucose metabolism in chondrocytes[48], which express several glucose transporter isoforms, some of which are regulated by hypoxia and proinflammatory cytokines[41,48]. Once glucose is transported into chondrocytes, it is metabolized via glycolysis and the TCA cycle or used as a structural component for the synthesis of glycoproteins. Under normal regulatory homeostatic conditions and physiological normoxia (such as the oxygen environment in healthy cartilage), one molecule of glucose is oxidized by glycolysis, generating two molecules of pyruvate, which enter the mitochondria. Pyruvate is then decarboxylated by pyruvate dehydrogenase and enters the TCA cycle, producing $FADH_2$ and NADH, which donate electrons to the electron transport chain to generate 36 molecules of ATP per molecule of glucose by oxidative phosphorylation. Although chondrocytes rely primarily on glycolysis to meet their cellular energy requirements, they possess the metabolic flexibility to promote cell survival and support ECM biosynthesis during periods of nutrient stress by enhancing glycolysis and mitochondrial respiration through the TCA cycle[49]. Optimal mitochondrial function is therefore important for supporting the TCA cycle in healthy chondrocytes, and impaired mitochondrial function is implicated in OA pathogenesis[49].

Altered metabolism in OA

In pathophysiological situations such as OA, cellular metabolism is compromised and there is an increase in the production of antianabolic, procatabolic and proinflammatory factors[14]. The switch in metabolism that occurs to compensate for this compromised situation enables anabolic processes such as cell proliferation, protein biosynthesis, antigen presentation and phagocytosis still to occur in immune cells[3]. These anabolic processes equate to cell proliferation and protein biosynthesis in a variety of other cell types, including chondrocytes and other cells of the synovial joint. Indeed, emerging evidence suggests that in chondrocytes from patients with OA, proinflammatory pathways rely on energy generated by a metabolic switch from oxidative phosphorylation to glycolysis[50].

In healthy articular cartilage, chondrocytes have the metabolic flexibility to generate energy and promote cell survival during periods of acute nutrient stress by upregulating mitochondrial respiration and reducing the rate of reactive nitrogen and oxygen species production[49]. The metabolic adaptation of OA articular cartilage to new environmental conditions is evident in the early stages of the disease, when attempts to repair and regenerate the cartilage matrix have an increased likelihood of success[51]. However, cartilage from patients with OA at a later stage of disease does not seem to have this metabolic flexibility[51].

Cartilage and chondrocytes

The metabolic demands of fully differentiated and quiescent chondrocytes are very different from chondrocytes in an inflammatory microenvironment. Chondrocytes are highly glycolytic cells, which, like cancer cells, exhibit the 'Warburg effect' (also known as aerobic glycolysis)[52,53]. We do not yet understand the full molecular composition of the 'surfaceome' and 'membranome' of chondrocytes,

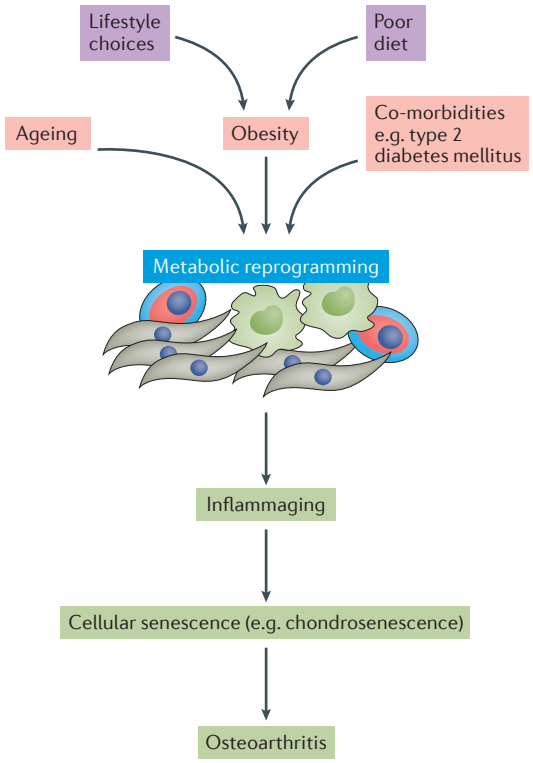

Figure 1 | **Factors underlying metabolic alterations in osteoarthritis.** Poor diet and lifestyle choices can contribute to weight gain and lead to obesity. Ageing, obesity and other co-morbidities associated with osteoarthritis (OA) contribute to metabolic reprogramming in a variety of cells and tissues, leading to inflammaging and cellular senescence, which in turn cause further changes in cellular metabolism in OA.

Pentose phosphate pathway
(PPP). An anabolic metabolic pathway parallel to glycolysis that branches out from glycolysis with the conversion of glucose-6-phosphate to ribose 5-phosphate and generates the reducing equivalents NADPH, ribose-5-phosphate (used in the synthesis of nucleotides and nucleic acids) and erythrose-4-phosphophosphate (used in the synthesis of amino acids).

Fatty acid oxidation
A metabolic process that produces ATP from the oxidation of acetyl-CoA derived from the mobilization of fatty acids.

Inflammaging
The low-grade proinflammatory phenotype that accompanies ageing.

Warburg effect
The high utilization of glycolysis by rapidly proliferating cells and the subsequent release of lactate into the extracellular milieu; a phenomenon first described by Otto Warburg.

Metabolic syndrome
The collective term used to describe the combination of type 2 diabetes mellitus, high blood pressure, dyslipidemia and obesity.

Electron transport chain
A series of proteins in the inner mitochondrial membrane that transfer electrons from one to the other in a series of redox reactions, resulting in the movement of protons out of the mitochondrial matrix and in the synthesis of ATP.

Oxidative phosphorylation
A metabolic pathway that produces ATP from the oxidation of acetyl-CoA and the transfer of electrons to the electron transport chain via NADH and $FADH_2$.

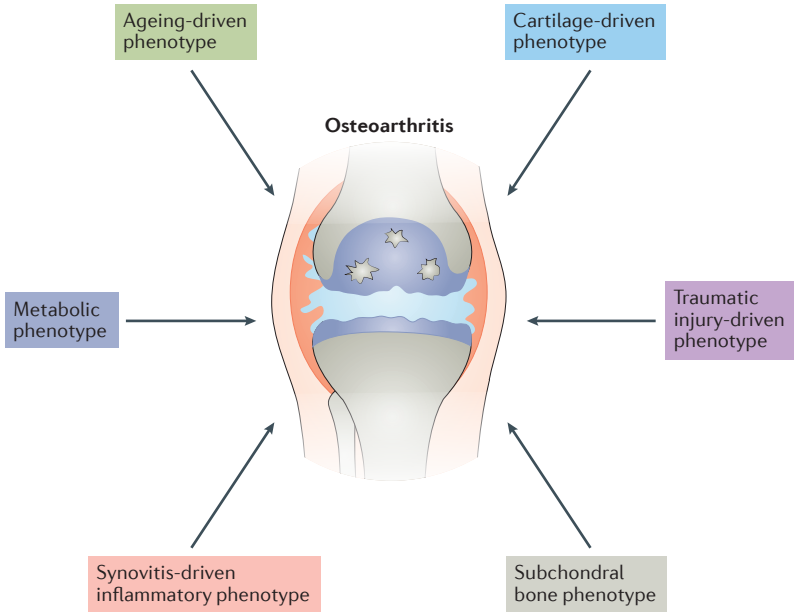

Figure 2 | **Phenotypes of osteoarthritis.** Evidence suggests that patients with osteoarthritis (OA) fall into multiple phenotypic subgroups defined on the basis of the main driver of disease, one of which is a distinct metabolic phenotype, although all OA phenotypes probably involve metabolic alterations. Cartilage, bone and synovium are all affected by external and internal drivers of disease such as inflammation, injury or biomechanical alterations, metabolic reprogramming and immunomodulation, but different synovial joint tissues dominate the disease in different patients with OA.

but proteomic studies have revealed that metabolic adaptation of chondrocytes to an inflammatory microenvironment has a direct effect on the composition of membrane proteins in these cells (A.M., unpublished data). Chondrocytes are also able to sense the concentrations of oxygen and glucose in the ECM and respond appropriately by adjusting their cellular metabolism, thus becoming glycolytic during periods of acute nutrient and oxygen stress[41].

Glycolytic pathways. The metabolic switch in activated chondrocytes means that these cells derive ATP from glycolysis, diverting pyruvate away from oxidative phosphorylation and thereby enabling ATP generation during periods of low oxygen availability (FIG. 4). Chondrocytes express the glucose transporter GLUT1 (REF. 54), which is upregulated in response to hypoxia[55], thus increasing their ability to take up glucose in low oxygen conditions. Levels of glucose-6-phosphate dehydrogenase are also increased in cartilage explants exposed to oxidative damage[56], indicating increased glycolytic activity. Anaerobic glycolysis occurs at an increased rate in chondrocytes in OA[57]; lactate dehydrogenase converts two pyruvate molecules into lactate in the cytosol, generating two molecules of ATP (instead of the 36 molecules generated by oxidative phosphorylation) and leading to an accumulation of lactate, further reducing the pH of an already acidic microenvironment[58]. Profound ATP depletion in chondrocytes is associated with increased production of nitric oxide (NO) in the osteoarthritic joint[49]. Consequently, activity of ectonucleotide pyrophosphatase/phosphodiesterase family member 1 (an ATP scavenger) increases, causing a subsequent increase in extracellular levels of inorganic pyrophosphate. This increase in inorganic pyrophosphate might in turn stimulate chondrocalcinosis, eventually leading to matrix calcification (an important contributor to OA progression[59]). It should be noted, however, that the ubiquitous presence of calcification in patients with OA identified in a CT imaging study[60] has raised questions over the appropriateness of the term 'chondrocalcinosis'.

Mitochondria and oxidative stress. Mitochondria are the powerhouses of the cell, providing energy in the form of ATP for a range of activities including movement, cellular differentiation, cell death, regulation of signalling and control of the cell cycle[61]. Furthermore, mitochondria serve as molecular platforms integrating multiple innate immune signalling pathways[62]. However, in degenerative conditions (such as OA), alterations occur in mitochondrial structure, dynamics and genome stability, resulting in reduced mitochondrial respiration and excessive production of reactive oxygen species (ROS) leading to oxidative damage. Mitochondrial dysfunction and oxidative stress are hallmarks of OA[63], with increased mitochondrial DNA (mtDNA) damage being seen in chondrocytes from patients with OA compared with chondrocytes from healthy individuals[64]. This damage in chondrocytes from patients with OA is accompanied by a reduced capacity for mtDNA repair and an increased rate of apoptosis[64].

Alterations in mitochondrial membrane potential are observed in chondrocytes from patients with OA[65]. Analysis of mitochondrial electron transport chain activity in chondrocytes from patients with OA has shown a decrease in complexes II and III compared with chondrocytes from healthy individuals, along with a reduction in mitochondrial membrane potential[57] (maintenance of mitochondrial membrane potential is essential to driving ATP synthesis by oxidative phosphorylation). Although most ATP in chondrocytes in OA comes from glycolysis rather than oxidative phosphorylation[66], mitochondrial ROS help to maintain the cellular redox balance in favour of glycolysis[67]. Treatment of chondrocytes from patients with OA with 4-hydroxynonenal (4HNE) (an end-product of lipid peroxidation and a second messenger in oxidative stress) results in the depletion of ATP, NADPH and glutathione and the inhibition of glucose uptake and TCA cycle activity[68]. Additionally, inhibition of complexes III and V of the electron transport chain modulates the expression of matrix metalloproteinases (MMPs) in chondrocytes and proteoglycan levels in cartilage[69]. Therefore, the loss of energy reserves within chondrocytes coupled with a shift in metabolic pathways towards glycolysis contributes to the impaired ECM synthetic function, anabolism and reduced viability seen in chondrocytes in OA[69,70]. Furthermore, NADPH oxidase 4 is increased in chondrocytes from patients with OA and can modulate matrix degrading enzymes

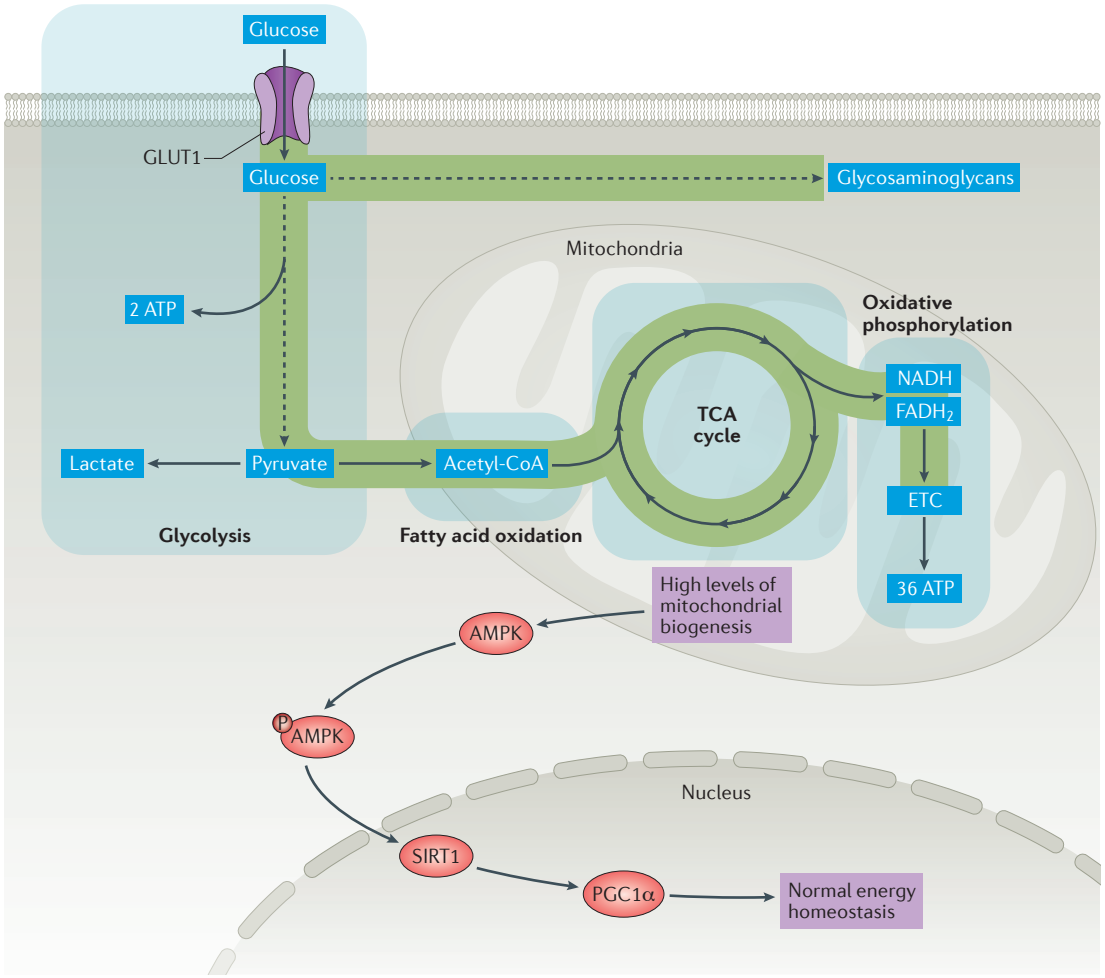

Figure 3 | **Metabolism in homeostatic chondrocytes.** In healthy joints, chondrocytes utilize glucose as well as other metabolic fuels and sources of energy. Glucose utilization via glycolysis and oxidative phosphorylation helps to maintain an optimal level of mitochondrial function and biogenesis. The metabolism of healthy chondrocytes is therefore optimized to maintain normal energy homeostasis via signalling through the AMPK–SIRT1–PGC1α pathway. AMPK, AMP-activated protein kinase; ETC, electron transport chain; GLUT1, glucose transporter type 1; PGC1α, peroxisome proliferator-activated receptor γ co-activator 1α; ROS, reactive oxygen species; SIRT1, NAD-dependent protein deacetylase sirtuin-1; TCA, tricarboxylic acid.

such as MMPs and the a disintegrin and metalloproteinase with thrombospondin motif (ADAMTS) family of proteins by inducing ROS production[71].

Oxidative stress mediated by ROS and NO also has an important role in metabolic dysregulation within the osteoarthritic joint[72–74]. NO production is elevated in human OA, animal models of spontaneous OA, animal models of experimentally-induced OA and in cytokine-treated or activated chondrocytes[75–77]. Furthermore, inducible nitric oxide synthase (iNOS) is present in both the synovium and cartilage, and its expression has been observed in degenerating regions of OA cartilage[76,77]. NO and other ROS are involved in the accumulation of mtDNA damage following exposure to cytokines; the mitochondria-targeted DNA repair enzyme hOGG1 was able to rescue mtDNA integrity, preserve ATP levels, re-establish mitochondrial transcription and diminish apoptosis in chondrocytes following exposure to IL-1β and TNF[78]. Studies in Kashin–Beck disease (KBD), a chronic and endemic osteochondropathy prevalent mainly in Tibet and China, have also increased our understanding of the role of metabolism in osteoarticular disease. In KBD, chondrocytes exhibit increased numbers of de-energized mitochondria, a reduction in cellular ATP levels and an increase in mitochondrial mass, release of cytochrome *c* (a key component of the electron transport chain in mitochondria) and activation of caspase 9 and caspase 3, leading ultimately to cell apoptosis[79]. Markers of oxidative stress are also higher in cartilage from patients with KBD than in cartilage from healthy individuals[80].

Increased levels of lipid peroxidation, as found in the osteoarthritic joint, also lead to an increase in breaks in mtDNA in chondrocytes from patients with OA, which in turn affects the telomeric DNA and replicative lifespan of chondrocytes, as well as the subsequent integrity of proteoglycans in osteoarthritic cartilage[45,81]. The adverse microenvironment of the osteoarthritic joint leads to the

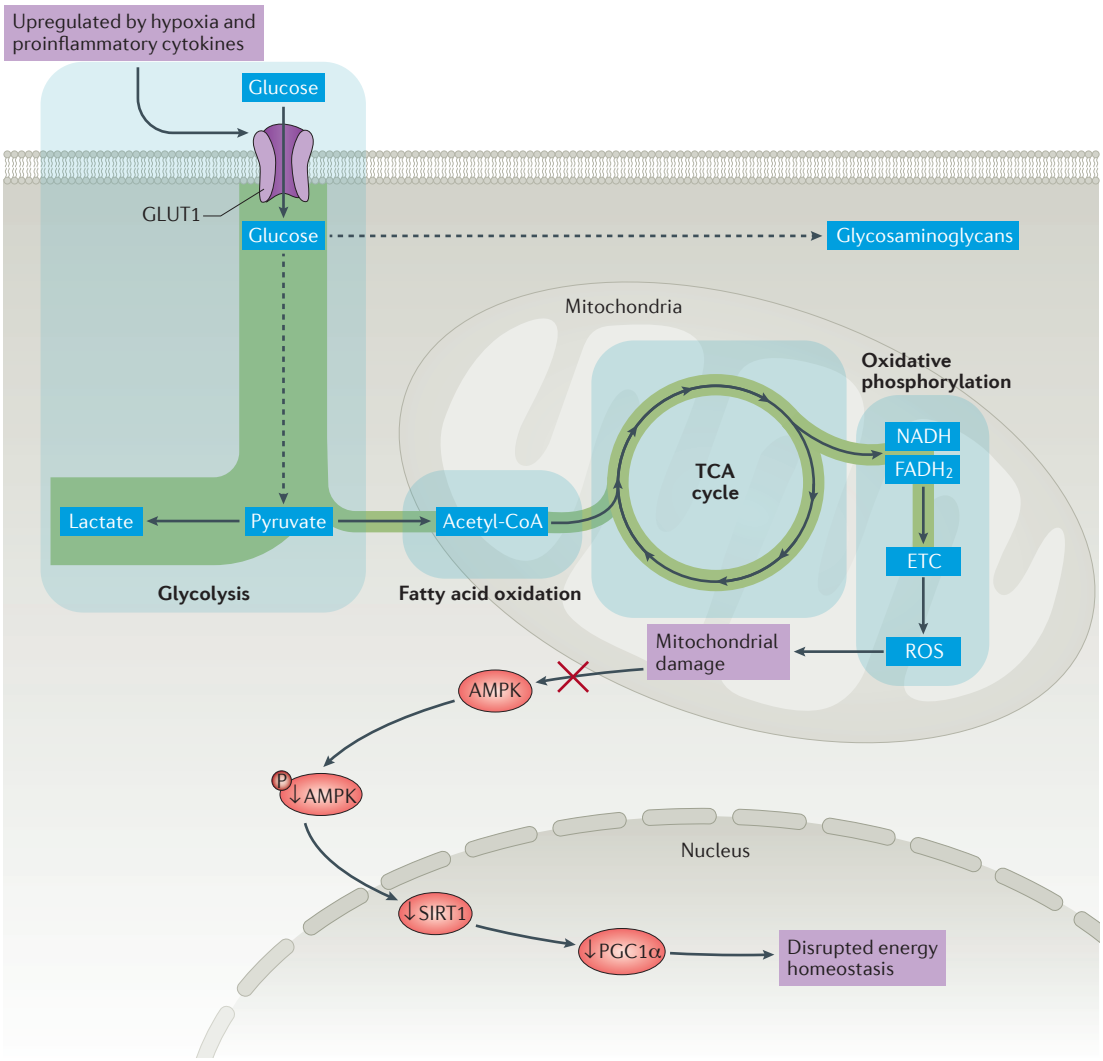

Figure 4 | **Altered metabolism in chondrocytes in osteoarthritis.** Chondrocytes in osteoarthritis (OA) switch from oxidative phosphorylation to glycolysis as their main source of energy metabolism. In osteoarthritic joints, chondrocytes are exposed to proinflammatory cytokines and microenvironmental alterations, including hypoxia and nutrient stress. Mitochondrial metabolism is impaired and reactive oxygen species (ROS) accumulate, causing damage to mitochondria which inhibits AMPK signalling and activity, downregulate SIRT1 and decrease levels of PGC1α, the master regulator of mitochondrial biogenesis. AMPK, AMP-activated protein kinase; ETC, electron transport chain; GLUT1, glucose transporter type 1; PGC1α, peroxisome proliferator-activated receptor γ co-activator 1α; SIRT1, NAD-dependent protein deacetylase sirtuin-1; TCA, tricarboxylic acid.

increased generation of ROS and NO by chondrocytes[82] (and synoviocytes[83]), inducing more mtDNA damage and suppressing mitochondrial oxidative phosphorylation[69,84,85], acting as a feed-forward loop. These changes increase the production of MMPs[85–87] and can enhance the responsiveness of chondrocytes to cytokine-induced inflammation through nuclear factor-κB activation[87]. ROS scavengers slow down cartilage loss in animal models of joint inflammation[88] and decrease levels of MMPs in chondrocytes[85,89].

Key regulators of metabolism. A key molecule associated with metabolism in chondrocytes is AMP-activated protein kinase (AMPK), which regulates energy metabolism through the downstream mediators, NAD-dependent protein deacetylase sirtuin-1 (SIRT1) and mechanistic target of rapamycin (mTOR). Depletion of AMPK in chondrocytes increases their catabolic response to proinflammatory cytokines[90]. A decreased capacity for mitochondrial biogenesis in chondrocytes is linked to reduced AMPK activity and decreased expression of SIRT1, peroxisome proliferator-activated receptor γ co-activator 1α (PGC1α; the so-called master regulator of mitochondrial biogenesis), TFAM (transcription factor A, mitochondrial), nuclear respiratory factor 1 (NRF1) and NRF2 (REF. 91). TFAM-mediated activation of the AMPK–SIRT1–PGC1α pathway increases mitochondrial biogenesis in chondrocytes, limiting OA progression[91]. Furthermore, deficiency in AMPK and SIRT1 modulates PGC1α activity, leading to reduced oxidative

stress and procatabolic responses in chondrocytes from patients with OA[91], and so potentially represents a mechanism to inhibit the progression of cartilage damage in OA[92]. Inhibition of SIRT1 results in increased procatabolic responses to IL-1β and TNF in chondrocytes from patients with OA[93,94]. Additionally, autophagy, which is known to have chrondroprotective effects but is defective in chondrocytes from patients with OA, is promoted by AMPK and SIRT1, resulting in the subsequent repair of damaged mitochondria[95].

In the destabilisation of medial meniscus (DMM) mouse model of OA, cartilage-specific deletion of mTOR upregulated autophagy and protected mice from disease[96], whereas aberrant mTOR signalling associated with peroxisome proliferator-activated receptor γ deficiency resulted in severe and accelerated OA[97]. Cell survival and matrix synthesis is suppressed in chondrocytes from patients with OA via microRNA 634 targeting of *PIK3R1*, thus modulating the PI3K–AKT–ribosomal protein S6 kinase (S6) and PI3K–AKT–mTOR–S6 signalling pathways[98]. Many other regulatory molecules are also implicated in chondrocyte physiology and pathophysiology and have links to metabolism[5,99–101], but the overt effects of activation and inhibition of these pathways on cellular metabolism are not yet understood.

Chondrosenescence. Once activated by stressors such as proinflammatory cytokines, prostaglandins and ROS, normally quiescent articular chondrocytes become activated and undergo a phenotypic shift through a phenomenon recently described as 'chondrosenescence', leading to further disruption of homeostasis and metabolism in cartilage[6]. The chondrosenescent phenotype is highly procatabolic and is intimately linked with a disturbed interplay between autophagy and inflammasomes[102], and with the development of a senescent secretory and inflammatory state[6]. The production and secretion of soluble and insoluble factors by senescent chondrocytes further contributes to the inflammatory microenvironment that is believed to drive the catabolic degradation of ECM macromolecules in articular cartilage. Furthermore, the secreted molecules, in particular NO, act as potent inducers of gene expression, further supporting the aberrant expression of proinflammatory and catabolic genes. These secreted molecules also suppress mitochondrial dysfunction and impair oxidative phosphorylation[103] which in turn can promote calcification of the ECM and formation of inflammatory hydroxyapatite crystals[69,84].

Synovium

In addition to cartilage, other joint tissues such as the synovial membrane[104,105], subchondral bone[106] and periarticular soft tissues[107] contribute to the disease process in OA. Inflammation of the synovium occurs in early and late phases of OA and is associated with degenerative alterations in cartilage[108]. This synovitis is qualitatively and histologically similar, but not identical, to that seen in patients with RA. Despite some similarities, there are important differences too; notably, the polymorphonuclear leukocytes that are prominent in synovitis in RA are absent in synovitis in OA[109]. Synovitis linked to the innate immune system[59] has a key role in OA pathogenesis and influences metabolism in joint tissues[108]. Catabolic and proinflammatory mediators produced by the inflamed synovium such as cytokines, ROS, NO, prostaglandin E_2 and neuropeptides alter cellular metabolism and the balance of cartilage matrix degradation and repair[110]. Synovitis seems to be a common feature of later stages of OA, which are characterized by infiltrating macrophages, T cells and mast cells and high levels of proinflammatory cytokines[111]. Inflammation of the synovium leads to increased production of the proteolytic enzymes responsible for cartilage breakdown[112]. Increased catabolism in cartilage releases molecules that induce further synovial inflammation, creating a feed-forward loop that exacerbates clinical symptoms and joint degradation in patients with OA[31]. Inflammatory mediators released by chondrocytes and synoviocytes also drive oxidative stress, causing damage to joint tissues via ROS[113].

Immune cells. Evidence for metabolic changes in immune cells in the inflamed osteoarthritic joint is scarce and indirect. There is evidence from metabolomics studies for metabolic changes in immune cells in OA. Metabolic profiling has identified changes in metabolites specific to collagen metabolism, branched-chain amino acid metabolism, energy metabolism and tryptophan metabolism in OA, suggesting that the metabolic state alters as the disease progresses[114]. Metabolomics is particularly well suited for OA research because of the tremendous heterogeneity in the disease process and recognition that no single biomarker can reflect the breadth of temporal and pathological processes involved.

Fibroblast-like synoviocytes. In contrast to the metabolic profile of chondrocytes in OA, which has been extensively studied, little is known about the metabolic profile of FLSs and immune cells that infiltrate the synovium in patients with OA. To date, the majority of studies have focused on FLSs in RA, in which a hypoxia-induced shift towards glycolysis is associated with increased migration and invasiveness[95,115]. Chronic hypoxia alters cellular bioenergetics by inducing mitochondrial dysfunction and glycolytic pathways, thereby supporting abnormal angiogenesis, cellular invasion and pannus formation in the joints of patients with RA[115]. Glucose metabolism therefore has a critical role in the activity and behaviour of FLSs in RA[116]. The glycolytic enzyme glucose-6-phosphate isomerase (GPI) also promotes the proliferation of and inhibits the apoptosis of FLSs from patients with RA[117]. Interestingly, GPI is a multifunctional protein that also acts as an angiogenic factor to stimulate endothelial cell motility[118]. Upregulation of glucose transport and a switch to glycolysis have been implicated in the regulation of angiogenesis in RA and OA[119].

In a 2016 study, an increase in the ratio of glycolysis to oxidative phosphorylation was observed in FLSs, although this increase was lower in FLSs from patients with OA than in those from patients with RA[115]. Similar levels of the glucose metabolism-related genes *LDHA* and

PDHK1 were seen in FLS from patients with OA and RA; however, expression of *GLUT1* and *HK2* were increased only in FLSs from patients with RA[115]. Following stimulation with lipopolysaccharide, GLUT1 expression and lactate levels were increased in FLSs from patients with OA, and blockade of glycolysis inhibited the migratory capacity of these cells[115]. In another study, administration of high concentrations of glucose to FLSs from patients with OA induced the expression of vascular endothelial growth factor (VEGF) and the production of ROS via the PIK3–ATK signalling pathway[120]. Blockade of the universal oxygen sensor prolyl hydroxylase domain-containing protein 2 (PHD2; also known as Egl nine homologue 1) in FLSs from patients with OA increased the expression of angiogenic factors, which were subsequently able to induced tube formation by endothelial cells[121]. Connective tissue growth factor-induced IL-1β expression in FLSs from patients with OA is mediated by αvβ3/αvβ5 integrin-dependent generation of ROS, the blocking of which with berberine prevented cartilage damage in a rat model of OA[122]. Furthermore, oxidative stress induces prostaglandin G/H synthase 2 (also known as COX2) expression in FLSs from patients with OA, an outcome that can be reversed by the antioxidant N-acetyl cysteine[123]. Collectively, these studies highlight a critical role for glucose transport and metabolism in FLSs in the synovium of patients with OA, as well as in patients with RA[116].

Metabolic targets in OA therapy?

Several studies have reported the consequences of blocking metabolic regulators such as AMPK and mTOR in *in vitro* and *in vivo* models of OA. Intra-articular injection of rapamycin (which targets mTOR) into mice with experimental OA substantially reduced the severity of damage to articular cartilage, an effect mediated by an increase in autophagy and by inhibiting the production of VEGF, collagen type X α1 chain and MMP13 (REF. 124). In another study using a mouse model of OA, treatment of mice with rapamycin reduced the severity of cartilage degradation and synovitis, an effect that was accompanied by a decrease in the expression of ADAMTS5 and IL-1β in articular cartilage[125]. Taken together, these studies suggest that pharmacological activation of autophagy via mTOR signalling pathways might be an effective therapeutic approach for treating OA. Decreased AMPK activity is also associated with cartilage damage; chondrocytes from patients with OA that have been depleted of AMPK exhibit increased catabolic responses to proinflammatory cytokines and biochemical injury, effects that are attenuated by molecules thought to activate AMPK[126,127]. Thus AMPK-activating drugs such as methotrexate, metformin and sodium salicylate could have therapeutic effects in this disease[127].

The glycolytic switch also represents a potential therapeutic target in arthritis. Inhibition of glycolysis might seem counterintuitive, but modulation of glycolytic pathways could directly modulate the responses of FLSs and chondrocytes to inflammatory mediators, thereby making inhibition of glycolysis a potentially effective treatment strategy for OA and RA. Specifically, overexpression of the key glycolytic enzyme 6-phosphofructo 2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) (the activity of which is impaired in cartilage in OA) reduces the activity of caspase 3 and promotes the production of aggrecan and type II collagen in explants of cartilage and chondrocytes from patients with OA[128]. These results indicate that PFKFB3 might also provide a therapeutic target for the treatment of OA. A more detailed understanding of the molecules that regulate these metabolic switches could enhance the efficacy of biological therapies for patients with RA so that treatments can be more rationally applied and personalized for patients. There are currently no such treatments for OA[129], but increasing our knowledge of metabolism within the joint could reveal mechanistic insights necessary for the development of new therapies for OA. Therapeutically targeting metabolic pathways to treat rheumatic diseases is covered in depth in a Perspectives article[130] in this journal.

Conclusions

The pathogenesis of OA involves metabolic alterations in articular cartilage, subchondral bone and synovium. These changes influence metabolic pathways in chondrocytes, synoviocytes and bone cells and their interactions with the immune system via inflammatory mediators. Accumulating evidence suggests that a metabolic switch towards glycolysis is important for immune responses and the activation of inflammatory pathways in chronic diseases, including OA and RA. This change in metabolism enables immune and inflammatory cells to gain energy to meet the increased demands for the biosynthesis of proinflammatory and degradative proteins during periods of acute cellular stress or nutrient deprivation. Similar mechanisms seem to operate in cells of the synovial joint in OA. A deeper mechanistic understanding of these complex metabolic pathways is therefore likely to provide insight into potential novel therapeutic strategies for treating OA and other inflammatory diseases of joints. At this point, research into immunometabolism in OA is still in its infancy; however, if the availability of glucose and oxygen are impaired in immune cells in OA, then regulators such as mTOR, AMPK and hypoxia-inducible factor 1α represent potential starting points for the discovery of therapeutic targets. An improved understanding of physiologic and pathophysiologic regulators of cartilage and synovial metabolism is also likely to provide new insights into the aetiology and pathophysiology of OA. Omics techniques such as metabolomics are likely to identify some of the underlying metabolic changes in OA[131] and help to define the metabolic phenotype of OA[132,133], especially in the early stages of disease[134]. When combined with proteomics, lipidomics and bioinformatics, metabolomics will help to reveal the pathways, proteins and metabolites that drive inflammatory processes in synovial joints, hopefully also revealing new therapeutic targets. Future research should also focus on delineating the role of metabolism in macrophages that infiltrate the synovium in OA and in FLS in OA.

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Author contributions

All authors researched the data for the article, provided a substantial contribution to discussions of the content, contributed to writing the article and reviewed and/or edited the manuscript before submission.

Competing interests statement

A.M. declares that he has served as a Scientific Advisory Board Member for AbbVie and has received honoraria from AbbVie and Bioiberica. J.S. declares that he has served as a Scientific Advisory Board Member for AbbVie, BMS, MSD and Roche. The other authors declare no competing interests.

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Review criteria

We searched the MEDLINE and PubMed databases for original articles on immunometabolism published before February 2017, using the search terms "inflammation", "mitochondria", "inflammasome", "cytokine", "immunometabolism", "osteoarthritis", "articular cartilage", "chondrocyte", "synovitis", "synovium", "synoviocyte", "macrophage", "homeostasis", "ageing", "glycolysis", "oxidative phosphorylation", "cell signalling", "nutrient", "glucose", "oxygen", "adipokine", "adiposity", "diabesity". All articles identified for inclusion in the review were full-text English-language articles or reviews. We also searched the reference lists of the identified manuscripts for additional relevant articles.