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REVIEW

The Involvement of Glucose and Lipid Metabolism Alteration in Rheumatoid Arthritis and Its Clinical Implication

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Abstract: Obviously, immune cells like T cells and macrophages play a major role in rheumatoid arthritis (RA). On one hand, the breakdown of immune homeostasis directly induces systemic inflammation; on the other hand, these cells initiate and perpetuate synovitis and tissue damages through the interaction with fibroblast-like synoviocytes (FLS). In recent years, the pathological link between metabolic disorders and immune imbalance has received increasing attention. High energy demand of immune cells leads to the accumulation of metabolic byproducts and inflammatory mediators. They act on various metabolism-sensitive signal pathways as well as relevant transcription factors, such as HIF-1α, and STATs. These molecular events will impact RA-related effectors like circulating immune cells and joint-resident cells in return, allowing the continuous progression of systemic inflammation, arthritic manifestations, and life-threatening complications. In other words, metabolic complications are secondary pathological factors for the progression of RA. Therefore, the status of energy metabolism may be an important indicator to evaluate RA severity, and in-depth explorations of the mechanisms underlying the mystery of how RA-related metabolic disorders develop will provide useful clues to further clarify the etiology of RA, and inspire the discovery of new anti-rheumatic targets. This article reviews the latest research progress on the interactions between immune and metabolism systems in the context of RA. Great importance is attached to the changes in certain pathways controlling both immune and metabolism functions during RA progression.

Keywords: rheumatoid arthritis, metabolism, inflammation, immune cells

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease, characterized by chronic inflammation in synovial tissues and excessive production of autoantibodies.[1] The pathogenesis of RA is related to many factors, typically immune dysfunction, epigenetic factors, environmental pollution, infections, lifestyle, and so on. Because of the complexity, it has not been thoroughly clarified yet.[2] At present, the clinical treatment of RA mainly relies on conventional disease modifying anti-rheumatic drugs (cDMARDs) and biological agents. cDMARDs typically take weeks to months to take effect, and the related regimens may cause liver and bone marrow toxicity. Even though, they are still taken as first-line drugs because of their economic merits.[3] Comparatively, biological agents produce more promising clinical efficacies, as they are designed to target specific molecules or cells that play key roles in RA. There are many commercially available products already, such as TNF inhibitors (etanercept, infliximab, and adalimumab), IL-6 receptor inhibitors (tocilizumab and sarilumab), and Janus kinase (JAK) inhibitors (tofacitinib, baricitinib). Basically, all biologics are more effective when used in combination with cDMARDs than prescribed alone.[4–7] However, biologic agents are expensive, and not all patients respond well.[8,9] Furthermore, current treatments cannot address all aspects of RA, especially the extra-articular manifestations like cardiovascular disease.[10] In this context, a novel anti-rheumatic strategy is still in urgent need.

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Recently, the pathological link between metabolic complications and immune imbalance in RA receives increasing attention. In fact, inflammation–metabolism interaction had been revealed decades ago.[11,12] Metabolic diseases such as obesity and diabetes are always associated with chronic inflammation.[13,14] Meanwhile, patients with inflammatory diseases tend to develop metabolic disorders. For example, the prevalence rates of hyperlipidemia were estimated as 42% and 31% in the patients enduring early and long-term RA, respectively.[15] In addition, levels of metabolites related to glucose, amino acid, and lipid metabolism are all changed, and the metabolic alteration correlates to an increase in C-reactive protein (CRP) and many other inflammatory indicators.[16] Insulin resistance (IR) is also very common in RA patients, which is believed to be caused by certain inflammatory cytokines, typically TNF-α and IL-6.[17] As for the link between metabolic alteration and RA, the logic is simple. All cellular functions and physiological activities rely on energy supply. Given that RA is a condition characterized by elevated energy expenditure resulting from inflammation and associated symptoms, it is plausible that altered metabolic conditions may play a significant role in its pathological manifestations. That is, accelerated catabolism would sustain the proliferation, invasion, differentiation, and secretion of many RA-related cells such as fibroblast-like synoviocytes (FLSs), immune cells, and osteoclasts.[18] Above changes are mediated by many signaling pathways, and the roles of those dominating both metabolism reprogramming and immune rebalancing are especially worthy of investigation. This review selectively focuses on the major energy metabolism changes occurred under RA conditions, and their impacts on immune system, based on currently known key signaling transduction mechanism. It is supposed to benefit a better understanding of the issue of how altered energy utilization and metabolism affect the course of RA. By discussing representative metabolism-targeting drugs, we highlight the prospect of this novel anti-rheumatic strategy.

Involvement of Energy Metabolism Alteration in RA

The majority of energy demands in mammals are met by glucose and fat catabolism. It is a priority for us to thoroughly clarify their metabolism profiles in RA. Meanwhile, we should realize that mitochondrion is the pivotal organelle responsible for energy regeneration. Any disturbance in glucose and fat metabolism will be reflected in functional changes in mitochondria, which will eventually impact metabolism status in return.[19] In the following paragraphs, the relevance of mitochondrial dysfunction and RA-related inflammation is first discussed. Next, we review the current points about glucose and lipid metabolism alteration in RA. In these descriptions, FLSs and T cells are taken as representatives of effector cells, because they account for majority of RA-related clinical manifestations, and their functions are tightly controlled by their metabolic status.

Mitochondrial Dysfunction in Leukocytes Promotes Inflammation

Mitochondria serve as a major source of cellular energy by regulating multiple cellular signaling pathways; however, dysfunctional mitochondria generate reactive oxygen species (ROS), leading to oxidative stress and inflammation. Mitochondrial dysfunction has been shown to be common in T cell-mediated autoimmune diseases, including RA.[20–22] Premature senescence of T lymphocytes in RA patients is a key characteristic differentiating them from normal cells, which is closely related to the acquired inflammatory phenotype.[23–25] One reason for this is the decreased expression of MRE11A, the double-strand break repair nuclease. In healthy individuals, the expression of MRE11A protein in T cells decreases with age. However, in patients with RA, the majority of naive and memory $CD4^+$ T cells exhibit low levels of MRE11A protein expression as early as middle age.[26] The premature aging of T cells with damaged telomeres has been shown to be caused by a deficiency in MRE11A activity, and T cells with decreased expression of MRE11A differentiate into effector cells that are invasive to tissues, which contribute to the development of destructive synovitis.[27] In fact, the abnormal MRE11A expression decrease directly leads to a series of unfavorable consequences, including chromosome disintegration and senescence markers up-regulation, in addition to telomeres damages.[27] Accordingly, overexpressing MRE11A in RA T cells can reverse phenotype remodeling and ease synovial inflammation. It should be noted that MRE11A is also presented in cytoplasm and mitochondria.[28] Loss of MRE11A functions will cause a significant decrease in oxygen consumption and ATP production within mitochondria.[26] It implies the indispensable role of MRE11A in mitochondrial biogenesis. Indeed, MRE11A has an ability to bind to mitochondrial DNA (mtDNA). Inhibition on MRE11A expression will induce the leakage of mtDNA into cytoplasm, which is then recognized by

NLRP3 and AIM2 inflammatory vesicles. This event is a corner stone of inflammatory cascades, and it triggers procaspase-1 cleavage, IL-1β release, and T cell pyroptosis.[26] Some studies have reported that proteins encoded by nuclear DNA (nDNA) are also involved in mitochondrial dysfunction in RA patients. Specifically, these proteins participate in ROS generation, membrane potential maintenance, mitochondrial electron transport, energy metabolism, and intrinsic apoptosis.[29] These properties partially explain the significant decreases in mitochondrial membrane potentials, superoxide, cellular ATP levels, and mitochondrial mass under RA circumstances when the expression of the relevant proteins is insufficient.[30] Due to the aforementioned changes and many other mechanisms including these still unknown, mitochondrial structures in RA leukocytes are inevitably altered. In RA macrophages, mitochondria and endoplasmic reticulum together form an organelle named as "mitochondria-associated membranes" (MAMs). MAMs can inactivate glycogen synthase kinase-3β (GSK-3β), an upstream regulator of highly active mitochondria, probably through serine phosphorylation. In addition to its impact on mitochondrial biogenesis, the inactivation of GSK-3β should also account for the deteriorated RA severity directly, as it is related to the increased production of proteinase K, a collagenase implicated in joint tissue injuries.[31]

The consequences caused by mitochondrial structural changes are still largely unknown. However, current evidence suggests that mitochondrial dysfunction contributes significantly to RA pathology by increasing oxidative stress.[32] Oxidative stress is a potent inducer of inflammation. Mitochondria are the main source of ROS. Many changes occurred in mitochondria including nutrient overloading, potential loss, and electron leakage can result in ROS accumulation, which are all evidenced in RA patients.[33] It was observed that mitochondrial ROS levels in both whole blood and monocytes of RA patients increased by 5 times compared to the normal healthy controls.[34] Because of its pro-inflammatory nature, ROS was found to be positively correlated with DAS 28 and RA diagnosis indicators CRP and anti-CCP (cyclic peptide containing citrulline).[35,36] The pro-inflammatory properties of ROS rely on lipid peroxidation, and the products are deeply implicated in inflammatory arthritis and cartilage degeneration.[37] Therefore, monitoring mal-ondialdehyde and other similar derivatives becomes a routine when estimating RA severity and oxidative stress.[37] It reminds us about the necessity of restoring antioxidant capacities during anti-RA therapies. Because of the excessive ROS production, reduced glutathione is consumed in a large amount in the cells enduring mitochondrial dysfunction. Replenishing reduced glutathione or any other approach that can potently ease oxidative stress will benefit the improvement of leukocytes-mediated inflammation in RA patients.[38]

Glycolysis Fuels FLSs-Mediated Pathological Changes

Glucose utilization includes three main approaches: glycolysis, aerobic oxidation, and pentose phosphate pathway (PPP). Both aerobic oxidation and glycolysis are vital for ATP production, and the ratio of glucose entering each metabolic pathway is determined by specific physiological and pathological conditions. For example, during intense exercises, glycolysis is the primary manner of glucose catabolism for ATP generation because of the speed merits and independence of oxygen supply. In contrast, during most of the time in daily life, aerobic oxidation is the primary way for glucose utilization because it produces more ATP per molecule of glucose and is more efficient and sustainable in the presence of oxygen.[39] When oxidative stress is escalated, PPP becomes more active to generate NADPH, which is needed for scavenging ROS.[40]

According to the clues described above, we can conclude that cells tend to utilize glucose by aerobic oxidation under normal conditions. However, in many RA effector cells, like FLSs, ATP production is switched from oxidative phosphorylation to glycolytic pathway.[41] It is known that RA is a wasting disease, and the resting metabolic rate is higher than the general population. It requires an efficient way to replenish energy.[42] Under this circumstance, it is not surprising to reveal that glycolysis in RA patients is substantially up-regulated in certain hyper-activated cells. From the mechanism perspective, synovial hyperplasia directly creates a hypoxic environment. Even if oxygen supply is sufficient, glycolysis can still occur in FLSs because of persistent inflammation.[43] Hence, abnormally activated glycolytic pathway in FLSs is an important factor implicated in the occurrence and development of articular manifestations in RA.

There are many convincing evidences about the up-regulation of glycolysis in FLSs and its involvement in RA.[41] When activated by inflammatory $CD4^+$ T cells, energy demand of FLSs is increased to sustain enhanced cellular behaviors, including proliferation, invasion, adhesion, and cytokines synthesis.[44] To adapt to the metabolic requirement

changes, some decisive enzymes should change accordingly. Indeed, the expression of two main rate-limiting glycolytic enzymes, glyceraldehyde 3-phosphate dehydrogenase (GAPD) and lactate dehydrogenase (LDH), are significantly up-regulated in the synovial tissue of RA patients.[45] As a result, lactate production is increased.[46] When glucose enters cells, it depends on glucose transporter (GLUT), the first step for glycolysis is catalyzed by hexokinases (HKs), which synthesizes glucose-6-phosphate (G-6-P) by using glucose.[47] Therapeutic targeting of hexokinases (HKs) has the potential to significantly alleviate symptoms and slow the progression of RA.[48,49] Glucose intake-related transporters are also important for glycolysis, as they control intracellular glucose availability. In most cases, cellular intake of glucose depends on GLUT.[50] Interestingly, deletion of SLC2A3 the gene encoding GLUT3 can prevent RA-related joint injuries, indicating that as a glycolysis-related protein GLUT3 is a potential therapeutic target for RA.[51] It is apparent that up-regulation of either HKs or GLUT would facilitate glycolysis. Indeed, HK2 and GLUT are highly expressed in RA synovium, which is believed to be a driving force for the enhanced migration and invasion ability of FLSs.[48,52] The fore-mentioned clues basically explain the underlying mechanism, but meanwhile we should realize that both HK2 and GLUT are versatile molecules, which can induce the production of many pathological mediators such as MMPs and IL-6.[41,48] HIF-1α is one of the most important regulator of glycolysis. When enriched in synovial fluid, it can promote the expression of many glycolysis-related genes/proteins, such as LDH, HK2, and GLUT1 in FLSs. In fact, HIF-1α increase is a driving force for many FLSs-related pathological changes, such as vascular proliferation, inflammation, and cartilage damages.[53] Although FLS is the main source of HIF-1α in joints, the latter does not only solely impact FLSs but also greatly reshapes the microimmune environment. HIF-1α increases glycolytic flux in a variety of immune cells, including dendritic cells, classically activated M1 macrophages, neutrophils, lymphocytes, and B cells.[54,55] This metabolic status confers inflammatory phenotypes of the cells, allowing immune responses to be persistent under hypoxic conditions.[56] Taking T lymphocytes as an example, HIF1-α controls metabolic checkpoints and induces glycolysis there, a metabolic event favoring Th17 cells development but hampering Treg cell differentiation (Figure 1).[57] Collectively, glycolytic status in synovial tissues thereby can be taken as a gauge of disease activity of RA.

PPP Shunt Promotes the Development of Inflammatory $CD4^+$ T Cells in RA

The properties of T cells, including lifespan, proliferative capacity, differentiation profile, and mobility ability are all greatly altered in RA patients.[58,59] It is reasonable to conceive that they would prefer glycolysis due to the timely provision of energy, which indeed occurs under many pathological conditions like cancer.[60] Interestingly, the metabolism of glucose in RA T cells is shifted to PPP, which is largely different from glycolysis, although they share some common steps.[61,62] When studying $CD4^+CD45^+$ T cells in RA patients, it was found that 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) expression was decreased compared to normal healthy controls.[63,64] This enzyme accounts for the production of fructose-2,6-diphosphate (F-2,6-P), a substrate and agonist of a rate-limiting glycolytic enzyme phosphofructokinase 1 (PFK1). Via this manner, PFKFB3 determines glycolytic flux and the downstream oxidative phosphorylation.[65,66] In the context of aerobic oxidation inhibition, this finding raised a question, how glucose in these cells is utilized. Further studies revealed that T cells in RA patients tend to utilize glucose through PPP.[67] When the T-cell receptor (TCR) is activated, it triggers a metabolic program that boosts mitochondrial function, increases glycolysis to produce ATP quickly and facilitates the generation of biosynthetic precursor molecules by shifting glucose to the (PPP).[68] It distinguishes RA naïve T cells from their normal counterparts. A key molecule driving this change has been identified as glucose-6-phosphate dehydrogenase (G6PD), which is significantly up-regulated under RA conditions.[69] G6PD is the rate-limiting enzyme of PPP and controls the production of nicotinamide adenine dinucleotide phosphate (NADPH).[70] In $CD4^+$ T cells of healthy people, expression of PFKFB3 and G6PD is finely tuned to balance the ratio of glycolysis/PPP, while the balance is tilted toward G6PD-controlled PPP in RA T cells.[64] This metabolic phenotype is required by T cells to proliferate and differentiate into inflammatory subtypes.[71] Hence, PPP at least partially accounts for the deterioration and recurrence of RA by affecting T cells.[68]

During inflammatory differentiation of T cells, PPP shunt provides large amounts of NADPH, which is the most abundant reducing molecule in cells and plays an important role in balancing redox/oxidation status. By donating electrons, NADPH does not only scavenge ROS,[70] but also participates in the synthesis of many biomolecules. As a result, the over-production of NADPH promotes the replication of RA T cells.[67] Meanwhile, NADPH derived from PPP

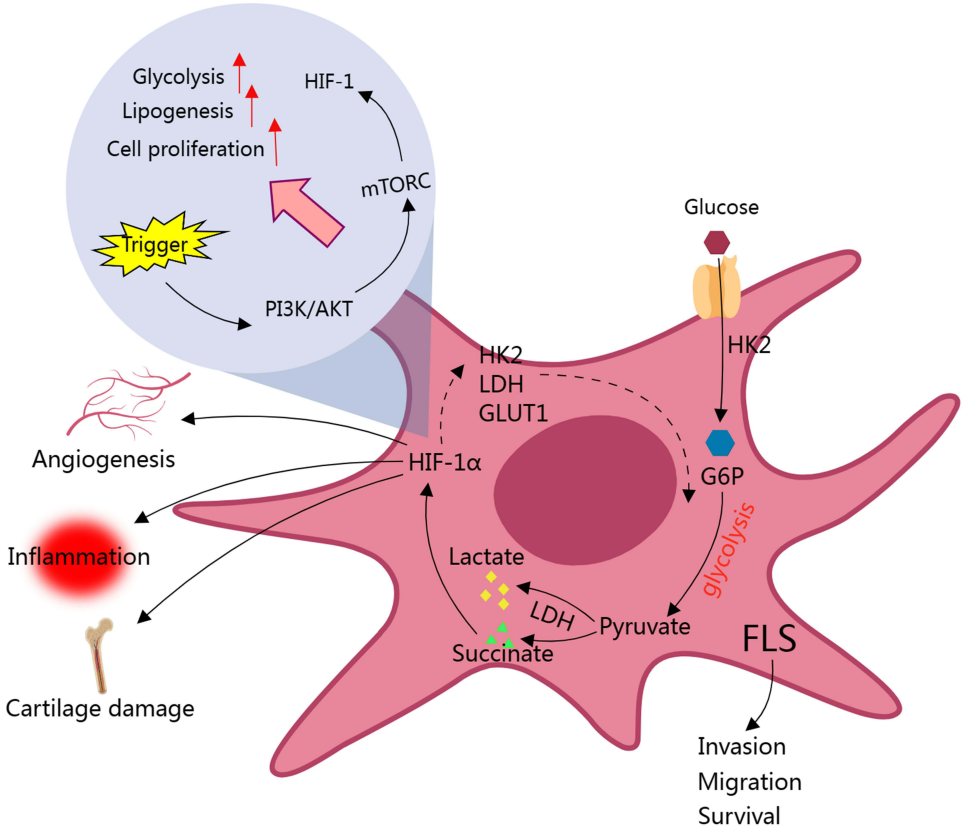

Figure 1 Glycolytic activity is enhanced in FLS of RA patients. Up-regulation of HK2 enhances the migration and invasion ability of FLS, which serves as an example how glycolysis drives RA. Many glycolytic intermediates like succinate up-regulate glycolysis-related genes via HIF-1α, further facilitate this metabolic process. Above changes eventually fuel vascular proliferation, inflammation, and cartilage damages. HIF-1α plays a key role in related signal transduction and pathological changes.
Abbreviations: FLS, fibroblast-like synoviocyte; HK2, Hexokinase 2; G6P, glucose-6-phosphate; GLUT-1, Glucose transporter 1; LDH, lactate dehydrogenase; HIF-1α, Hypoxia-inducible factor 1-alpha; mTOCR, mammalian target of rapamycin complex; PI3K, Phosphatidylinositol 3-hydroxykinase.

protects inflammatory T cells from ROS injuries, and ensure their longevity. In fact, ROS has multiple facets about its impacts on T cells development.[72] Insufficient intracellular ROS has a negative influence on ataxia telangiectasia mutation (ATM), a key kinase monitoring DNA damages and controlling cell cycle progression. When ATM levels in T cells are low, they bypass the G2/M cell cycle checkpoint, leading to abnormal proliferation, and predominantly differentiate into Th1 and Th17 cells.[73] Via this mechanism, low ROS levels under PPP up-regulation status will induce the development of these inflammatory T cells. Meanwhile, NADPH is required for lipid synthesis. PPP up-regulation will accelerate lipogenesis, which provides the essential lipid components to build membranes, allowing the cells to replicate and migrate. With these changes, T cells are eventually activated in RA patients (Figure 2).[74]

Inflammation Milieu in RA Promotes Lipid Catabolism

The risk of developing cardiovascular-related diseases (CVD) in RA patients is increased by 50% approximately, which is closely related to the increased mortality of RA.[75,76] Apparently, chronic inflammation should account for this, in addition to some other well-known risk factors, such as smoking, obesity, hypertension, and diabetes.[77] It also reminds us about the possibility of lipid metabolism alteration in RA, because high circulating lipid concentrations are always the main concern when evaluating CVD risks. Indeed, many RA patients are diagnosed with obesity and hyperlipidaemia.[78–80] But the fact is much more complicated than one could assume. In fact, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), and high-density lipoprotein cholesterol (HDL-c) are all decreased in most RA population, especially during the acute recurrence stages.[81,82] Effective therapies will restore their levels. This situation together with the facts stated above lead to the conceptualization of RA lipid metabolism paradox.[83] Many theories have been proposed in the attempts to clarify this mystery, but no convincing conclusion has been accepted yet. Herein we briefly discuss the relevance between cholesterol

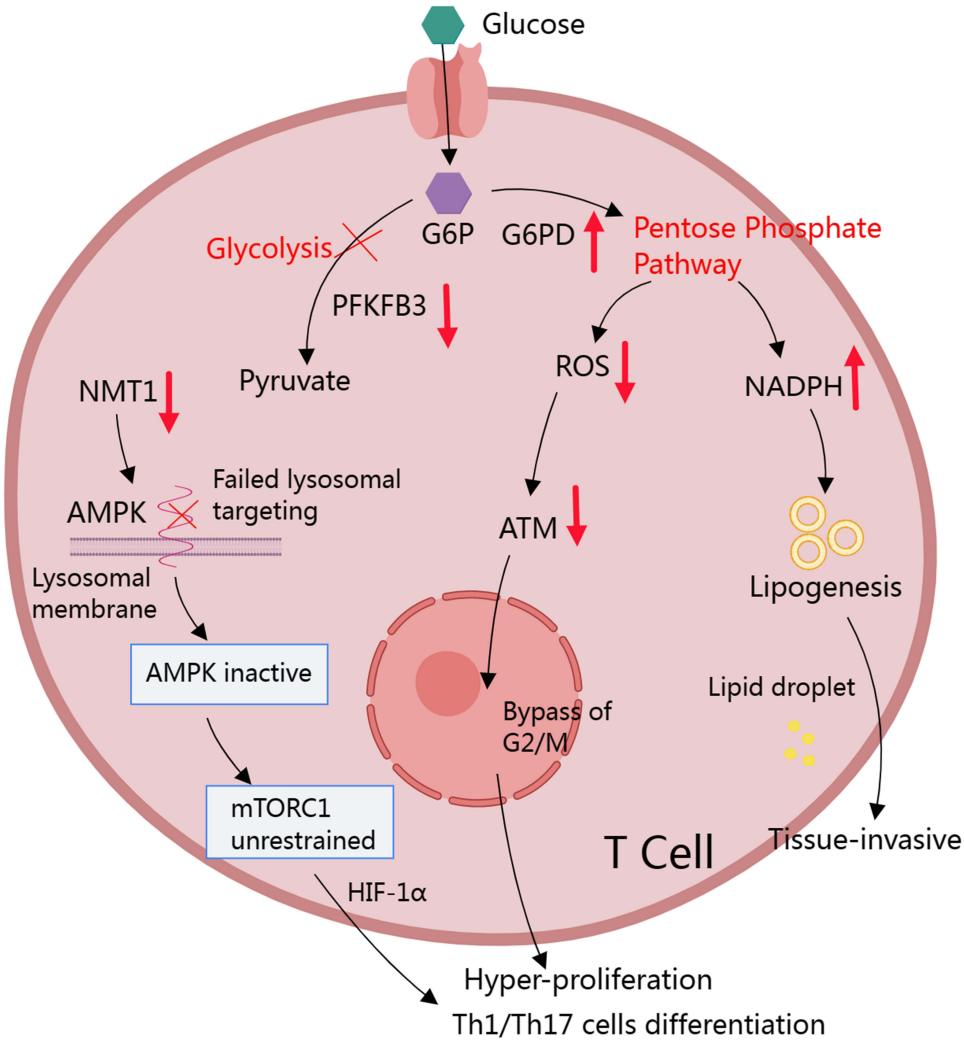

Figure 2 RA conditions favor PPP in CD4$^+$ T cells. Increased PFKFB3/G6PD ratio serves as the fundament for the accelerated PPP in RA T cells. It leads to the production of large amounts of NADPH in cytoplasm. By supporting lipid synthesis, NADPH facilitates membranes construction, which makes T cells more reproductive and invasive. The increase in NADPH eventually depletes ROS. It directly prolongs the longevity of T cells, and induces them to rapidly proliferate by bypassing ATM-controlled G2/M cell cycle checkpoint. The low oxidative stress condition is also favorable for Th1 and Th17 differentiation. Concurrently, decreased NMT1 expression in T cells results in the inability to target AMPK to lysosomes, leading to elevated and unrestricted activation of mTORC1, which promotes Th1 and Th17 differentiation by mediating HIF-1α.
Abbreviations: G6P, glucose 6-phosphate 6; G6PD, Glucose-6-phosphate Dehydrogenase; ROS, Reactive oxygen species; NADPH, Nicotinamide Adenine Dinucleotide Phosphate; ATM, ataxia telangiectasia mutated; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3; NMT1, N-myristoyltransferase 1; AMPK, AMP-activated protein kinase; HIF-1α, Hypoxia inducible factor-1 alpha; Th, T helper.

metabolism alteration and RA-related inflammation, because the implication of fat metabolism changes in RA had been reviewed well.

Studies have shown that lipids decline is closely related to CRP increase, while a decrease in CRP can be observed when LDL-c and HDL-c increase.[84] Under this condition, it is not very difficult to understand the phenomenon that hypolipemia is closely related to the high incidence of CVD in RA patients. Increasing the potent inflammatory mediator CRP can induce a variety of inflammatory syndromes, including CVD.[83,85] Inflammation affects the antioxidant and delivery capacity of HDL-c. When RA-related inflammation is exacerbated, HDL-c is detected with low contents of apolipoprotein A1 (apoA1) and paraoxonase-1 (an antioxidant enzyme).[86] Hence, its capacity for transferring cholesterol and scavenging ROS is significantly impaired. Cholesterol will be accumulated in the vascular resident macrophages, endowing them with notable pro-atherosclerotic potentials.[84,87] Based on these narrations, it can be easily noticed that inflammation-caused alteration of cholesterol metabolism is deeply implicated in RA-related extra-articular complications. A piece of convincing evidence is that high levels of TNF-α in RA patients induce the production of scavenger

receptor class A (SR-A) and lectin-like oxidized low density lipoprotein receptor-1 (LOX-1), two proteins accounting for cholesterol catabolism and arteriosclerosis development.[88] Furthermore, another pro-rheumatic cytokine IL-6 can stimulate the expression of LDL receptors.[89] This change enhances the capacity of liver absorbing LDL, which in turn promotes the secretion of cholesterol by means of bile secretion. Cholesteryl ester catabolism is accelerated accordingly. Cholesteryl esters are carried by mature HDL particles and eventually transferred to LDL particles with the aid of cholesteryl ester transfer protein (CETP).[90] According to this mechanism, the increase in cholesteryl ester catabolism in RA patients requires less HDL-c and LDL-c. These facts show that the shrink in cholesterol pool as well as HDL-c and LDL-c contents reflects the inflammatory conditions in vivo. The above evidence hints that improvements in immune environments will restore cholesterol metabolism alteration. Indeed, tofacitinib, a JAK1/JAK3 inhibitor and biological anti-rheumatic agent, can inhibit cholesteryl ester catabolism in RA patients, and therefore restore levels of HDL-c and LDL-c.[90] Blocking IL-6 with tocilizumab will benefit the restoration of lipid levels too, especially for LDL-c.[91] Although we have made great progress in elucidating the relationship between lipid levels and RA severity, our knowledge about the details of how cholesterol metabolism changes affect the immune environment is still poor.

Key Pathways Involved in RA Metabolism Alteration

Regardless of exact incentives, metabolism alteration in RA patients is controlled by certain signal transduction pathways. They respond to immune changes, and their changes directly create unfavorable metabolism environments. From this sense, a better understanding of their roles in RA would benefit the elucidation of many metabolism paradoxes, and inspire the introduction of novel anti-rheumatic strategies. More importantly, many pathways are evolved as dual functions roles. They control immune and metabolism systems simultaneously. As a result, they bridge the gap between inflammation and metabolic complications, and are therefore ideal therapeutic targets for RA-related CVD and other extra-articular syndromes.

PI3K/AKT

As discussed above, glycolysis is the predominant glucose utilization form for most immune cells in RA patients.[92] As a key regulator of glycolysis, PI3K/AKT pathway induces the expression of GLUT1 and many other glycolytic enzymes, such as HK2 and PFK-2.[93–96] The stimulation on TCR-CD3 and TLR will induce PI3K/AKT activation in lymphocytes and monocytes/macrophages, respectively. The activated AKT promotes glycolysis indirectly through its downstream GSK-3β, which can phosphorylate a panel of proteins/transcription factors related to metabolism.[97–100] More importantly, PI3K/AKT activates mammalian target of rapamycin (mTOR). mTOR constructs two different complex isoforms, namely mTOR complex 1 and 2 (mTORC1/2). They are well known because of their ability to control cellular growth and proliferation. In fact, they are also indispensable for glucose metabolism reprogramming. AKT and mTORC2 form a positive feedback loop concerning their effects on glycolysis. On one hand, mTORC2 expression is up-regulated by AKT. On the other hand, mTORC2 activates AKT via phosphorylation at S473, and consequently induces the expression of GLUT1, HK2, and PFK-1.[101] mTORC1 is also a direct downstream effector of PI3K/AKT that promotes protein/lipid synthesis and glycolysis.[102] Up-regulation of mTORC1 will similarly induce the expression of GLUT1 and HK2, which leads to increased glucose intake and accelerated glycolysis, respectively.[103] Besides the fore-mentioned impacts on AKT, mTOR can up-regulate glycolysis by promoting HIF-1 expression. As summarized above, HIF-1 initiates the expression of many glycolytic genes, such as GLUT1, HK2, PFKFB3, and LDHA by acting as a transcriptional factor (Figure 1). Meanwhile, it represses tricarboxylic acid cycle (TCA) by promoting the expression of its negative regulators like PDK.[104–106] The net outcome from these changes is switching glucose from aerobic oxidation to glycolysis. Due to the abundance of TLR4 ligands, PI3K/AKT is always up-regulated in monocytes/monocytes in RA patients.[107] This situation amplifies the hyper-activation of innate immune system. Interestingly, many cDMARDs and biological agents show the potential in regulating PI3K/AKT, and therefore their anti-rheumatic effects should be at least partially attributed to the inhibition of glycolysis-fueled inflammation and tissue injuries.[108] Although T cells tend to utilize glucose through PPP in RA patients, regulating PI3K/AKT also affects the differentiation and development of this cell population, and affects the prognosis of RA. This implies that even for T lymphocytes, their functions are not thoroughly glycolysis-independent.

AMPK

Eukaryotes are endowed with the ability to rebalancing metabolism status according to the availability of nutrients, and AMP-activated kinase (AMPK) plays a key role in sensing environmental changes and reprogramming metabolism.[109] AMPK controls many aspects of the fate of immune cells, like senescence, differentiation, apoptosis, and proliferation. We here discuss its role in immunometabolism by taking T cells as an example. Coordinating with mTOR, AMPK governs intracellular energy supply, which is decisive for memory and effector T cells development.[110] Generally speaking, AMPK acts as a self-adapting buffer of energy generation in cells. It is activated when energy supply is insufficient, as indicated by the increased ratio of AMP/ATP or ADP/ATP. Once activated, AMPK phosphorylates a variety of metabolism regulators, and consequently stimulates mitochondrial biogenesis,[111–114] affecting both lipid[115–117] and glucose metabolism.[118–121] In short, AMPK activation promotes catabolism of lipids and glucose, and hampers their anabolism, ultimately favoring ATP generation. When nutrients are sufficient, mTOR antagonizes the functions of AMPK mentioned above.[122] In cells and tissues from RA patients, AMPK activation deficiency is extensively observed. This causes insufficient capacity of oxidative phosphorylation, and makes the cells depend on glycolysis for ATP replenishment. Interestingly, although the availability of ATP is reduced in RA T cells, AMPK activation does not occur there. To the contrary, its activity is down-regulated. It has been elucidated that this phenomenon is caused by dysfunction of signaling transduction within this pathway. Co-localization with mTORC1 in lysosome surface is required by AMPK to sense nutrient availability and ATP levels. RA conditions reduce the expression of protein-modifiable N-myristoyltransferase 1 (NMT1) in $CD4^+$ T cells, which is necessary for AMPK to locate in lysosome and interact with mTORC1. Absence of NMT1 consequently causes unrestricted mTORC1 activation.[123,124] As a result, HIF-1α is excessively produced, which then initiates the transcriptional expression of many inflammatory genes required by Th1 and Th17 differentiation (Figure 2).[125] Another aspect of AMPK-related metabolism regulatory properties is mediated by its downstream target SIRT1. This deacetylase negatively regulates HIF-1α and NF-κB, and therefore inhibits glycolysis.[126] Considering the pro-inflammatory impacts of glycolysis on both innate and adaptive immunity, deficiency of AMPK will contribute to RA-related inflammation. Chemical stimulus or genetic overexpression of AMPK would attenuate RA severity, which has been confirmed by many studies.[127]

JNK

Unlike the two fore-mentioned, JNK is usually categorized as an immune pathway rather than a metabolic regulator. In fact, many inflammatory pathways including JNK and NF-κB can also regulate metabolism.[128,129] They exert metabolism regulatory effects through similar mechanisms. Here, we use JNK as an example to demonstrate how immune pathways change metabolic profiles of RA patients. JNK belongs to MAPK family, a group of pathways sensitive to both intracellular and extracellular stress. There are three isoforms of JNK, namely JNK1, JNK2, and JNK3. JNK1 and JNK2 are widely distributed, while JNK3 is selectively expressed in brain, heart, testis, and pancreatic β cells.[130] Disturbance in JNK, especially the type 1 isoform, has been revealed to be implicated in many metabolic syndromes, such as diabetes, CVD, and fatty liver. Mice knocked out of JNK1 are protected from high-fat diet-induced obesity, insulin resistance (IR),[131] oxidative damages to liver and adipose tissues.[132,133]

JNK regulates metabolism mainly through indirect manners. JNK can restrain the activity of peroxisome proliferator-activated receptor alpha (PPAR-α). This in turn inhibits the release of fibroblast growth factor-21 (FGF-21), which is involved in ketogenesis, insulin sensitivity, blood glucose maintenance, and obesity. Insulin receptor substrate 1 (IRS-1) is another key target for JNK to affect glucose metabolism. When activated by TNF-α, free fatty acids (FFAs), and some other inflammatory stimuli, JNK1 phosphorylates IRS-1 and prevents its interaction with insulin receptors.[134,135] As a result, the potential for IRS-1 lowering blood glucose is impaired because of the altered gluconeogenesis and adipogenesis status. JNK also prevents insulin clearance in hepatocytes, which highly express insulin receptors.[136] These factors cripple the physiological functions of insulin, but maintain it at high levels, which eventually results in the development of IR. Meanwhile, the role of JNK as an inflammatory cytokines inducer cannot be ignored, because these cytokines contribute to metabolic syndromes directly. For example, both of TNF-α and IL-1β can inhibit insulin signaling from activation by suppressing IRS-1 phosphorylation.[137–139] Besides, they can regulate the expression and function of many metabolism-related signals such as PPAR-γ, suppressor of cytokine signaling (SOCS), and adiponectin.[140,141]

Based on this understanding, it was assumed that the anti-IR effects from JNK1 knockdown in adipose tissues may be caused by the decreased production of inflammatory mediators like IL-6. But this acclaim was questioned by a recent study, which showed that adipocytes-specific deletion of IL-6 gene had no effect on glucose tolerance in obese mice.[142,143] Therefore, all aspects of JNK in metabolism regulation should be taken into consideration, and changes of cytokines cannot thoroughly explain all the consequences.

As a crucial pro-inflammatory signal, JNK is up-regulated in RA patients with no doubts. In addition to the direct consequence of inflammation, the metabolic complication is another contribution of JNK up-regulation to RA, which should be seriously treated as the secondary pathological factor. For example, hyperglycemia will cause nutrient overloading and toxicity to most cells.[144] Consistently, high levels of ROS and mitochondrial dysfunction are observed in RA patients, and inhibition of JNK attenuates these situations, achieving similar metabolism-regulatory and anti-rheumatic effects to hypoglycemic therapies. Adipose tissues greatly account for the metabolic changes brought by JNK-targeting anti-RA regimens, which have been confirmed as the largest secretion organ and a governor of energy metabolism in mammals.[145] Disruption of adipokine network is very common in RA patients, which serves as a foundation for developing metabolic complications.[146] Under RA conditions, adipose tissues tend to secrete more inflammatory adipokines, and this process is controlled by JNK. Leptin is a good representative when elucidating the relevance between JNK-controlled adipokine secretion and RA pathology.[147] Aside from effects of JNK on leptin production, leptin receptor sends signals through JNK.[148] Because leptin levels in RA patients are elevated, it will amplify the unfavorable consequences from JNK up-regulation via positive feedback.[149,150] In conformity to this, reducing leptin levels in RA patients by fasting improves overall clinical symptoms of RA.[151] Perhaps due to the complicated metabolism regulatory properties of the adipokines, the availability of both FFA and glucose was observed to be reduced in RA animal models when JNK was suppressed. As a result, many metabolism-fueled pathological changes in peripheral tissues will be attenuated.[152]

Metabolism-Regulatory Anti-Rheumatic Therapies and the Prospect

Due to the importance of metabolic alterations in the occurrence and development of RA, regulating metabolism and related pathways could be a feasible anti-rheumatic strategy. In fact, many conventional drugs show impressive metabolism-regulating properties. Methotrexate (MTX), a first-line DMARD, can significantly down-regulate the expression of HK2 and SLC2A5 (a glucose/fructose carrier) in RA FLSs, and therefore restrain glycolysis.[153] DMARDs and prednisolone combination therapy significantly elevate cholesterol levels when achieving notable improvement in disease activity in RA patients.[154] Another report also revealed that this therapy would increase the levels of total cholesterol and HDL-c, which are inversely correlated to erythrocyte sedimentation rate (ESR) and CRP values.[155] Likewise, the use of hydroxychloroquine (HCQ) in anti-RA regimens improved blood lipid composition profiles, indicated by the changes in TC, LDL-c, and HDL-c.[156] Similar effects can also be achieved by biological anti-rheumatic therapies. Anti-TNF-α treatment was revealed to reduce the expression of GLUT1 and PKM2 in RA patients,[157] and there is growing evidence that TNF inhibitors can reduce CVD risk.[158,159] The inhibitor of JNK Tofacitinib can also inhibit LDH and HK2 expression in FLSs and inhibit their pathological activities by restraining glycolysis.[160] No matter if it is monotherapy or in combination with cDMARDs, this drug can increase the levels of LDL-c and HDL-c by approximately 10–20%, which can be sustained for 3 months after treatments. This outcome is generally beneficial, as the incidence of CV did not increase with the increase in blood lipids.[161–165] According to the current understanding, compounds with metabolism regulatory effects must have certain anti-rheumatic potentials. 2-Deoxyglucose (2-DG), a derivative of glucose, can inhibit downstream of HK2-catalyzing steps.[166] Interestingly, 2-DG alleviated the severity of a spontaneous arthritis developed in mice. With a similar mechanism, it can also inhibit cancer cell proliferation. In fact, 2-DG has entered Phase I/II clinical trials for the treatment of advanced cancers. Cancer-related researches suggest that this compound would only induce mild side effects such as nausea and hypoglycemia. This safety merit motivates the evaluation of it as a therapeutic drug for many inflammatory diseases like RA.[167,168] The hypoglycemic drug metformin partially acts as an agonist of AMPK. By affecting AMPK activity and downstream AKT/mTOR, metformin improved both metabolism and immune situations in animals with experimental autoimmune arthritis. FLSs-mediated arthritic manifestations were effectively contained.[169] Metformin will bring extra benefits to patients with

inflammatory diseases, who underwent glucocorticoids treatment, evidenced by improvements in metabolic conditions, disease activity, and infection risks.[127] Many naturally occurring reagents possess dual pharmacological properties similar to metformin. A triterpenoid derivative lupeol can inhibit JNK-mediated neuroinflammation, and possesses anti-hyperglycemic and anti-dyslipidemic effects.[170,171] Gingerol, a bioactive compound from common food ingredients, shows the potential in treating both obesity and c-Jun activation-caused inflammatory cytokine secretion.[172] α-Mangostin, the main component identified in mangosteen, is well-known because of its impressive anti-inflammatory activity. However, increasing research has demonstrated that it is a promising reagent for treating obesity, diabetes, and CVD, and many metabolism pathways are involved in its therapeutic actions, like PPAR-γ.[173] With these properties, α-mangostin can improve the immune and metabolism conditions in rheumatic subjects simultaneously.[174]

Considering these encouraging findings, more endeavors should be done to explore metabolism-related anti-rheumatic therapies from both synthetic and natural products. Traditional Chinese Medicine (TCM) usually emphasizes the importance of metabolism changes in diseases and will provide us useful clues to achieve this goal. A previous study demonstrated that Qingluoyin, a representative anti-rheumatic TCM decoction, eased RA severity mainly by affecting fatty acid and glucose metabolism.[175] This paradigm encourages us to investigate the anti-rheumatic mechanism of TCM therapies from the mechanism perspective. Meanwhile, many conventional hypoglycemic and lipid-regulating drugs are also good candidates. We had known that metformin and rosiglitazone can help control RA progression,[176] but more drugs are to be investigated.

Abbreviation

AMPK, Adenosine 5'-monophosphate (AMP)-activated protein kinase; apoA1, apolipoprotein A1; ATM, Ataxia Telangiectasia Mutated; CCP, cyclic peptide containing citrulline; CRP, cyclic peptide containing citrulline; CVD, cardiovascular-related diseases; CETP, cholesteryl ester transfer protein; DAS 28, Disease Activity Score 28; DMARDs, disease modifying anti-rheumatic drug; F-2,6-P, Fructose-2,6-diphosphate; FLS, Fibroblast-like synoviocytes; GAPD, Glyceraldehyde 3-Phosphate Dehydrogenase; G6PD, Glucose-6-Phosphate Dehydrogenase; G-6-P, Glucose-6-Phosphate; GSK-3β, Glycogen Synthase Kinase-3β; GLUT, Glucose Transporter; IR, Insulin Resistance; HDL-c, High-density lipoprotein cholesterol; HIF-1α, Hypoxia-inducible factor-1α; HKs, Hexokinases; JAK, Janus kinase; JNK, c-Jun N-terminal kinase; LDH, Lactate Dehydrogenase; LDL-c, Low-density Lipoprotein cholesterol; LOX-1; Lectin-like Oxidized Low density lipoprotein receptor-1; MAMs, Mitochondria-Associated Membranes, MAPK, Mitogen-Activated Protein Kinase; MetS, Metabolic Syndromes; MRE11A, Meiotic recombination 11 homolog A; mTOR, mammalian target of rapamycin; NADPH, Nicotinamide Adenine Dinucleotide Phosphate; NF-κB, Nuclear Factor kappa-B; NMT1, N-Myristoyltransferase 1; PDK, Pyruvate Dehydrogenase Kinase; PFK1, Phosphofructokinase 1; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3; PPAR-α, Peroxisome Proliferator-activated Receptor alpha; PPP, Pentose Phosphate Pathways; RA, Rheumatoid arthritis; ROS, Reactive Oxygen Species; SIRT1, Silent Information Regulator 1; SR-A, Scavenger Receptor class A; TCA, Tricarboxylic Acid Cycle; TC, Total Cholesterol; Th, T helper; Treg, T regulatory cell.

Summary

In recent years, researches on metabolism-related inflammatory diseases have gained increasing knowledge about the complex interactions between metabolic pathways and immune system. Metabolic complications in inflammatory diseases like RA have been confirmed as an important part of the disease pathology itself, and provide an opportunity to introduce novel therapies. Metabolic pathway components, enzymes, and metabolites are emerging as potential biomarkers for the diagnosis of RA, which enable early intervention, personalized medication, and nutritional caring. Related researches will provide new directions for new anti-rheumatic drug discovery. More attentions are usually paid to signal transduction pathways, because they control every aspect of physiopathology functions. In fact, enzymes and metabolites are similarly important. In addition to the traditionally defined roles in metabolism, they usually also participate in signal transduction. That is, besides the biologics specifically targeting certain signaling pathways, agonists/antagonists of some enzymes and metabolic intermediates can all be used to rectify the abnormal metabolism alteration in RA as well as the immune consequences. However, our knowledge of the interplay between immune and

metabolism systems especially under RA circumstances are still limited. Many immune/metabolism mediators have multiple facets in this feedback network. Targeting any of them will have a series of consequences. Even the so-called selective agonists or antagonists would cause certain unfavorable outcomes. Under these circumstances, thoroughly clarifying the signaling transduction mechanisms and identifying strictly target-specific reagents are the priority for developing novel anti-RA regimens.

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Disclosure

The authors declare that they have no conflict of interest.

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