# Unraveling the Role of Glucose Transporters (GLUTs) in Rheumatoid arthritis & autoimmunity: A Review

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**KEYWORDS**
Glucose Transporters (GLUTs), Rheumatoid Arthritis (RA), Autoimmunity, Immune Cell Metabolism, Inflammation Targets, Glucose Metabolism, Immune Response, Cellular Glucose Uptake, Disease Pathogenesis

**ABSTRACT**
The involvement of glucose transporters (GLUTs) in rheumatoid arthritis (RA) and other autoimmune disorders is crucial. This review comprehensively explores their expression patterns, regulatory mechanisms, and impacts on immune cell metabolism in RA, a chronic inflammatory condition affecting 0.24 to 1 percent of the global population. Despite recent therapeutic advancements, the exact cause of RA remains poorly understood, and there is currently no known cure. Autoimmunity, influenced by genetic and environmental factors, plays a central role in the development of RA. Epigenetic studies have revealed global hypomethylation in synovial cells, potentially contributing to the overexpression of inflammatory cytokines. The emerging field of immunometabolism has highlighted metabolic changes in autoimmune diseases, such as RA, which leads to increased glucose uptake. This review aims to understand better how GLUTs contribute to RA and autoimmunity by delving into the intricate relationship between glucose transport and immune cell function. Ultimately, this may lead to the developmentof novel therapeutic strategies to target glucose metabolism to modulate immune responses and alleviate disease symptoms.

## 1. INTRODUCTION:

Rheumatoid arthritis (RA) is a chronic inflammatory condition caused by an autoimmune disorder. It can damage joints and extra-articular organs, such as the heart, kidneys, lungs, digestive system, eyes, skin, and nervous (1).High levels of inflammation are associated with fatigue and impaired participation in occupational, recreational, and societal roles(2).Rheumatoid arthritis (RA) affects approximately 0.24 to 1 percent of the population, with twice as many women affected as men (3).The global prevalence of rheumatoid arthritis (RA) is 0.24%, According to the Global Burden of Disease 2010 Study (4), the global prevalence of RA is 0.24 %. RA affects between 0.1 and 2.0% of the worldwide population. Despite recent therapeutic advancements, the etiology of RA remains poorly understood and there is no known cure(5–8).RA is a multifactorial disease influenced by genetic and environmental factors(9,10) leading to variations in its prevalence within and across countries (11)Although its pathogenesis remains unclear, it has been shown that inflammation induced by abnormal immune responses plays a crucial role in developing RA(12). Immune dysfunction, inflammation, synovial hyperplasia, and joint destruction characterize rheumatoid arthritis (RA).The autoimmune disease concept is supported by the production of autoantibodies, genetic association with HLA-DRβ1 polymorphism, release of pro-inflammatory cytokines and chemokines, infiltration of leukocytes into inflamed synovial tissue, and the positive effects of anti-inflammatory and immunosuppressive therapies.Autoimmunity refers to the presence of autoantibodies or T cells that react with self-antigens.However, this does not necessarily imply that self-reactivity has pathogenic consequences (13).Autoimmune diseases have different origins, epidemiology, pathology, and symptoms but share a complex nature(14). Autoimmune diseases are caused by changes in the genes within the human genome.These alterations occur at multiple loci and affect several repertoires

of genes that share similar immunogenetic mechanisms.Numerous studies have been conducted over the years and all point to the fact that autoimmune diseases are complex and have a multifactorial etiology (15).Several epigenetic studies on rheumatoid arthritis (RA) have focused on synovial cells because they are believed to be the main cause of this condition.Researchers have discovered global hypomethylation in these cells, which may be responsible for the overexpression of inflammatory cytokines in the synovial fluid.(16–18).Notably, epigenetics is not the only factor that can lead to autoimmunity.Other factors, such as mutations, polymorphisms, and environmental factors, can also make a person more susceptible to autoimmune diseases.DNA methylation is the most widely studied among the various mechanisms involved in autoimmune diseases.Previous studies have reported that certain diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) exhibit global hypomethylation in the promoter regions of their target cell DNA (19).

The field of immunometabolism has exponentially increased our knowledge of the metabolic phenotypes of different immune cell subsets.Recently, increasing attention has been paid to evaluating metabolic changes in human autoimmune diseases(20).It is widely known that rheumatoid arthritis (RA) leads to an increase in glucose uptake. RA is a complicated disease that causes damage to cartilage and bone owing to the disordered immune responses of the body and its effect on resident stromal cells (21).Cells take up glucose through glucose transporters.The first step in glucose metabolism involves its entry into the cell.Glucose transporters (GLUTs) are proteins that belong to the solute transporter (SLC2A) family. They are present in various tissues and cells of the body, including the brain, erythrocytes, adipocytes, and the liver.GLUTs mediate glucose (22) (Figure 1).

Members of the solute carrier family 2 (SLC2A and GLUT) help transport glucose across the plasma membrane.The 14 different isoforms of GLUT are divided into three distinct protein classes based on their sequence homology.Each isoform has unique tissue distribution, substrate specificity, and physiological function (23).GLUT proteins were initially thought to facilitate the movement of hexoses into and out of the cells.This is also true for class 1 GLUT proteins (GLUTs 1–4 and 14).However, class 2 (GLUTs 5, 7, 9, and 11) and class 3 (GLUTs 6, 8, 10, 12, and 13) GLUT proteins do not necessarily play primary roles in glucose transport (24).GLUT-1 is found in highly glycolytic tissues, such as erythrocytes, which take up glucose in high-need cells (22)(24)

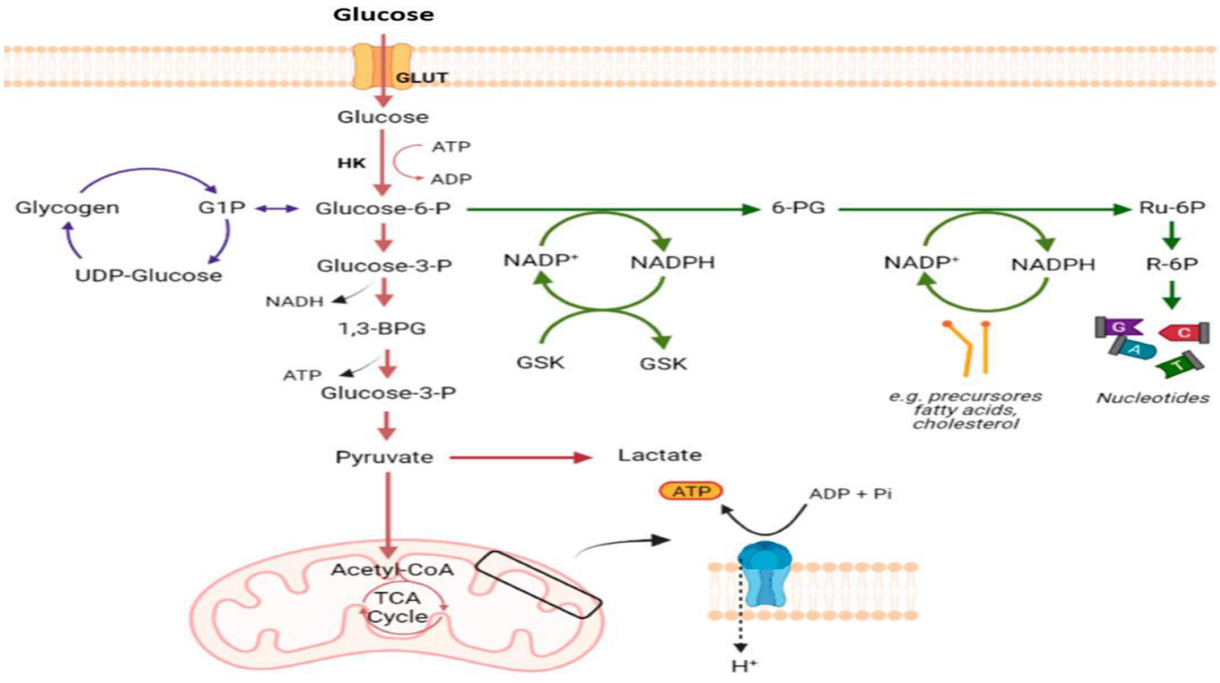

**Figure 1.(** Glucose metabolism in mammalian cells. Illustrative scheme of glycolysis, TCA cycle,and the electron transport chain (red). Glucose from the bloodstream is taken up by the cells, converted into G6P by HK, and subsequently by pyruvate.In the absence of oxygen, pyruvate is converted to lactate, whereas in the presence of oxygen, pyruvate is completely oxidized to acetyl-CoA, which enters the mitochondrial TCA cycle.The generated NADH was then fed with OXPHOS-producing ATP (blue).PPP (green) synthesizes ribose-5-phosphate, which is required for nucleic acid synthesis, and NADPH.Excess glucose was used to synthesize glycogen via glycogenesis (purple).Created by authors using BioRender.com.ATP, adenosine triphosphate; G6P, glucose-6-phosphate; HK, hexokinase; NADH, nicotinamide adenine dinucleotide; NADPH, nicotinamide adenine dinucleotide phosphate; OXPHOS, oxidative phosphorylation; PPP, pentose phosphate pathway; TCA cycle, tricarboxylic acid cycle**).**

Although various glucose transporters are expressed by immune cells, most studies have focused on the role of GLUT1 in inflammation.Upon in vitro activation, GLUT1, GLUT3, and GLUT4 are upregulated in the plasma membrane of human white blood cells (25,26). GLUT1's role is particularly crucial in tissues with high basal glucose requirements, such as the brain, where it contributes to energy metabolism and normal neuronal function(27).Unlike GLUT1, which is constantly expressed on the cell surface, GLUT4 is mainly present in intracellular vesicles in insulin-sensitive tissues, such as adipose tissue and skeletal muscle.When insulin is stimulated, GLUT4 moves from intracellular vesicles to the cell surface, increasing glucose uptake by cells.Insulin-mediated translocation of GLUT4 is a crucial mechanism for regulating glucose homeostasis in the body.Disruption of GLUT4 translocation is associated with insulin resistance, characteristic of type 2 diabetes mellitus (28).When T cells are activated, they switch to aerobic glycolysis as their primary energy source to support rapid phenotypic changes(29).This metabolic change provides energy and building blocks for rapid cell growth, division, and immune functions.The shift to glycolysis in activated T cells regulates gene expression, and glucose uptake through the GLUT3 transporter is crucial for Th17 cell function in autoimmune diseases(30,31).It regulates the metabolic pathways controlling gene expression in Th17 cell inflammatory response(32).Metabolic reprogramming in immune cells is essential for cell differentiation, proliferation, and effector functions.However, it may also disrupt immune homeostasis, contributing to the development and progression of autoimmune diseases (33).GLUT-6 (SLC2A6) and GLUT-8 (SLC2A8) are the glucose transporter family members and may be involved in immune responses and autoimmune conditions.The role of GLUT-6 in autoimmune diseases is not fully understood, but it is likely to influence disease progression. Studies have found a connection between glycolytic metabolism and innate immune cells such as neutrophils, macrophages, and dendritic cells. Autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, vasculitis, and ankylosing spondylitis may be affected by pathways related to GLUT-6 (34).GLUT-8 expression is influenced by cytokines and other immune modulators, suggesting its role in the metabolic changes of immune cells during inflammation and autoimmune responses(35). GLUT-8 is upregulated in activated T cells, suggesting a potential link to autoimmune conditions due to its role in T cell activation and proliferation(36). Glucose metabolism and inflammatory processes are closely related and GLUTs may regulate inflammation in autoimmune diseases.Irregular expression of GLUTs has been linked to escalated inflammation in various pathological conditions, indicating their potential significance in autoimmune-mediated inflammation, similar to that observed in RA (37).

**1. Glucose Metabolism & Immune function:**

Glucose is essential for energy production. Carbohydrates and proteins are broken down into glucose, the primary metabolic fuel for mammals, and the universal fuel for the fetus(38).Glucose metabolism includes glycolysis, gluconeogenesis, glycogenolysis, and glycogenesis.Liver glycolysis utilizes enzymes to support glucose breakdown within cells(37).Glycolysis is a vital process that unlocks energy from glucose, resulting in two pyruvic acid molecules. This series of chemical reactions yields a net gain of two ATP molecules from one glucose molecule(39).Glucose is the most crucial biological sugar, serving as the essential fuel of the brain and playing a pivotal role in powering intense muscular work.The concentration of blood glucose is rigorously regulated by insulin, which robustly promotes glucose uptake

and storage in the muscles and liver. Additionally, counterregulatory hormones such as glucagon and epinephrine forcefully encourage the breakdown of glycogen and gluconeogenesis in the liver(40). The primary mechanism by which the body takes up glucose is through the transportation of insulin-stimulated glucose to the skeletal muscle and adipose tissue.This process is primarily mediated by type 4 glucose transporter protein (GLUT-4).GLUT-4 is crucial for maintaining glucose balance and removing glucose from the bloodstream(41).Cellular homeostasis is a fundamental physiological condition essential for maintaining the human body(42).Without disease, blood glucose levels are precisely and constantly regulated, necessary for maintaining individuals' energy balance(43). An excess or deficiency of glucose can have harmful effects on health. Long-term disruption of glucose balance in the body can affect immune cells and lead to the development of diseases such as type II diabetes, obesity, Alzheimer's disease, and cancer(44).Multicellular organisms rely on regulating energy and fighting infections for survival. The interactions between metabolism and immunity significantly impact human health, known as "immunometabolism"(45). The immune system consistently detects and responds to potential environmental threats throughout the life of an organism.This process has a high bioenergy cost.When a pathogen or ecological threat is detected, innate immune cells release cytokines, chemokines, and inflammatory mediators and adaptive immune cells undergo clonal expansion.Because immune cells do not store large amounts of nutrients, these responses can only be maintained if they can significantly increase the uptake of glucose, amino acids, and fatty acids from their immediate surroundings. As observed more than a century ago, the development of an effective innate immune response relies heavily on glucose (46). The main role of immune cells in protecting the body and maintaining tissue balance is to provide instructions to control metabolic activities.To better understand these complex regulatory systems, it would be helpful to categorize these instructions into specific functional groups (see Table 1).In the basic sense, immune activation can be divided into four main parts:

1. Inducers: These signals trigger an inflammatory response.
2. Sensors: These proteins detect the presence of inducers.
3. Mediators: These molecules communicate to activate response mechanisms.
4. Effectors: These downstream metabolic activities help develop the desired response(47,48). Innate and adaptive immune cells are typically activated by various signals, including pathogen-associated molecular patterns (PAMPs), processed antigens, cytokines, and growth factors.These signals are detected by cell surface receptors such as pattern recognition receptors (PRRs), antigen receptors (TCRs and BCRs), cytokine receptors, and co-stimulatory molecules such as CD28, which then initiate specific signaling pathways.These pathways ultimately converge on metabolic regulators such as the PI3K-Akt-mTOR pathway to trigger metabolic adaptations required for the immune response (49).Rheumatoid arthritis (RA) is a classic autoimmune disease characterized by ongoing immune system activation(50,51). The most significant genetic risk factors have been linked to the human leukocyte antigen region and genes that determine the cytoplasmic signaling threshold (52). Under pathogenic conditions, the immune system involves excessive cytokine production, uncontrolled bone-destructive osteoclast activity, dysregulated synovial fibroblast proliferation, and autoantibody production.Identifying autoantigens has been the focus of research; however, antigen-nonspecific abnormalities have also been implicated in the dysregulated immune system of patients with RA.This raises the question of how much metabolic dysregulation contributes to the breakdown of self-tolerance. Several glycolytic enzymes, such as glucose-6-phosphate isomerase, aldolase, and enolase, have been identified as antigens targeted by autoantibodies(53–55). Patients with RA tend to lose tolerance to a wide range of antigens.It is unclear how autoantibodies against glycolytic enzymes would affect the metabolic functions of immune cellanalysis

In immunology and metabolism, the activation of innate and adaptive immune responses can be divided into four components: inducers (activate immune cells), sensors (detect inducers), mediators (transduce signals downstream of sensors), and effectors (support immune cell function). Various immune cells use these components to achieve specific functional outcomes.

Table 1
**Architectural Principles for Metabolic Control in Immune Cells.**

| Cells | Inducers | Sensors | Mediators | Affectors | Outcomes |
|---|---|---|---|---|---|
| Neutrophil | PAMPs, chemokines | PRRs (TIRs) | HIF-1 | Glycolysis, Glutaminolysis | ROS |
| Mast cells | PAMPs, IgE cross-linking, cytokines, growth factors | PRRs, FceRI | Unknown | Glycolysis | Degranulation, cytokine production |
| Resting dendritic cell | Growth factors (GM-CSF, FLT3) | Growth factor receptors | unknown | FAO | Growth, survival activation, Ag |
| Activated dendritic cell | PAMPs | PRRs (TIRs) | P13K/Akt HIF-1 | Glycolysis | Presentation, cytokine production |
| Classically activated macrophages (CAM) | PAMPs | PRRs (TIRs, NODs) | HIF-1 | Glycolysis, GlutaminoIysis | ROS, cytokine production |
| Alternatively activated macrophage (AAM) | IL-1,IL-13, Parasites | IL-4Ra,IL-13Ra | STAT6 PPARs PGC1 | FAO | Differentiation |
| Naïve CD4+ T cell | IL-7, Ag | IL-7R, TCR | PI3K/AKt | Mitochondrial OXPHOS, FAO | Survival |
| Activated CD8+ T cell | Ag, CD3/CD28 | TCR | PI3K/Akt/Mtor/ERK/MAPK c-Myc HIF-1 | Glycolysis, Glutaminolysis, Mitochondrial OXPHOS | Activation, proliferation, cytokine production |
| Memory CD8+T Cells | IL-15 | IL-15R, TRAF6 | AMPK | FAO | Survival, Quiescence |
| B cell | Ag, PAMPs | BCR, PRRs (TLRs) | P13K/AKt | Glycolysis | Activation, proliferation |

synovial fluid has shown that proteins involved in glycolytic pathways are highly expressed in RA patients but not in synovial fluids from osteoarthritis patients.This suggests increased glycolytic activity in synovial lesions of patients with RA (56).

## 2. Types of Glucose Transporters (GLUTs):

Monosaccharides, polyols, and other tiny carbon molecules are transported across the membranes of cells in eukaryotes through components of the GLUT family of fundamental membrane proteins, which are generated by SLC2 genes and are members of the significant facilitator superfamily reviewed in(57–59).The 14 human GLUT proteins are involved in the transport of many hexoses, including myoinositol, and have different substrate specificities(60), urate(43,61,62), glucosamine(63), and ascorbate (64).Based on sequence similarity, the 14 GLUT proteins—which have a combined length of around 500 amino acid residues—can be divided into three classes: the first class (GLUTs 1–4, 14), the second class (GLUTs 5, 7, 9, and 11), and the third class (GLUTs 6, 8, 10, 12, and HMIT).

## FUNCTIONAL ASPECTS OF GLUTS:

### Class 1 facilitative glucose transporters:

GLUT1 through GLUT4 and the recently released GLUT14 are among them. First discovered and cloned in 1985, GLUT 1 was the GLUT family(65). It appears that all GLUT proteins have 12 transmembrane segments, one N-linked glycosylation site, a large central cytoplasmic linker domain, and topologies where the N and C termini are located in the cytoplasm(65).All cells have this abundant glucose transporter, although it is particularly significant for red blood cells and the blood-brain barrier. It is crucial to the activation of CD4 + T cells. Due to GLUT1's widespread distribution in the brain's microvasculature, glucose can reach the area. Glutathione deficiency syndrome is a neurodevelopmental condition that is severely impaired when there is a mutation in the gene that codes for GLUT1 (SLC2A1). These individuals have microcephaly, spasticity, dystonia, ataxia, hypoglycorrhachia, and poor brain development. According to a recent study, early GLUT1 supplementation may reverse some of this disease's symptoms(66).Additionally found on the erythrocyte membrane, GLUT1 modifies the entrance and departure of glucose in type 2 diabetes patients (67). Malignant cells also express GLUT1 extensively, which gives them more energy to handle the fast development of tumors. Through regulating glycolysis, recent research showed its function in carcinogenesis and tumor growth in prostate cancer (68).The hormones, including thyroid hormones, regulate the bidirectional transport of glucose in hepatocytes through GLUT1. Hepatocyte membrane protein GLUT2 governs hepatic glucose metabolism by controlling the entrance and departure of glucose into and from the cell, respectively. The absorption of glucose is linked to GLUT2 in digestive stroke border cells and renal tubule cells, respectively. Brain tissue is the primary site of GLUT3 expression. Its ability to transport glucose into cells with a greater need for glucose is consistent with its strong affinity for the substance(69).In the brain, skeletal muscle, adipose tissue, and heart, GLUT4 is an insulin-responsive glucose transporter. Insulin causes it to move from its location in the cytoplasm of cells into the plasma membrane. The recruitment of GLUT4 by insulin causes a 10- to 20-fold increase in the transport of glucose(41). GLUT14 is a newly discovered facilitative glucose transporter. One may find the SLC2A14 gene on chromosome 12p13.3 (17.1M). There are now two known isoforms of GLUT14: GLUT14-S, which is shorter, and GLUT14-L, which is longer. The testis has both GLUT14 isoforms at a four-fold greater mRNA level than GLUT3 does(70).Different research made assumptions about how GLUT14 functions in the pathophysiology of IBD(71)

### Class II facilitative glucose transporters:

Class II facilitative glucose transporters are GLUT5, GLUT7, GLUT9, and GLUT 11. While GLUT7 and GLUT11 can transport both glucose and fructose, GLUT5 is only capable of transporting fructose. The urate transporter GLUT9 is. The kidney, testes, and small intestine are home to GLUT5, which has critical physiological and pathological functions. Type 2 diabetes, obesity, and cancer have all been associated with its overexpression. Possible targets for various illnesses, particularly malignancies, include inhibitors of this transporter(72).Prostate, testicular, colonic, and small intestine cells contain GLUT7, which has a strong affinity for both glucose and fructose(73). The remaining member of this family, urate transporter GLUT9, is mostly expressed in the liver and kidney and has a modest affinity for deoxyglucose(74). The GLUT9 gene's polymorphisms impact the metabolism of uric acid and glucose. Its genetic variations are linked to hyperuricemia, which is elevated in diabetic mellitus(75). With 42% sequence homology,

GLUT11 and the fructose transporter GLUT5 are quite similar. In humans, GLUT11A, -B, and -C are the three isoforms that have been discovered(76). Heart, skeletal muscle, and kidney cells include GLUT11A; placenta, adipose tissue, and kidney cells contain GLUT11B; and pancreatic, adipose, heart, and skeletal muscle cells contain GLUT11C. In contrast to GLUT5, GLUT11 promotes fructose and glucose transport. Notably, the rodent genome lacks the gene for this transporter(77)

**Class III facilitative transporters:**

This class includes the five recognized facilitative transporters GLUT6, GLUT8, GLUT10, GLUT12, and GLUT13 (HMIT). The glycosylation site is located differently in each of these transporters. Unlike classes I and II transporters, where it is positioned on loop 1, this class's location is on loop 9 (78).Peripheral leukocytes and brain and spleen cells are the primary sources of GLUT6 expression. Its affinity (Km 5 mM) for glucose is modest. Insulin is unable to cause GLUT6 to translocate its membrane. There is evidence that the dileucine (LL) motif at the amino terminus of the transporter is crucial for the transporter's internalization and translocation(79). (80) that GLU8 is predominantly expressed in testis germinal cells. It is a low-affinity glucose transporter that is located intracellularly. However, its translocation to the membrane is not mediated through insulin(79). GLUT8 is a high-affinity transporter of glucose, while fructose and galactose inhibit this transport. Although the translocation of GLUT8 is hormonally regulated, it is not regulated by insulin (81).GLUT10 is located in cells of tissues—for example, skeletal muscle, heart, lung, brain, placenta, kidney, liver, and pancreas. GLU12 is expressed in cells of adipose tissue, small intestine, skeletal muscle, and placenta. It exhibits sequence similarity with GLUT10, but in many respects it resembles GLUT4. Similar to GLUT4, insulin can induce translocation of GLUT12 to the cell membrane in skeletal muscle (82). However, a recent study using isolated cardiomyocytes of healthy and T1DM rodents showed that GLUT12 expression on the surface of cardiomyocytes is not insulin-dependent, indicating a role of basal glucose transporter for GLUT12 (83). HMIT (H+ -driven myoinositol transporter) or GLUT13 is expressed in adipose tissue and kidney cells. It is also predominantly expressed in the brain, especially in the hippocampus, hypothalamus, cerebellum, and brain stem. It is mainly located intracellularly, and its translocation occurs by depolarization or protein kinase C activation in neuronal cells (59)

**3. GLUTS in Innate immune cell:**

The immune system consists of different cells, tissues, and organs that can respond to self-endogenous stimuli and non-self-exogenous pathogens. The adaptive immune system induces a specific response, and an unspecific and fast response is exerted by innate immune cells (84,85). Innate immunity comprises monocytes, macrophages, dendritic cells, neutrophils, mast cells, and natural killer (NK) cells (84).Innate immune cells, such as macrophages and T cells, depend on glucose transporters to regulate their energy metabolism. The two main glucose transporters found in these cells are GLUT1 and GLUT3, which promote the uptake of glucose required for the metabolic processes linked to immune responses. High-affinity glucose transporter GLUT1 has a substantial upregulation after immune cell activation. It is essential for T cells' metabolic reprogramming, which enables them to efficiently go from a resting state to an active state that needs a lot of energy for effector activities and proliferation (86). For T cells to fulfill their higher energy demands during activation, the glycolytic pathway is engaged, and GLUT1 activity is essential for supporting this route (49,87). GLUT3 is predominantly connected to neurons, but it is also present in different types of immune cells. It has been identified as having the capacity to promote glucose uptake in situations where a quick energy source is required(88). Innate immune cells such as macrophages that express and activate GLUT3 have an increased ability to use energy during immune challenges, which allows these cells to continue producing phagocytosis and cytokines (49). It is known that glucose transporters, in particular GLUT1, control inflammation and tissue homeostasis in macrophages. When macrophage activation occurs, energy generation mostly depends on glycolysis (89,90). Metabolic reprogramming is essential to stimulate an inflammatory phenotype and allow macrophages to combat infections and eradicate pathogens (88) efficiently. Environmental variables including oxygen levels, extracellular pH, and glucose concentration affect the expression of glucose transporters, including GLUT1 and GLUT2. For example, decreased expression of these transporters in

response to high glucose levels may affect T cell activation and function in inflammatory conditions(90). Targeting these transporters may offer therapeutic advantages since autoimmune disorders exhibit overexpression and modification of GLUT expression. Research has demonstrated that inhibiting GLUT1, for instance, can enhance disease phenotypes in mouse models of systemic lupus erythematosus and rheumatoid arthritis. This suggests that GLUTs are potential targets for novel therapeutics that aim to restore immunological balance in autoimmune illnesses (91).

**4. GLUTS in Adaptive immune cell:**

Glucose transporter (GLUT) expression is essential for adaptive immune cells' activation, proliferation, and general function, particularly T and B cells. GLUT1 emerges as the primary transporter in both T cell types, whereas GLUT2 particularly contributes to glucose metabolism in T cells. When developing treatment techniques that target immune responses, it might be crucial to comprehend GLUT expression and its functional consequences. The main glucose transporter in T cells, GLUT1, has a markedly increased expression level during T cell activation. The higher glucose absorption made possible by this GLUT1 upregulation is essential for driving the glycolytic pathways that sustain T-cell expansion and proliferation during immunological responses(91). Research reveals that effector CD4+ T cell (Teff) growth requires GLUT1, but regulatory T cell (Treg) expansion does not need GLUT1, indicating distinct metabolic needs for these subsets (86,91). In addition to GLUT1, activated T cells, particularly CD8+ T cells, express GLUT2, which aids in glucose absorption and glycolysis. Environmental variables such as glucose content and oxygen levels influence GLUT2 expression, making it useful in various metabolic situations during T-cell activation(92). The activation of GLUT2 promotes the development of effector T cells, demonstrating its importance in adaptive immunological responses (92). GLUT1 plays a crucial and irreplaceable role in B cells, serving as an absolute necessity for the formation of germinal centers and the activation of B cells. The uptake of glucose by GLUT1 is indispensable for satisfying the metabolic needs required for the differentiation of B cells into antibody-secreting plasma cells and for their proliferation(93). Any impairment in GLUT1 activity can directly lead to reduced antibody production and compromised affinity maturation within germinal centers, emphatically emphasizing its critical importance for successful B cell responses(93). The predominant glucose transporter in B cells is GLUT1, though GLUT2 is also expressed and is believed to contribute to metabolic regulation within B cells, particularly in high glucose conditions(86,94). Studies indicate that GLUT2 allows B cells to adapt to varying nutrient availability during immune activation, demonstrating their metabolic flexibility(92).GLUT1 and GLUT3 regulation holds promise for treating autoimmune diseases. Deletion or inhibition of GLUT1 has shown benefits in rheumatoid arthritis and lupus models, highlighting the importance of glucose metabolism in immune function and the potential for modulating immune responses in autoimmune conditions (88)

**5. Mechanism linking GLUTS to Autoimmunity:**

The regulation of glucose uptake and metabolism in immune cells is mostly dependent on GLUT transporters, namely GLUT1, GLUT2, and GLUT3. This in turn affects the differentiation and activation of immune cells. For example, CD4 T cell activation, effector expansion, and survival depend on GLUT1, but CD8+ T cell effector responses depend on GLUT2's promotion of glucose uptake and glycolysis(92,95). Furthermore, GLUT3 is known to control Th17 cell effector activities, which are essential in autoimmune disorders(32). Immune cells express GLUT isoforms differently, which suggests that each isoform has a unique function in promoting immunological responses. The control of GLUT expression plays a critical role in autoimmune disorders by controlling the generation of cytokines and immune cell activation. In several autoimmune types, including rheumatoid arthritis, increased glucose absorption via GLUT1 is necessary for immune cell activation (96). The transporter plays a crucial role in maintaining a pro-inflammatory milieu since inhibiting GLUT1 reduces inflammatory responses and the release of cytokines such as interferon and TNF-α (89). Moreover, GLUT3's role in Th17 cell activity emphasizes its importance for cytokine signaling pathways in autoimmune diseases(91). Through their impact on immune cells' metabolic pathways, GLUT transporters especially GLUT1 contribute to persistent inflammation. Adipose tissue macrophages that have upregulated GLUT1 have been shown to

produce more inflammatory mediators, which may be the cause of disorders connected to metabolic syndrome and cardiovascular risks(97). studies have shown that GLUT-driven glucose metabolism in macrophages promotes a pro-inflammatory phenotype and strengthens the chronic inflammation associated with inflammatory illnesses(98). The metabolic reprogramming of GLUT transporters shows their potential as therapeutic targets for reducing chronic inflammation.

**6. GLUTS in Rheumatoid Arthritis:**

Rheumatoid arthritis (RA) patients differ from osteoarthritis patients in that they have increased glucose absorption and GLUT1 expression. With a reported p-value of 0.0003 (99), GLUT1 expression was specifically considerably higher in RA synovium compared to osteoarthritis synovium. This GLUT1 overexpression is associated with the metabolic requirements of activated immune cells in the inflammatory milieu typical of RA. In the pathophysiology of synovial inflammation in RA, GLUTs are essential. Several autoimmune disorders, including rheumatoid arthritis (96), are associated with increased GLUT1 glucose absorption, which is necessary for immune cell activation(96). Immune cells respond to inflammatory stimuli by altering their metabolic pathways, which requires increased glucose availability to maintain their activities.Glutamate excess in RA patients' synovial fluid can cause phenotypic alterations that lead to joint degeneration(100). Regarding the inflammatory processes that cause injury to joints, GLUTs—in particular, GLUT1—help with glucose metabolism. The ability to reduce the severity of RA symptoms in mouse models by inhibiting GLUT1 and related glycolytic pathways highlights the importance of this protein for joint health. Studies reveal a favorable relationship between GLUT activity and the severity of the illness in RA patients. Increased inflammatory responses are linked to synovial tissues' elevated GLUT1 and GLUT4 activities (101). Treatments that target GLUT expression can potentially lessen the disease's severity, indicating that GLUT activity modification may be a useful RA management tactic(102).

**7. Clinical Studies and Evidence:**

In mouse models of inflammatory disorders, including arthritis, genetic deletion, and small molecule inhibitors targeting GLUT1 have demonstrated encouraging outcomes in ameliorating disease characteristics. In these mice, GLUT1 inhibition lessened the severity of the illness, indicating the therapeutic potential of adjusting glucose metabolism.(96). It was shown that this glycolytic inhibitor inhibited the pathogenic activity of RA fibroblast-like synoviocytes (FLS), which reduced cytokine production, migration, and proliferation of cells. These results were shown in RA animal models both in vitro and in vivo, indicating that by inhibiting FLS activities linked to the illness, glycolysis inhibition may help treat inflammatory arthritis.(103). In mice with RA, BrPa, another glycolytic inhibitor, decreased cartilage degradation, inflammation, and joint edema. Mice treated with BrPa showed reduced expression of GLUT1 and decreased pro-inflammatory cytokines including IL-1β and IL-6 in the joints, suggesting that GLUT1 targeting may be useful in treating RA.(103).

**8. Possible treatments and pharmaceutical developments:**

There are new avenues for treating RA thanks to the discoveryof a carrier-free nano-drug that regulates glucose metabolism in inflammatory joints. This approach targets the local glucose metabolic pathways to alter the inflammatory environment within the joints to alleviate the metabolic abnormalities associated with RA.(104). Studies reveal that insulin sensitizers, like metformin, commonly used for type 2 diabetes (T2D), might also affect synovial inflammation in RA by reducing the spontaneous generation of inflammatory cytokines in synovial fibroblasts, such as MCP-1, IL-6, and IL-8.(101). A possible metabolic intervention for RA is the dual suppression of glycolysis and glutaminolysis, which targets two crucial metabolic processes involved in immune cell activation and function and has a synergistic anti-inflammatory impact (105).

**DISCUSSION:**

In rheumatoid arthritis (RA) and other autoimmune diseases, the function of glucose transporters (GLUTs) is a crucial point of contact between cellular metabolism and immunology. Because they provide a sufficient supply of glucose for energy and biosynthesis during activation, GLUTs are essential to immune cell activity. Their crucial role in the pathophysiology of RA is highlighted by the

overexpression of GLUTs, especially GLUT1 and GLUT3, in RA synovial cells and immune cells. In order to examine the molecular processes, immunological ramifications, and therapeutic possibilities of targeting GLUTs in RA, this discussion summarizes results from the literature.

**CONCLUSION:**

This thorough review emphasizes the critical role of glucose transporters (GLUTs) in the complex interplay between metabolism and immune function in rheumatoid arthritis (RA) and various other autoimmune disorders. By mediating glucose uptake in immune cells, GLUTs significantly influence the activation of these cells and the subsequent inflammatory response, revealing a promising and innovative therapeutic strategy that warrants deeper investigation. Moving forward, it is essential to integrate metabolic understanding with current treatment approaches for RA, aiming to enhance disease management, optimize therapeutic outcomes, and ultimately improve the quality of life for patients.

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