Harmful effects of high amounts of glucose on the immune system: an updated review

Running Title: Metabolic system of immunity

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Abstract

Release and storage of energy can be regulated by the metabolic parameter dependent on the CNS (Central nervous system). Macrophages are one of the most professional APCs (antigen-presenting cells) that are formed by the accumulation of dead or damaged cells or in response to the infection, which the main function is phagocytosis, secretion of cytokines and presenting antigen to T cells. The proper immune response needs to the production of effector cytokines along with comprehensive and rapid cell proliferation and growth. Activation of the immune system and immune cells need to increased glucose metabolism. When the immune system responds to pathogens, chemokines inform immune cells such as macrophages and T cells to travel to the infected area. Although glucose is vital for the proper function of immune cells and their proliferation, a high amount of glucose may lead to impaired function of the immune system and pathological conditions. However, a suitable amount of glucose is indispensable for the immune system, but its elevated amount leads to excessive pro-inflammatory cytokines production. In this study, we focused on the master regulatory role of glucose on the immune system.

Keywords: Metabolic regulation; Glucose, Immune system

1. Introduction

The conversion of food into energy is done by a chemical reaction which is named metabolism in the body. Thermodynamics' first law states that energy does not be created or destroyed, it must be used or stored in biological systems (1). Metabolic processes do not happen by chance in biological systems, they are regulated to create the most efficient energy obtained from the foods. CNS-dependent metabolic parameters regulate the release and

storage of its energy (2). Metabolic regulation is regulated by enzyme activity and energy metabolism is regulated by glucose, one of the most important factors in metabolism (3). G6P (Glucose 6-Phosphate) as one of the glucose derivatives has two major metabolic pathways, pentose phosphate, and glycolysis (4). G6P can also be converted to glycogen that enzymatic activity of hexokinase carries out this reaction through the action of one molecule ATP. Glucose-1-phosphate can be formed by glycogen which can undergo a glycogenolysis reaction (5, 6). Extreme production of NADPH (Nicotinamide adenine dinucleotide phosphate) may lead to the formation of G6P by G6PD, which is the first phase of the pentose phosphate pathway (7). Furthermore, if the body necessitates nucleotide precursors of DNA for synthesis and growth, G6P will enter the pentose phosphate pathway (8). G6PD produces NADPH as an essential enzyme in RBC (red blood cells), which carries oxygen from the lungs to the tissues. This enzyme protects red blood cells from premature destruction and damage (9-11). Many studies have revealed the association between immune receptors and immune responses with glucose. It has been proved that there is an association between a high amount of glucose an inflammatory response induction. Furthermore, it has been revealed that the macrophage infiltration depends on glucose levels in the body; and also some parameters could contribute to inflammatory responses and inhibit the G6PD and glucose levels (12, 13).

2. Glucose effects in innate immunity

Macrophages are the main effector cells in the innate or unspecific immune system with several roles, for instance, secretion of cytokines, antigen presentation, and phagocytosis. The generation of ROS/RNS and superoxide enhances its phagocytic activity (14). G6PD in macrophages stimulates the expression of RNS- and ROS-producing genes. ROS and RNS contribute to different signaling pathways by phosphorylating and activating MAPKs

(Mitogen-Activated Protein Kinases) (15, 16). The regulation of gene expression that is performed by ROS during the regulation of transcription factors such as NF-κB (Nuclear Factor-KB) is accountable for the expression of pro-inflammatory cytokines. The frequency of ROS is produced by NOX 2 (NADPH Oxidase 2) molecular enzymatic reactions in macrophages. G6PD is the enzyme of the pentose phosphate pathway, which can generate the NADPH (17). G6PD contributes to several metabolic pathways, such as reductive biosynthesis and oxidative stress regulation. One of the indispensable factors in regulating macrophages pro-inflammatory roles is oxidative stress. It has been hypothesized that macrophage G6PD might affect inflammatory cascades and cellular redox in response to metabolic actions. It has also been revealed that macrophage G6PD is involved in pro-inflammatory responses along with oxidative stress (18).

It has been shown that specified metabolic actions of cytokines, especially TNFα (Tumor Necrosis Factor-α), may be carried out via coordination or downstream expression of MIF (Migration inhibitory factor) in macrophages. Accordingly, MIF is expressed by different kinds of cells that are generated in response to intracellular receptor activation (19, 20). The immune neutralization of MIF regulates the levels of fructose 2, 6-bisphosphate (F26P2) in muscle tissues, which have been evaluated in Tiff mice treated with anti-MIF, and reveals the intrinsic function of MIF in catabolic responses of liver and muscle (21-25). It has also been proved that fructose 2, 6-bisphosphate is able to regulate the PKA (Protein kinase A) and PP-1 (Protein phosphatase 1) which ultimately leads to inhibition of anti-inflammatory cytokines production (21). Some studies showed that cultured adiposities secrete MIF in response to TNFα (22, 23). The result of a study conducted by Crowley et al. showed that the TNFα action on adipose tissue during the inflammation could be explained by the autocrine/paracrine action of MIF (19, 24). The relation between high glucose levels and the expression of monocyte productions came to light by in a study that had been done by Chida

et al (23). Recent studies have established that the pro-inflammatory phenotype in high glucose conditions such as diabetes was characterized by CRP (C-reactive protein), chemokines, cytokines, monocytes activity, and adhesion molecules (25-27). High glucose levels have been shown to induce ROS, inflammatory cytokines and chemokines, NF-κB, protein kinase C, and p38 mitogen-activated protein kinase activity in immune systems. Increased levels of glucose can induce superoxide anion production in monocytes and macrophages (28-30).

High glucose conditions have a direct relation to functional activation in human monocytes. Recent studies on THP-1 cells as human monocytes cell line showed its increment via up-regulating of innate immune system receptors such as Toll-Like Receptors (TLRs) with activation of NF-κB (31-33).

Calder et al. suggested that the increase of superoxide anion production in monocytes or macrophages via the up-regulation of glucose levels can increase pro-inflammatory cytokines from monocytes, and these cytokines can increase the TLRs via NF-κB factors (34). Macrophage G6PD activates NF-κB and p38 MAPK, which are the main regulators of pro-inflammatory responses and oxidative stress that cause insulin resistance in the adipose tissue of obese animals. Previous data of conducted studies on monocytes showed the presence of G6PD activity is closely associated with their phagocytic/bactericidal capacity (35). Also, studies have revealed that a high amount of glucose impairs neutrophil mobilization, which may be due to the elevated expression of PKC and TLRs (36, 37).

3. High levels of glucose enhance TLRs activation

Toll-like receptors discovered in *Drosophila* and are known as an indispensable part of innate immunity which can target several mechanisms leading to the synthesis and secretion of cytokines. TLRs act as interfaces in the development of adaptive or innate immunity by

activating other host defense programs. (38). Some data showed increased expression of TLRs in preadipocytes, human endothelial cells, keratinocytes, smooth muscle cells of coronary arteries, macrophages, and DCs (39-41). An increase in glucose levels may lead to increased expression and elevated activity of TLR2 and TLR4, resulting in culminating in NF-κB trans-activation and MyD88 (Myeloid differentiation primary response gene 88)-dependent signaling. Inhibition of TLRs such as TLR2 and TLR4 can decrease the NF-κB factors as well as macrophage activations. These mechanisms include Nox activation, involving the stages that accelerate and potentiate TLR2 and TLR4 activation performed by inflammation (33, 42). MyD88-dependent and independent pathways are two main types of signaling pathways in TLRs. MyD88 can modulate the Toll-IL-1 receptor domain. The Death domain in the N-terminal and TIR (Toll/Interleukin-1 receptor) domain in the C-terminal is processed by MyD88. Also, MyD88 may have an association with TIR domains of TLRs (43).

MyD88 employs IRAK4 (IL-1 receptor-associated kinase 4) by linking the death domains of both molecules. IRAK4 interacts with TRAF6 (TNF receptor-associated factor) before activating IRAK1, which is mediated by its phosphorylation. TRAF6 can activate AP-1 (Activator protein 1) transcription factors through the activation of MAP kinase. In addition, TRAF6 can activate TAB and TAK1 complexes, which enhances the activity of the IB kinase complex. Activation of the JNK (c-Jun N-terminal kinases) complex can be accomplished by activating TAK1, which results in the activation of the IKK (IκB kinase) complex. Activation of these complexes leads to NF-κB translocation. MyD88 is essential for the production of cytokine inflammation by all TLRs (44, 45). IRAK-1 is related to TRAF6 and activates the NF-κB transcription factor and IKK complex. But the question is how high glucose can activate TLRs in innate immune cells such as monocytes? TLR2 activity requires alteration of TLR1 and/or TLR6 to induce sensitivity to agonists. Plomgaard et al. showed that high

levels of glucose did not accumulate TLR2 and TLR6 through cytokine production and NF-κB activation. TLR2 receptor fading is caused by high glucose levels (46). It has been reported that increased TLR2 and TLR4 expression in high glucose level condition in mice, such as diabetic mice, correlates with increased pro-inflammatory cytokines and increased NF-κB activation in response to endotoxins (47, 48).

4. Effect of glucose metabolism on T cells activation and its relations with complement

The immune response function requires extensive and rapid production of effector cytokines and cell proliferation, and growth (49). The biosynthetic and metabolic necessities of lymphocytes are enhanced after activation, which has an association with glucose metabolism via increased expression of GluT1 (Glucose transferase 1). Increased GluT1 and glucose uptake leads to deficient responses of activated T cells (50, 51). The activation of T cells requires TCR (*T-Cell Receptor*) signaling and CD28 co-stimulation. TCR can mediate the adjustment of glucose metabolism via distinct pathways that induce GluT1 expression. The PI3K/Akt pathway can regulate GluT1 localization on the cell surface, which is potently activated by the CD28 co-stimulatory signal. In relation to this role for Akt, transgenic expression of constitutively active Akt increases glucose uptake and T cell size and decreases the necessity to CD28 during TCR stimulation (52, 53). Also, studies have been revealed that a high amount of glucose contributes to impaired lymphocyte activity to promote inflammation along with the reduced number and impaired functions of T-reg and NK cells (13, 54, 55). Recent studies have been revealed that that glucose releases in the presence of CRP and complement system. CRP is an acute-phase protein that activates the classical pathway of complement. CRP has a critical role in the activation of complement-dependent glucose (56, 57). It has

been revealed that glucose release was related to the quantity of CRP present with liposomes. They suggested that incubation of complement with the maximally reactive liposomes may result in a comparatively high baseline of glucose release (58, 59).

CRP can lead to elevated levels of glucose and inhibition of CRP can inhibit the complement cascades and may cause complement deficiency. Deficiency of one of the components parts before C5 results in an elevated risk of both autoimmune phenomena and pyogenic infections, such as glomerulonephritis and systemic lupus erythematosus (60).

5. Signal Transduction, receptors and metabolic regulation of cytokines

Energy augmentation and protection of immune functions in the human immune system approximately account for as much as 25% of the daily energy consumption in healthy people (61, 62). While the immune system fighting against pathogens, a special group of chemokines and/or cytokines alert the immune system by triggering signaling and specific cells, such as macrophages and T-cells to immigrate to the site of infection. These transmitters of signals activate the cells and then arouse the production of more cytokines. A direct or indirect manner in many metabolic processes reacts against pro-inflammatory cytokines to certify a constant reserve of nutrients for antibody production and proliferation of phagocyte cells. The current hypothesis says that within an immune response, cytokines lead the nutrients far from tissue growth. Thus, the major adjustments in human metabolism are caused by infections (63).

After a reduction of energy in patients, oxidation of fatty acids and protein degradation to produce amino acids for the production of acute-phase proteins are increased to provide energy.

The role of immune cells in the utilization of glucose as a vital fuel and expression of insulin receptor and respond to insulin are explained in many studies (64-66).

Moreover, glutamine as an indispensable factor for immune cell function is extremely used in nitrogen and carbon donor for nucleotide precursor synthesis as a primary fuel. Fatty acids are also used as fuel, but they are not oxidized for functioning the immune cells. IL-6, as pro-inflammatory cytokines influence the metabolism of nutrients and also act in the brain to induce fever and behavioral and physiological alterations that affect complete energy balance. (67-69). Factors such as IL-6, TNF-α, IL-1ß, and LIF (Leukemia Inhibitory Factor) are synthesized and released from adipose tissues and /or adipose which have an essential role in a wide range of metabolic and physiological processes, and body metabolism. Circulating levels of these factors are aroused by an increased expression of inflammatory cytokine (70). AS soon as TNF is released from activated immune cells, it causes glucose entrance to these cells and increases the glucose levels inside them (71).

GluT1 activity mediates glucose transfer into immune cells (72, 73). TNF has been shown to increase GluT1 expression and glucose uptake. TNF also reduces insulin-dependent glucose uptake in adipocytes and muscle under the control of the Glut4 function (74, 75). Active immune cells obtain glucose through TNF secretion via inhibiting glucose uptake by muscle cells. This process can be considered as an energy application process (76, 77).

Pro-inflammatory cytokines such as members of the IL-1 family and IL-6 were initially recognized as modulators of the immune response. A large amount of circulating IL-6 is produced by macrophages in adipose tissue in normal immune cells (Figure 1) (78). Infection and stress can cause high circulation of these cytokines in the body. However, cytokines play an important role in metabolic regulation. Polymorphisms in IL-1 and IL-6 are associated with changes in their activity and expression. IL-6 is an effective factor in the acute phase response, and CRP is an important prognosticator and also a risk factor for metabolism. Other

pro-inflammatory cytokines such as TNFα and IL-1 are also capable of regulating the acute phase response (79-81).

Downstream signaling activation by receptor binding, the profusion of the complementary receptor on the cell surface, and cytokine levels affect the cytokine's effect on cells (82, 83). Each cytokine binds to a precise cell-surface receptor and then cell functions are adjusted by following cascades of intracellular signaling. Redundancy is a feature of cytokines that makes the cytokines to share receptor subunits and perform resembling functions (84). For the transfer of glucose into the immune cells, the IL-1RI complex, which is composed of IL-1RI and IL-1 ACP (The IL-1 Accessory Protein), is essential. This complex accounts for signal transmission (85). IL-1RI together with its subsequent protein is followed by phosphorylation and recruitment of the IRAK through the docking molecule MyD88, leading to NF-κB activation (86). IL-1a/ß and its receptor antagonist drive its role through a heterodimer including IL-1RI and the IL-1AcP. Initiation of the activation of IRAK/TRAF pathway and recruitment of MyD88 is induced by binding of agonists, leading to NF-κB activation (87, 88)

The LIF and IL-6 cytokine family shares the gp130 (Glycoprotein 130) signal transducer and signal through the ligand-specific receptor and gp130. gp13 cannot transduce signals without the ligand-specific receptor whereas it has expression across all cell types. IL-6 / IL-6Ra can activate all gp130 cells even in the absence of a ligand-specific receptor. Binding of agonists causes JAK (Janus kinase) phosphorylation and initiates JAK / MAPK or JAK / STAT (Signal transducer and activator of transcription) activation (89, 90).

6. Conclusion

Metabolism is a life-sustaining chemical reaction in organisms that converts food into energy to supply the energy needed by the cells. Regulated glucose metabolism is associated with the

proper function and activation of the immune system. However, the infiltration of the high amount of glucose into the immune cells may have a worse effect on the immune system and related signaling pathways which ultimately leads to pro-inflammatory cytokines production. This may lead to impaired function of the immune system and trigger pathological conditions. The comprehensive relation between high glucose level with the immune system regulation and signaling pathways are summarized in Fig 2 and Fig 3. As a final remark, further research is needed to provide further evidence to show the relationship between different parts of the immune system and immune cells with and glucose.

Author contributions

N.S. wrote the manuscript. **J.M** and **A.M.** co-wrote and edited the manuscript. **R.E.Z.** helped in revision. M.A. drew the figures and flowchart. **H.X.** and **J.M.** supervised the work. All authors read and approved the final version of the work to be published.

Conflict of interest

None.

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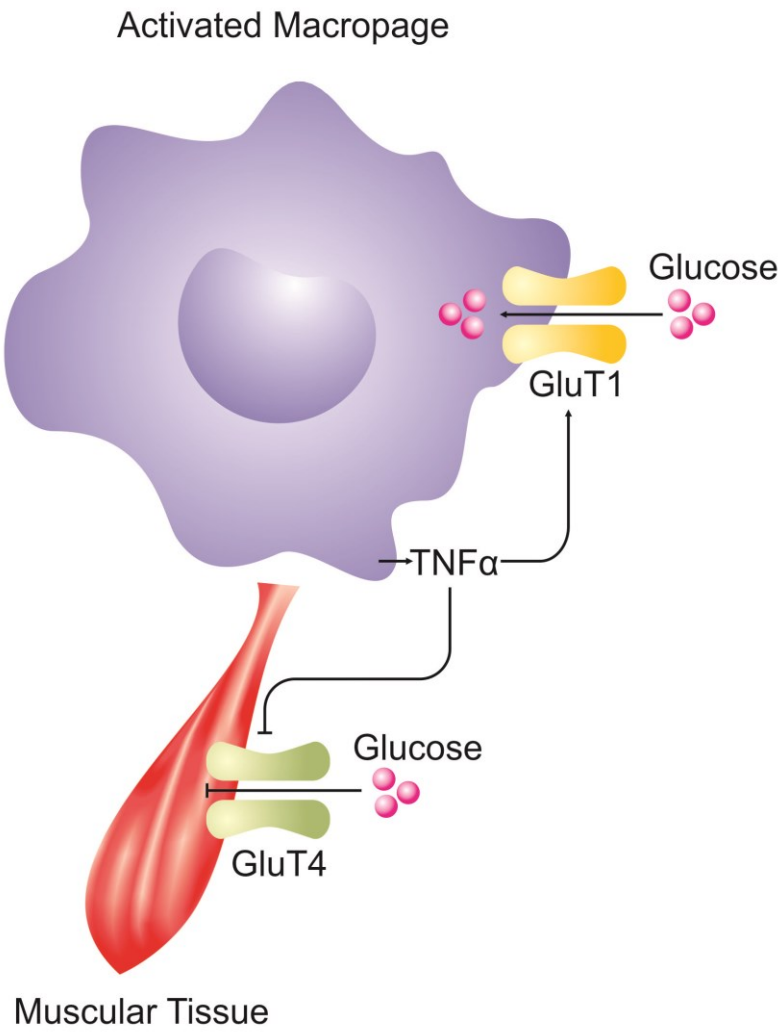

Fig 1. Modulatory role of macrophage with the secretion of TNFα in the regulation of glucose via activation and inhibition of GLTU1 and GLTU4, respectively.

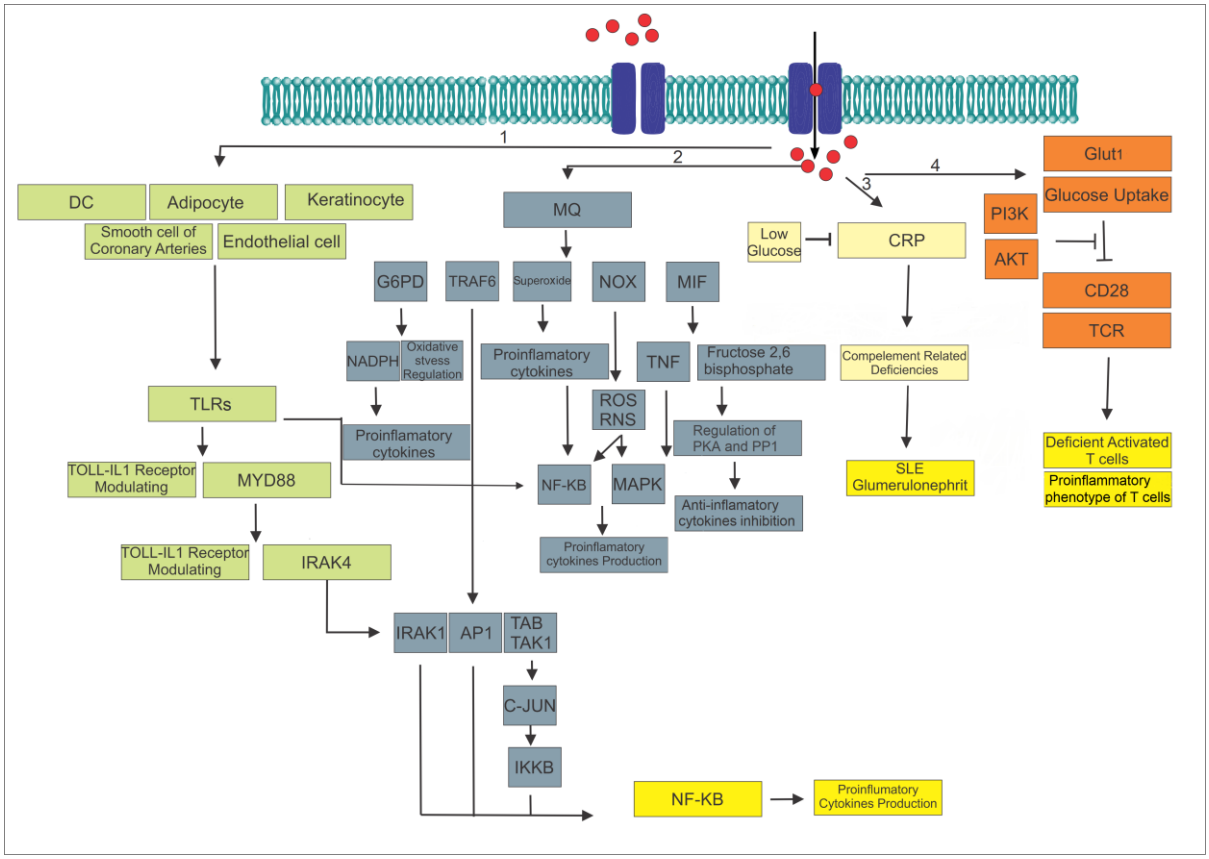

Fig 2. The diverse functional role of Glucose on immune cells and other cells.1) A high amount of glucose alters different cells to express TLRs which trigger IRAk1 and TRAF6 and ultimately leads to activating NF- kB signaling pathway and pro-inflammatory cytokines. 2)Elevated levels of glucose on macrophages have several effects, including as follows: first stimulates G6PD for NADPH and oxidative stress regulation which leads to pro-inflammatory cytokines production, second produces superoxide that enhances macrophage ability to release pro-inflammatory cytokines and NF-kB signaling activating, third produces ROS-RNS by stimulating NOX (NADPH oxidase) and induce MAPK activation along with NF-kB signaling pathways that lead to pro-inflammatory Cytokine production, fourth produce MIF (migration inhibitory factor) that leads to pro-inflammatory cytokine production via TNF upregulation and anti-inflammatory cytokines inhibition via prompting fructose 2, 6-bisphosphate (F26P2) and PKA (protein kinase A) and PP-1 (protein phosphatase 1). 3) An increased amount of glucose leads to elevated CRP (c-reactive protein) and complement

related deficiencies. 4) High levels of glucose upregulate GLUT1 expression and glucose uptake which leads to impaired CD28 and CD3 signaling and deficient activating of T cells and pro-inflammatory cytokines production, while PI3K (Phosphoinositide 3-kinases) and AKT (Protein kinase B) reverse this effect.

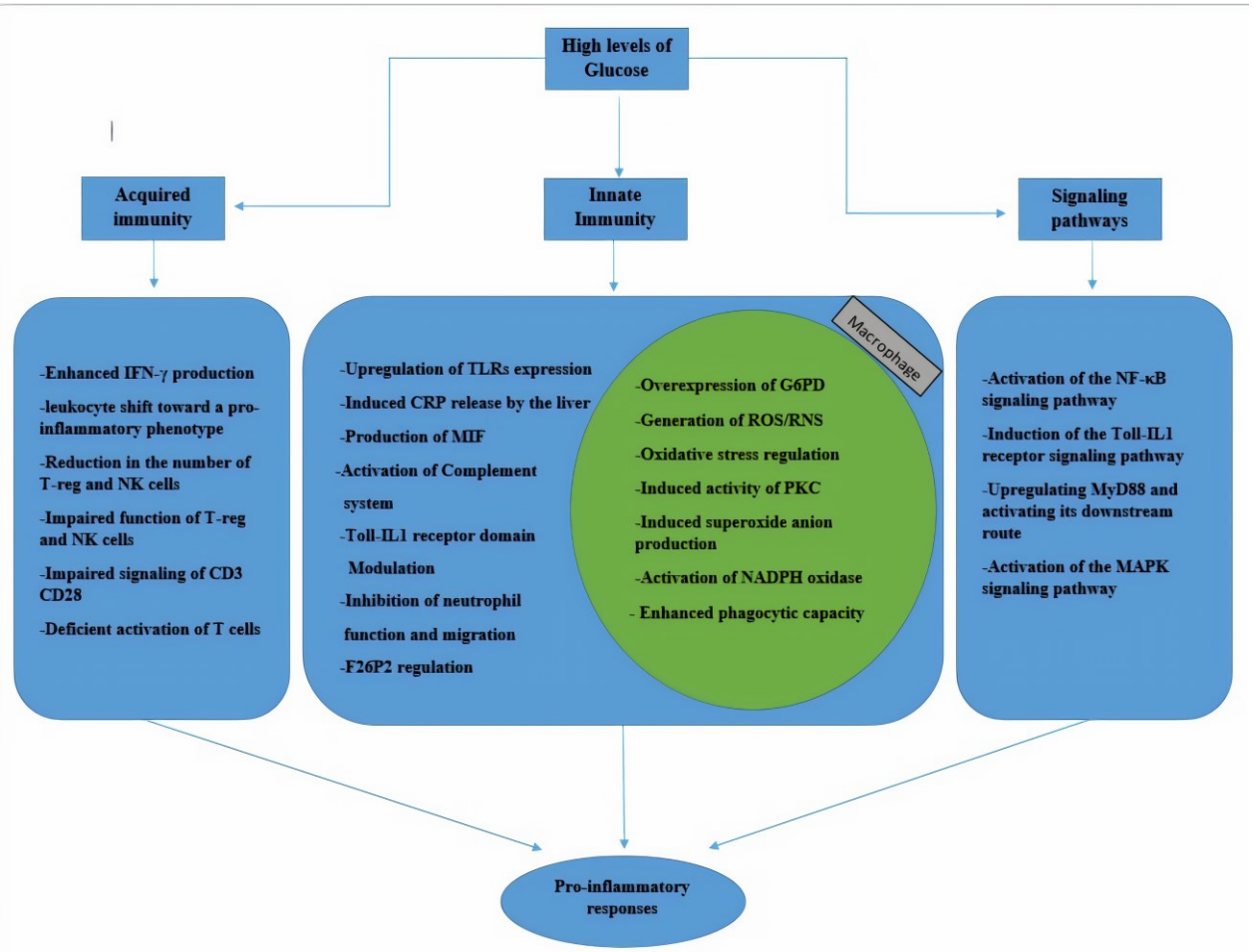

Fig 3. Effect of a high amount of glucose on the immune system and immune-related signaling pathways.