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Glutamine metabolism and its effects on immune response: molecular mechanism and gene expression

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Abstract

This article aims to review glutamine metabolism and its effects on the immune response. Selected topics are addressed, particularly the effect of glutamine on cell survival and proliferation, as well as its importance in some biochemical pathways. The impact of glutamine on muscle, intestine, and liver metabolism are described, and a special section about glutamine regulation of the immune response is included. In this context, the modulation of glutamine on relevant signaling pathways as nuclear factor kappa B (NF-kB), mitogen-activated protein kinases (MAPKs), and heat shock protein and the influence of this amino acid on cell migration and adhesion molecules are highlighted. Some important immune response pathways modulated by glutamine were described as its action in critically ill patients. In summary, this review describes some important actions of glutamine, and a range of reactions and modulatory effects in different organs, which may inform new therapeutic strategies. However, further studies are necessary to provide information about glutamine use, especially about situations in which it can be better used as well as fine-tuning dose and administration.

Keywords: Glutamine, Immune response, Nuclear factor kappa B

Background

Glutamine is an α-amino acid and is the most abundant free amino acid in the body. The first description about the glutamine importance was made by Ehrensvard et al. [1] which described the importance of glutamine to cell survival and proliferation; however, a more detailed description about glutamine actions were made by Eagle et al. 1966 [2]. At the most basic level, glutamine acts as an important fuel in the cells and tissues and a high rate of glutamine uptake is characteristic of rapidly dividing cells such as enterocytes, fibroblasts, and lymphocytes [2, 3]. The extracellular concentration of glutamine is around 0.7 mM, the most abundant extracellular amino acid in vivo, while the most abundant intracellular amino acid is glutamate, depending on the type of cell ranging between 2 and 20 mM [3].

The most important enzymes related to the glutamine metabolism are glutamine synthetase and glutaminase. Glutamine synthetase catalyzes the conversion of glutamate to glutamine using ammonia as nitrogen source (glutamate + NH_4^+ + ATP ~ > glutamine + ADP + Pi). Glutaminase is an enzyme that catalyzes the hydrolysis of glutamine to glutamate and an ammonium ion [3, 4] (Fig. 1). The immediate product of glutamine metabolism is L-glutamate. In a transamination reaction, glutamate can donate its amino group for new amino acid synthesis and deaminated to 2-oxoglutarate [3].

Glutamine is involved in various biochemical pathways. Some of those are providing energy substrate, serving as a precursor to amino acid synthesis, the nitrogen donor in the formation of nucleic acids, aiding in the synthesis of intracellular proteins, and acting as an essential contribution to the acid-base balance [2–4].

Glutaminolysis provides metabolic intermediates for synthetic pathways of macromolecules and provides

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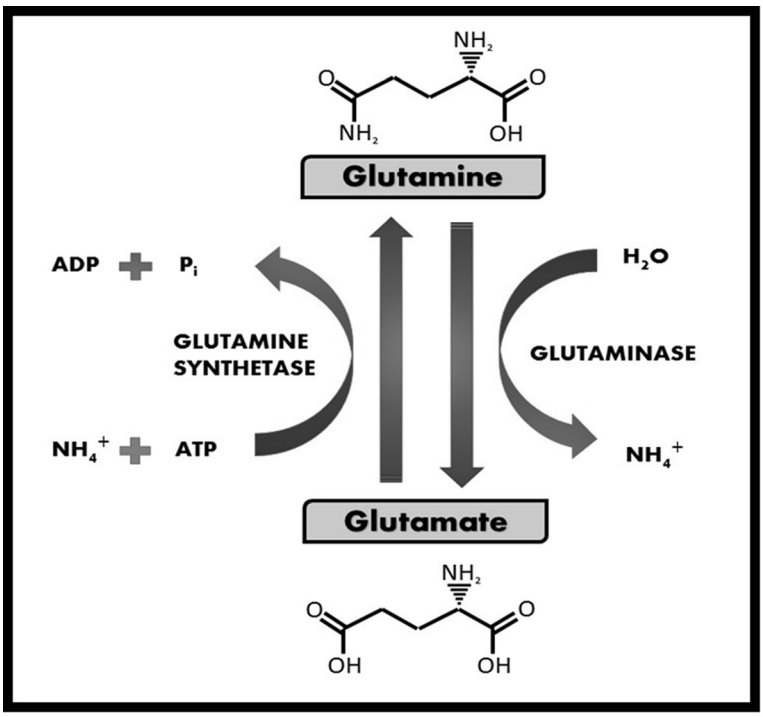

Fig. 1 Glutamine metabolism, glutamine synthetase catalyzes the conversion of glutamate to glutamine using ammonia as nitrogen source, and glutaminase is an enzyme that catalyzes the hydrolysis of glutamine to glutamate and ammonium ion

ammonia and aspartate for synthesis of purines and pyrimidines, which are necessary for the formation of DNA and RNA [5, 6]. Glutamine can generate pyruvate by a route involving conversion to glutamate, then by the activity of glutamate dehydrogenase in 2-oxoglutarate, which enters TCA cycle, followed by the action of $NADP^+$-dependent enzyme that catalyzes the conversion of malate into pyruvate. The pyruvate may be converted to L-alanine by amination, via lactate dehydrogenase in to lactate and then released, or it may enter the tricarboxylic acid (TCA) cycle. This process generates NADH and $FADH_2$ which may be used in the electron transport chain in the mitochondria, thereby promoting ATP synthesis [7].

Glutamine also can be metabolized by the gamma-glutamyl cycle and is required for glutathione synthesis. Glutathione is a tripeptide produced from glutamate, glycine, and cysteine, which can act on cells as a cofactor for the cytoplasmic enzyme [8]. In addition, the glutamine metabolism, via TCA cycle, promotes action of $NADP^+$-dependent enzyme, which increases NADPH production, consequently increasing the GSH/GSSG (glutathione reduced/glutathione oxidized) ratio [7].

Glutamine: muscle metabolism

The skeletal muscle is the major tissue responsible for glutamine synthesis in the body [9, 10]. Glutamine synthesis in the skeletal muscle not only preserves lean mass but also maintains plasma glutamine concentration in the body [9, 11, 12]. In humans, glutamine is the main intracellular amino acid (19.45 mM intracellular H_20 for the skeletal muscle). The skeletal muscle produces glutamine at high rates, on average 50 mmol/h, higher than any other amino acid. This high rate is essential to maintain plasma glutamine homeostasis and glutamine stores in the muscle [13, 14].

The key enzymes in the metabolism of glutamine, glutamine synthetase (GS), and glutaminase (GA) are regulated by transcriptional and post-transcriptional mechanisms. Only GS is responsible for de novo synthesis of glutamine. GS expression is mainly regulated by hormones such as glucocorticoids [10, 15], and activity of this enzyme changes with age [16]. GA activity has also been found in the muscle, but this activity is probably attributed to the infiltration of other cell types in this tissue [10, 17].

Glutamine transport in the muscle is performed by the N^m system, which controls the concentration of intramuscular glutamine and appears to be responsible for both the outflow and inflow of glutamine. This system is Na^+ dependent and differs from the N system in the liver by being pH independent. However, their activity is sensitive to insulin and glucocorticoids [15, 17, 18].

Glutamine also participates in the synthesis of glycogen in the muscle. In rats, intraperitoneal administration

of glutamine increased glycogen in the skeletal muscle [19]. In humans that showed a decrease in glutamine and muscle glycogen after exercise, an intravenous infusion of glutamine increased the plasma concentrations of this amino acid [20].

Glutamine: intestine metabolism

In intestinal epithelial cells, glutamine is quantitatively the most important fuel. It is metabolized to glutamate, which undergoes transamination, so the metabolites of this reaction are oxidized in the TCA cycle to generate pyruvate. Pyruvate then undergoes amination to produce L-alanine via the action of alanine aminotransferase [7].

For many years, the intestine was investigated merely as an organ of digestion, nutrient absorption, and fermentation. However, it is now known that the intestine is a complex organ that performs a diversity of critical physiologic functions. The intestinal mucosa contains secretory, immune, and neuroendocrine cells besides the absorptive enterocytes [21]. Besides serving as a major organ for nutrient digestion and absorption, the single layer of epithelium lining the gastrointestinal tract creates a selective barrier to prevent the transferring of damaging agents as toxins, allergens, and pathogens to the systemic blood circulation [22].

Newer research has shown since the studies conducted by Windmueller and Spaeth in 1980 [23] that glutamine is the main energy substrate of enterocytes. Rapidly dividing cells require glutamine, as glutamine supplies of half of nitrogen requirement for purine and pyrimidine synthesis via action the carbamoyl phosphate synthetase II within cytosol [24]. Glutamine is also a potential precursor in the synthesis of *N*-acetyl-glucosamine and *N*-acetyl-galactosamine, which may play a critical role in the intestinal mucin synthesis and therefore for the maintenance of passive barrier to bacterial invasion [25].

The entire gastrointestinal tract extracts around 20 % of circulating post-absorptive glutamine, and over 90 % of the glutamine extracted by the small intestine is metabolized by mucosal cells [26]. The high absorptive capacity in the apical region of enterocytes is the reason this cells capture glutamine priority from the lumen, and apparently, almost all glutamine contained in the diet is utilized by the enterocytes [23]. The measurements of intestinal glutamine metabolism also showed that glutamine is the precursor for a number of important metabolic pathways, especially those leading to the synthesis of ornithine, citrulline, proline, and arginine. Glutamine dipeptides induce mucosa proliferation of the ileum and colon in human in vitro [27].

It has been reported that glutamine supplementation increased villus height and area of the jejunum, but did not alter the mass of protein or DNA 4-day old piglets [21, 28]. Wu et al. [29] reported that a diet for weaned pigs supplemented with 1 % glutamine prevented atrophy of the villi of the jejunum. In 2011, Wu [30] demonstrated that dietary glutamine supplementation prevents jejunal atrophy in weaned piglets and glutamine supplementation reversed the elevation of jejunal corticotropin-releasing factor (CRF), which block the release of proteases and TNF-α from mast cells in the jejunum, thereby conferring a protective functional of the intestinal mucosa [31]. According to Li and Neu et al. [32], glutamine deprivation decreases the expression of claudin-1, a tightly junction protein, and increases permeability in cultured Caco-2 cells.

Glutamine: liver metabolism

The liver plays a central role in the nitrogen metabolism in the body. Transportation of nitrogen is performed mainly from the muscle and lung to the liver, as glutamine, alanine, and aspartate. The breakdown of glutamine releases NH_3 that through mitochondrial enzymes enters the urea cycle as a substrate. The urea cycle consumes two molecules of ammonia and one molecule of carbon dioxide, creates one molecule of urea, and regenerates a molecule of ornithine for another turn. In the kidney, the action of glutaminase produces the NH_3 and because that glutamine is quantitatively the most important donor of NH_3 in this tissue. In the collecting tubule, NH_3 combines with exported H^+ to form NH_4^+, which is excreted in the urine. Thereby, glutamine metabolism is essential for acid-base buffering [33] and also plays an important role in the biosynthesis of nucleotides, detoxification of ammonia, glutathione synthesis, and maintenance of nitrogen transfer between organs [5, 12, 34].

GS and GA are present in the liver, with the GS being expressed in perivenous hepatocytes and the GA in the periportal zone [12]. Krebs [35] was the first to describe hepatic metabolism of glutamine and hydrolysis of this amino acid to glutamate and ammonia. In the liver, glutamine metabolism is important in the regulation of the urea cycle, detoxification of ammonia, and the pH maintenance [12]. The glutamine transport can be dependent upon Na^+(ATB^0, $B^{0,+}$, y^+L) and SNAT carriers (sodium-coupled neutral amino acid transporter) of the SLC38 gene family. Such carriers include SNAT2, SNAT4, SNAT3, SNAT5, Lat2, and LAT1, and SNAT 3 and 5 are considered the most important in plasma membrane of hepatocytes [12, 35, 36]. Studies have shown the role of these transporters in the hepatic metabolism and glutamine flow [37–39].

The role of FXR nuclear receptor in hepatic glutamine has been also investigated. It is believed that this receptor and its ligand are involved in the regulation of glutamine and glutamate metabolism [40, 41]. Other studies have highlighted the importance of hepatic metabolism of glutamine in hepatic encephalopathy [42] and cancer [43].

Due to the important role of glutamine in hepatic metabolism, many studies have investigated this amino acid in liver injury situations [44–46]. In a study evaluating parenteral nutrition in premature infants, it was found that parenteral glutamine supplementation was beneficial to the liver in these individuals [46]. Previously, Wu et al. [47] evaluated the effects of parenteral administration of the alanyl-glutamine dipeptide in total parenteral nutrition associated with liver damage in infant rabbits and observed that this dipeptide supplementation can minimize liver damage and reduce malondialdehyde (MDA) production and hepatocyte apoptosis during total parenteral nutrition.

Glutamine and immune response

Glutamine is typically included in the list of "immunonutrients" that possess biological effects; glutamine is a major fuel for many cells including lymphocytes, macrophages, fibroblasts in culture, and malignant cells [6]. For example, Newsholme and Parry-Billings [9] demonstrated a close relationship between the rate of phagocytosis in murine macrophages and glutamine concentrations. Macrophages are metabolically active cells, characterized by high rates of protein secretion and membrane recycling. Accordingly, macrophages are dependent upon extracellular sources of glutamine [6, 48]. The maintenance of glutamine plasma concentrations has considerable influence on the function of some cells and tissues. It has been described in the literature that decreased glutamine plasma concentrations may have important influences on the lymphoid system, as well as the function of macrophages [6, 48].

Ogle et al. [49] found that in cells from burn patients, addition of glutamine in neutrophils improved the neutrophil bactericidal function. With glutamine, neutrophils were better able to kill *Staphylococcus aureus*. Glutamine addition resulted in restoration of cell function to normal levels. Furthermore, glutamine is important to the maintenance of functional integrity mitochondrial and the ATP production, protecting the neutrophils from apoptosis.

Cells of the immune system have higher glutamine requirements during inflammatory states such as sepsis and injury. As the consequence of the increased requirement, the demand for this nutrient may exceed production, leading to an imbalance. As a result, the bloodstream and tissue concentrations fall. These low concentrations of glutamine limit the ability of various tissues to achieve optimal function, especially for immunological tissues. Plasma glutamine concentrations reflect only the environment of cells in the lymph nodes or in the spleen, which are adjacent to the capillaries. As glutamine is extracted from the extracellular fluid, cells located a greater distance from the capillaries are exposed to a reduced glutamine concentration compared to the plasma. Kupffer cells may also be exposed to lower glutamine concentrations than observed in the plasma because their sinusoidal arrangement within the hepatic lobule does not allow all cells to come into direct contact with circulating blood. In addition, the blood supply to the liver via the portal system has a lower glutamine concentration because the small bowel has already extracted some of the glutamine for its own use. Therefore, based on the present knowledge, immunologic tissue is compromised by low concentrations of glutamine [6, 50].

Glutamine: critical illness

The systemic inflammatory response syndrome (SIRS) and the compensatory inflammatory response syndrome (CARS) were conceptually described in the 1990s [51]. SIRS are nonspecific and may or may not be related to infections by pathogens and is defined by the following clinical criteria: fever greater than 38 °C or less than 36 °C; heart rate >90 beats per minute; respiratory rate >20 breaths per minute and leukocytes >12,000/uL or <4000/uL or >10 % immature forms [52, 53]. The consensus for severe sepsis definition includes, among other factors, the presence of two or more criteria for SIRS; however, a recent study addressed cases of individuals with SIRS-negative severe sepsis [53]. Moreover, recently, the definition of sepsis was revised, the new definition consist in a systemic response to infection with the presence of some degree of organ dysfunction [53, 54].

The major pro-inflammatory factors that contribute to SIRS are TNFα, IL-1, neutrophil degranulation products, coagulation factors, platelet-activating factor and arachidonic acid derivatives, and others [52]. As with SIRS, CARS is a complex immune response involving anti-inflammatory and immunosuppressive mechanisms that are able to restore homeostasis after injury and SIRS or, if unchecked leads to a state of profound immunosuppression, predisposing the individual to infections [52, 55].

Mixed anti-inflammatory response syndrome (MARS) represents the transition from SIRS to CARS followed by homeostasis or predominance of one over the other [52] and even switching between the increase and decrease of anti- and pro-inflammatory mediators [56]. In the context of regulation of the immune system, the role of nutrients and bioactive compounds in the modulation of inflammatory responses is often discussed [57–59]. In recent decades, the immunomodulatory potential of glutamine has been demonstrated [59] as being essential for metabolism of immune cells such as neutrophils, lymphocytes, and macrophages which in some cases use more glutamine than glucose [5, 7, 59]. Additionally, glutamine is a precursor to glutathione which is responsible for preventing oxidative stress by reacting directly with reactive oxygen species [60, 61].

In critical situations, the reduction in plasma glutamine concentration affects the redox state and the metabolism of cells of the immune system, resulting in compromised immune response contributing to the development of sepsis. Thus, studies have evaluated the benefits of maintaining glutamine concentration in critically ill patients [62–64], especially in cases related to inflammatory response syndrome (SIRS) and sepsis [65–68]. Studies have been performed in an attempt to gather data demonstrating the effectiveness of glutamine supplementation in critically ill patients [62, 63]. Lin et al. [62] concluded that in glutamine supplementation for burn patients, a significant decrease in mortality and in the number of individuals infected with gram-negative bacteria was seen. Bollhalder et al. [63] analyzed the effects of parenteral nutrition with glutamine in randomized trials and concluded that supplementation decreased the length of hospital stay and the occurrence of infectious diseases. However, both studies had methodological inconsistencies such as start and time of supplementation, glutamine dose, disease severity, among other factors, and more clinical trials are needed to assess the effectiveness of glutamine supplementation in critically ill patients.

Recent research has shown that septic patients are usually hypercatabolic. Because of the impairment of the ability to use glucose and fat, there is an increasing dependency on muscle breakdown, providing essential substrates for acute phase protein synthesis and energy production [69]. Glutamine requirements increase markedly, and its utilization may exceed endogenous production [51, 70]. Glutamine depletion decreases proliferation of lymphocytes, influences expression of surface activation markers on lymphocytes, affects the production of cytokines, and induces apoptosis [71].

Contrary to the benefits of glutamine in critically ill patients, a randomized clinical trial evaluating 1223 adult patients undergoing mechanical ventilation, with failure of multiple organs receiving high doses of glutamine (30 g/day), antioxidants, glutamine and antioxidants, or placebo, revealed that glutamine supplementation was associated to increased mortality in these individuals [72, 73]. The authors attribute the difference in the results obtained in relation to literature to factors such as doses, route of administration, patient status, start of supplementation, and also the possibility of publications bias, once conclusions about the benefits of supplemental glutamine in critically ill patients started from meta-analyzes with small numbers of clinical trials, methodologically less robust [72].

However, those results are still controversial, and it is important to consider the timing of glutamine administration. In studies where glutamine was administered before the onset of infection, it prevented the infection, both in animals and in humans. This is most likely by maintaining glutamine concentrations and preventing a state of glutamine deficiency. Therefore, such patients are protected from the inadequacies of present day conventional nutrition, which makes them susceptible to infections [74].

Given the lack of full knowledge and the necessity to clarify some beneficial effects of glutamine supplementation in critically ill patients, this highlights the need to conduct more well-designed clinical studies.

Molecular mechanism and gene expression

Heat shock protein

Heat shock proteins (HSPs) are a family of highly conserved intracellular "housekeeping" proteins that maintain cell function [75]. They exert roles in antigen presentation, activation of lymphocytes and macrophages, and activation and maturation of dendritic cells, as well as acting as a stimulator of pro-inflammatory cytokine production. Thus, it has been suggested that HSPs provide the link between innate and adaptive immune systems [76]. HSP-70, one of the members of the HSP protein family, has powerful immune regulatory effects, providing cellular protection by preventing apoptosis and cell death. Under physiological circumstances, HSP-70 is detectable in plasma of healthy individuals, suggesting that during times of homeostasis, HSP-70 does not promote an inflammatory response and its immune regulatory/inflammatory functions are tightly controlled [75].

A model of sepsis, in vitro, reported that glutamine promoted HSP70 release, and addition of 2 mM glutamine significantly increased HSP-70 levels and promoted an early pro-inflammatory response [75]. In accordance with that, Jordan et al. [77] showed that in critically ill children after 5 days of glutamine supplementation, there was a remarkably higher level of HSP-70, in comparison with the sharp decline observed in control group.

Mitogen-activated protein kinases

Mitogen-activated protein kinases (MAPKs) are protein Ser/Thr kinases that convert extracellular stimuli into a wide range of cellular responses. MAPK pathways coordinately regulate gene expression, mitosis, metabolism, motility, survival, apoptosis, and differentiation [78].

Glutamine uptake is enhanced in activated lymphocytes. ERK signaling, a MAPK family member, is required for enhanced glutamine uptake and increased activity of key metabolic enzymes. Carr et al. [79] showed that glutamine uptake is blocked in lymphocytes when ERK was inhibited, thus demonstrating that in these cells, ERK is a central player in cellular metabolic control. In addition, glutamine inactivates p38 and JNK and exhibits a protective effect against endotoxic shock when administered after LPS injection [80].

Glutamine also possesses anti-inflammatory activity via deactivating cytosolic phospholipase A2 (cPLA2). Glutamine indirectly deactivates cPLA2 by dephosphorylating p38 MAPK, the major kinase for cPLA2 phosphorylation, through inducing MAPK phosphatase-1 (MKP-1). Lee et al. demonstrated a physical interaction between glutamine-induced MKP-1 and pcPLA2, suggesting that glutamine can directly deactivate cPLA2 via early induction of MKP-1 [81].

Zhu et al. [82] demonstrated that glutamine deprivation induced autophagy, disturbed amino acid metabolism, and inactivated mTOR and MAPK/ERK signaling pathways in porcine intestinal epithelial cells-1 (IPEC-1). In addition, supplementation with 5 mM of glutamine is able to increase ERK1/2 phosphorylation in IPEC-1. Thus, glutamine supplementation suppresses autophagy, increases cellular protein content, and promotes cell proliferation.

Nuclear factor-Kb

The nuclear factor kappa B (NF-kB) signaling pathway serves a crucial role in regulating the transcriptional responses of physiological processes including cell division, cell survival, differentiation, immunity, and inflammation [83]. The IkB family of inhibitory proteins sequester inactive NF-kB in the cytosol, therefore regulating NF-kB dimers. Activation of NF-kB/Rel proteins therefore requires degradation of IkB proteins via ubiquitin-mediated proteolysis to initiate nuclear translocation and DNA binding of active NF-kB/Rel complexes [84].

The central role of NF-kB in both innate and adaptive immunity is mediated by the coordinate expression of multiple genes essential for the immune response. The importance of NF-kB is revealed by the extensive list of NF-kB-inducible genes, including those for pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α as well as chemokines [85] (Fig. 2).

Oral supplementation with glutamine (1 g/kg) plus L-alanine (0.61 g/kg) or 1.49 g/kg L-alanyl-L-glutamine dipeptide was able to attenuate total NF-kB p65 expression in mouse gastrocnemius skeletal muscle after LPS stimulation in an animal sepsis model promoting anti-inflammatory effects via the NF-kB pathway [86].

There is evidence for redox imbalance and oxidative stress in human sepsis, as demonstrated by increased markers of oxidative damage with higher activation of NF-kB [87, 88]. Glutamine appears to be one of the antioxidants of possible clinical benefit. It is the most abundant amino acid in the body, and it is an important precursor of glutathione (GSH). Its supplementation in enteral and parenteral nutrition solutions can be used to maintain high levels of GSH and prevent oxidative stress-induced damage [88]. Glutamine treatment in a model of non-alcoholic fatty liver disease decreased NF-kB activation, and it was able to mediate the reduced

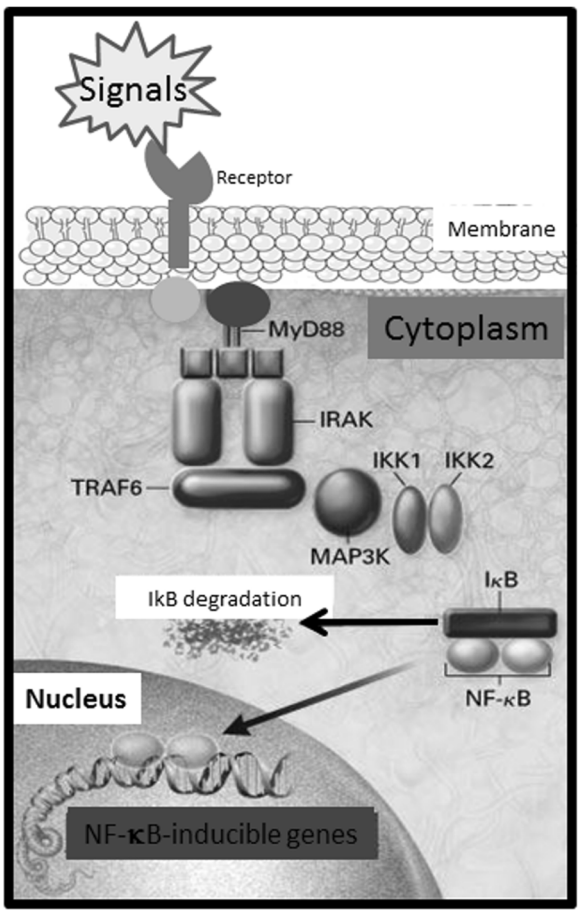

Fig. 2 Representation of the nuclear factor kappa B (NF-kB) pathway activation. An external inflammatory signal activates the signaling pathway, leading to the phosphorylation of proteins that culminated in the IKB activation and degradation, allowing the NF-kB to migrate to the nucleus and binding to specific regions of the DNA

transcription of downstream inflammatory factors, thereby decreasing hepatic damage and reducing ROS generation, alleviating the oxidative stress of the liver cells [89].

Macrophages supplemented with glutamine have revealed that stimulation with LPS increased NF-kB activation under 2 and 10 mM of glutamine supplementation in comparison to macrophages treated with 0 and 0.6 mM of glutamine, as examined by DNA binding activity of NF-kB using an electrophoretic mobility shift assay (EMSA) [90]. Alternatively, da Silva et al. [91] demonstrated lower expression of phosphorylated NF-kB in macrophages cultivated with higher concentrations of glutamine and stimulated with LPS, showing that glutamine negatively regulated NF-kB signaling pathway.

Role of glutamine on cell migration and adhesion molecules

Several studies have demonstrated the influence of glutamine on cell migration and adhesion molecules.

Chu et al. [92] induced colitis in a group of mice and then either supplemented with glutamine or received a control diet. Both groups exhibited mucosal ulceration, gland distortion, and leukocyte infiltration, but pretreatment with glutamine reduced leukocyte infiltration to tissues and resulted in less severe mucosal inflammation compared to animals without the addition of glutamine.

A study examining early-weaned mice (at the age of 14 days) and intraperitoneally inoculated with BCG (Mycobacterium bovis cepa Moreau) reported that glutamine supplementation increased leukocytes, lymphocytes, and neutrophils in the peripheral blood, while BCG inoculation reduced the percentage of lymphocyte and increased the count and percentage of neutrophils. Both in the spleen and in the bone marrow, glutamine supplementation led to an increase in granulocytes and lymphocytes. Thereby, the authors evidenced that the function of macrophages and hemopoiesis were increased by the intake of glutamine-supplemented diet in early-weaned and BCG-inoculated mice [93]. In addition, Kim et al. [94] indicated that glutamine dose-dependently enhanced migration of immortalized human dental pulp cells (HDPCs). They also demonstrated that glutamine favors growth, migration, and differentiation in HDPCs through the BMP-2, Wnt, and MAPK pathways, developing a better response in pulp repair and regeneration.

Zou et al. [95] evaluated the potential function of GS in reactive astrocytes at the site of mechanical spinal cord injury. Using siRNA-mediated GS knock-down to suppress astrocytic GS, the authors demonstrated increased cell migration into the scratch wound zone and decreased substrate adhesion. In addition, they showed that glutamine-enhanced migration and glutamate suppressed it. Glutamine is also known to regulate the expression of extracellular matrix ligands and their receptors. This may explain the increased motility observed in the presence of exogenous glutamine since the GS-silenced astrocytes express a considerably lower affinity for the extracellular matrix (ECM).

Adhesion molecules and chemokine receptors strictly regulate leukocyte migration to specific tissues through several mechanisms. Adhesion molecules present on the vascular endothelium allow leukocytes to tether, roll, and adhere [96]. The expressions of those molecules are upregulated by proinflammatory cytokines (TNF-α and IL-1) and NF-kB pathway [97].

Rogero et al. (2008) [93] investigated how glutamine supplementation in early weaning (EW) mice influences the adhesion capacity of peritoneal macrophages. EW macrophages have a decreased ability to adhere when compared with the control group, but glutamine supplementation at 1 and 2 mM were capable of reversing this effect. EW macrophages also showed less spreading ability when compared to the control group, an effect that was reversed by in vitro glutamine supplementation.

Rogero et al. [98] found that early weaning was associated with reduced glutamine ingestion which negatively affected the peritoneal macrophage adhesion, phagocytosis, fungicidal activity, and synthesis of NO, H_2O_2, and pro-inflammatory cytokines. Opsonization and phagocytic capacity are increased during inflammation when macrophages and monocytes are able to adhere to the extracellular matrix. Therefore, they hypothesized that the decreased phagocytic and fungicidal activities and the lower synthesis of TNF-α in the absence of glutamine is associated with diminished adhesion observed in peritoneal macrophages. However, it is necessary to define if the modulation caused by glutamine is due to its metabolism in these cells or their substrates generated by various biochemical pathways, or else the effect of direct or indirect action of this amino acid on the expression of genes involved in phagocytosis or inflammatory processes [98, 99].

Yeh et al. [100] analyzed the impact of dietary glutamine supplementation in adhesion molecules in mice with sepsis induced by cecal ligation and puncture (CLP). The progression of sepsis raised the concentrations of intracellular adhesion molecule-1 (ICAM-1) reaching the maximum at 12 and then declining by 24 h after CLP. The glutamine group displayed significantly lower plasma ICAM-1 levels at 6, 12, and 24 h after CLP compared with the control group. This group also exhibited higher expression of lymphocyte CD11a/CD18 and lower PMN expressions of CD11b/CD18. So, under a septic condition, glutamine administration may improve lymphocyte function, decreased PMN–endothelium interactions, and thus may diminish neutrophil infiltration into tissues.

Hou et al. 2014 [96] showed that adhesion molecules (PSGL-1 and CD 11a) and C-C chemokine receptor type 9 (CCR9) on Th cells and cytotoxic T cells significantly increased in both blood and mesenteric lymph nodes after induced colitis. Oral glutamine administration suppressed T cell expression of adhesion molecules and CCR9, downregulated the mRNA levels of adhesion molecules expressed by endothelium in colon tissues, and suppressed Th-cell infiltration into the colonic mucosa.

A study investigated the effect of parenteral glutamine supplementation on leukocyte integrin expression and immune cell recruitment after gastrectomy in Wistar rats. Surgery promoted higher CD11b/CD18 expression in polymorphonuclear leukocytes, and glutamine supplementation decreased CD11b/CD18 expression. Additionally, 3 days after surgery, more neutrophils were recruited to the site of injury, and both glutamine as

conventional parenteral nutrition group was associated with lower CD11b/CD18 expression than those on post-operative day 1 Sham group [101].

Other researchers evaluated the effects of glutamine supplementation in adhesion molecules in diabetic mice. Soluble adhesion molecule levels in diabetic patients are significantly higher than those in healthy controls, and excessive expression of adhesion molecules may induce an inflammatory response and tissue injury. Diabetic mice had higher concentrations of ICAM-1 and VCAM-1 than the normal group, but glutamine did not affect ICAM-1 and VCAM-1 level in the diabetic group. However, glutamine lowered CD11a/CD18 expression in the diabetic group (with or without glutamine). Thus, in a diabetic condition, leukocyte adhesion may be decreased when glutamine is administered [102, 103].

Human cells were also evaluated in the presence or the absence of glutamine in some studies. Spittler et al. [104] demonstrated for the first time that glutamine concentration in cell culture could affect the expression of several antigens on human monocytes.

With the aim to better understand the effect of glutamine in the treatment of sickle cell anemia, the adhesion of sickle RBC to human umbilical vein endothelial cells (HUVEC) was determined. Oral L-glutamine therapy significantly reduced adhesion of sickle RBC to HUVEC in both assays with autologous plasma-incubated cells and LPS-incubated cells, similar to the levels in healthy control. This effect may be explained by improvement of NAD redox potential of sickle RBC, which prevents oxidant damage, therefore decreasing stimulation of inflammation and expression of adhesion molecules [102].

In contrast with the other findings, a study performed with seven different concentrations between 0.05 and 2 mM of glutamine revealed that low concentrations of glutamine express significantly less CR4 (CD11c/CD18), CR3 (Mac-l, CD11b/CD18), and ICAM-1/CD54 than monocytes cultured with higher concentrations [103].

Over time, many studies have been demonstrated the importance of glutamine concentration in cell migration and the expression of adhesion molecules. Although most studies have demonstrated that the presence of glutamine decreased cellular infiltrates in tissues and reduced the expression of adhesion molecules, there are still controversial data. This can be explained by the use of different cell types, concentrations, time, and model study. The mechanisms by which glutamine modulates these parameters still need to be studied in order to improve understanding.

Conclusions

Glutamine supplementation leads to a range of reactions and modulatory effects of processes across different organisms. Although many studies have unveiled and evaluated the glutamine effects in numerous biological processes, further studies are necessary to provide information about safe dose usage of glutamine supplementation in patients.

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

DCO participated in the design of the study and wrote the introduction and molecular mechanism and gene expression sections. FSL wrote the glutamine, muscle metabolism, liver metabolism, and critical illness sections. TS wrote the glutamine, intestine metabolism, and immunologic response sections. ACAS wrote the role of glutamine on cell migration and adhesion molecules section. MMR participated in the design of the study and worked in all sections. RAF participated in the design of the study and drafting the manuscript, contributing in all review section. All authors read and approved the final manuscript.

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