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Dual Role of Arginine Metabolism in Establishing Pathogenesis

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Abstract

Arginine is an integral part of host defense when invading pathogens are encountered. The arginine metabolite nitric oxide (NO) confers antimicrobial properties, whereas the metabolite ornithine is utilized for polyamine synthesis. Polyamines are crucial to tissue repair and anti-inflammatory responses. iNOS/arginase balance can determine Th1/Th2 response. Furthermore, the host arginine pool and its metabolites are utilized as energy sources by various pathogens. Apart from its role as an immune modulator, recent studies have also highlighted the therapeutic effects of arginine. This article sheds light upon the roles of arginine metabolism during pathological conditions and its therapeutic potential.

Introduction

Arginine is a semi-essential amino acid which plays an important role during innate as well as adaptive immune responses [1•]. Arginine is a common substrate for four enzymes responsible for arginine catabolism in mammals: arginase, nitric oxide synthase (NOS), arginine decarboxylase (ADC) and arginine glycine amidinotransferase (AGAT). NOS is responsible for conversion of arginine to nitric oxide (NO) and citrulline. NO is a key player in innate immunity due to its antimicrobial potential. There are three isoforms of NOS – two constitutively expressed forms, neuronal NOS (NOS1) and endothelial NOS (NOS3), and inducible NOS (iNOS; NOS2), which is capable of high-output NO production. The rate-limiting step in NO production is the availability of arginine. The availability of arginine is determined by two factors, uptake into cells by cationic amino acid transporters (CATs) and the level of arginase [2]. Extracellular arginine is also known to increase iNOS expression at translational level by reducing the levels of phosphorylated eIF2 α , eukaryotic translation initiation factor which regulates translation [3].

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Arginase is a metalloenzyme which hydrolyzes L-arginine to ornithine and urea. The two isoforms of arginase exhibit differential subcellular localization and tissue distribution. Arginase I, a cytosolic enzyme, is predominantly expressed in hepatocytes. However, arginase II is a mitochondrial enzyme, and is expressed in brain, kidney, small intestine, monocytes and macrophages.

Arginine as an energy source during infection

Effective antimicrobial action in the intracellular environment in macrophages is brought about by molecules like nitric oxide (NO) and reactive oxygen species. The metabolism of arginine contributes to production of NO. The host cell maintains a basal level of free arginine in its cytoplasm. Intracellular pathogens like *Salmonella typhimurium*, *Mycobacterium tuberculosis*, etc. have the ability to utilize the host arginine pool. Arginine acts as a trigger for expression of various pathogenicity genes. The catabolism of arginine by the hydrolytic cleavage of arginine to ornithine and urea is well-studied in biological systems [4•]. Lately, extensive numbers of arginine utilization pathways have been discovered that highlight the importance of arginine as an energy source. The various pathways that operate in different microorganisms include the following: arginine to urea conversion pathway; arginine deaminase pathway; arginine succinyl transferase pathway; arginine transaminase, oxidase, and oxygenase pathways; and arginine decarboxylase pathways. The central enzyme to all these pathways is arginase [4•].

Agmatine is the product of the arginine decarboxylase pathway, which is efficiently utilized by bacteria as a source of energy [5••]. An example of a pathogen that utilizes its potential to metabolize arginine is *Pseudomonas aeruginosa*. It is an opportunistic pathogen, which colonizes the pulmonary system of the human body, especially the lungs. Agmatine has no deleterious effect on the pathogen. Further, agmatine is metabolized to putrescine, which acts as a source of ATP. A major cause of concern regarding *Pseudomonas* infection is its ability to form biofilms in the lungs. Biofilms are resistant to antibiotics and other antimicrobials owing to the rigid extracellular polymeric substance (EPS) [6]. Recently, it was shown that the presence of agmatine in the extracellular spaces of the lungs triggers biofilm formation. An alternate operon (*agu2ABCA'*) has been discovered, which detects the environmental agmatine in *P. aeruginosa*. In vitro experiments with the macrophage-like cell line, RAW 264.7, have also revealed the up-regulation of the arginine decarboxylase pathway in response to LPS and cytokines, resulting in increased agmatine concentrations [5••].

Leishmania genome includes an arginase encoding gene. Arginase-deficient *Leishmania* strain shows compromised intracellular survival in macrophages. In hosts, inhibition of arginase I and depletion of metabolites like agmatine result in decreased survival of *Leishmania* [7•]. These facts highlight the role of arginine metabolism during pathogenesis.

The importance of arginine metabolism has been reported in other pathogens like *Salmonella Typhimurium*, *Helicobacter pylori* and *Mycobacterium tuberculosis* [1•] as a source of energy and as a trigger for polyamine synthesis required for efficient pathogenesis (Figure 1). In the particular case of *H. pylori* infection, this bacterium possesses an arginase,

encoded by the gene *rocF*, which can attenuate availability of arginine substrate for host cell iNOS, thus reducing production of NO and leading to evasion from its antibacterial effects [8•].

Host Sources of Arginine

In the host, arginine is transported via the y⁺, B⁰+, and b⁰+ transport systems. One such transporter system is the cationic amino acid transporter (CAT; also known as solute carrier 7A) family, which includes CAT1–4. Arginine is mostly transported by CAT1–3. CAT1 shows ubiquitous expression with the exception of liver. However, CAT2 has two splice variants CAT2A and B. CAT2A is a low affinity isoform primarily in the liver, and CAT2B is a high affinity transporter known to be abundant in macrophages. CAT3 is expressed in the brain and thymus [9•]. Murine macrophages, upon activation by IFN- γ , IL-4 or IL-10, upregulate CAT2, whereas CAT1 is constitutively expressed in these cells. This CAT2 upregulation leads to sustained production of NO in macrophages [10].

Citrulline, a byproduct of NO synthesis from arginine, is exported out of macrophages for arginine regeneration via the ornithine cycle [11]. Depletion of the arginine pool and pathogenic encounters cause metabolic switching from arginine to citrulline utilization for NO production. T cells have also been shown to utilize extracellular citrulline for continued proliferation during arginine starvation. This highlights the intercellular sharing of citrulline between immune cells for efficient NO production [12••].

Arginine as an immune modulator: A double-edged sword

Arginine metabolism is a deciding factor in innate immune response as arginine availability is rate-limiting in NO production. Besides its role in antimicrobial defense, arginine metabolism is crucial to M1 and M2 polarization effects. M1 macrophages are proinflammatory in nature, produce NO and NO-derived peroxynitrite, and can lead to a Th1 adaptive immune response. In contrast, heightened expression arginase is a hallmark of M2 differentiation, thus giving rise to an anti-inflammatory, anti-parasitic Th2 response. Type 1 cytokines (IFN γ , TNF α , IL-1, and IL-12) induce NO production and inhibit arginase I activity [13,14]. In contrast, cAMP and anti-inflammatory cytokines like IL-4, IL-13, and IL-10 can increase arginase I activity and have an inhibitory role in iNOS expression. [14,15] (Figure 1). Treatment of murine macrophages simultaneously with LPS and IFN γ induces iNOS expression. However, induction of arginase I in response to LPS treatment alone is also reported [16]. Depletion of the extracellular arginine level inhibits proinflammatory cytokine production in LPS-activated macrophages via ERK1/2 activation [17]. The level of extracellular arginine, as well as arginine uptake are key requirements for macrophage iNOS expression, which is regulated at the protein level in response to *H. pylori* infection [18••, 19]. Arginase plays a crucial role during infection-induced fibrosis and inflammation, along with parasite clearance. Different levels of arginine are also reported to affect T-cell proliferation. Apart from the role of arginase I [20], a recent study suggests that repression of arginase II is critical during dendritic cell maturation in order to promote T-cell proliferation.

Preterm neonates are more enriched in immunosuppressive CD71+ cells. These cells show high arginase II activity, and are thus responsible for increased susceptibility to infections. Premature newborns with low NO and plasma arginine levels are more susceptible to necrotizing enterocolitis [21•]. In rats, susceptibility to *Toxoplasma gondii* depends on iNOS/arginase I balance. High and low iNOS/arginase I ratio confers resistance, and susceptibility, respectively [22•].

Arginase II mRNA is a direct target of micro RNA-155 and its expression is highly upregulated in human and murine DCs as a response to maturation signals. This study also reveals that arginine depletion from the extracellular milieu impairs *in vivo* proliferation of CD4+ T-cells [23••]. Silencing of miR-155 in microglial cells leads to an increase in NO production and heightened TNF- α and IL-6 levels [24]. MicroRNA miR-223 positively regulates arginase-I expression and abrogates proinflammatory cytokine expression in bone marrow- and adipose tissue-derived macrophages, thereby committing macrophages towards an M2 phenotype [25]. IL-4 treatment and LPS induction leads to up-regulation and suppression of miR223 expression, respectively. Previously, the role of miR-124 in determining M2 phenotype and arginase expression has been documented during neuronal inflammation [26]. Another microRNA, miR-let-7c down-regulates the transcription factor C/EBP- δ . During LPS induction of alveolar macrophages, C/EBP- δ regulates proinflammatory response; hence, miR-let-7c contributes to M2 phenotype and arginase expression [27]. Due to this dichotomy, several pathogens employ an array of mechanisms to fine tune arginine metabolism.

Alteration of Arginine Metabolism by Pathogens

NO produced in granuloma macrophages is a key immune response to *Mycobacterium* infection. Earlier data suggests that BCG infection of macrophages results in induction of arginase in an IL-6- and IL-10-dependent manner [28]. In accordance, *Mycobacterium tuberculosis* infection in *Arg1*-deficient mice shows higher NO production, aggravated granuloma pathology and lower bacterial burden [15,28,29]. Arginase I expression in hypoxic granulomas restricts the L-arginine concentration and polyamine levels, subsequently decreasing T cell proliferation [29]. Importantly, in experimental *M. tuberculosis* infection, the demand for arginine substrate for iNOS can be met by back-conversion of citrulline to arginine by argininosuccinate synthase after uptake of extracellular arginine becomes rate-limiting [28].

A recent report using a tuberculosis meningitis model suggested that in response to *Mycobacterium marinum* infection, a macrophage-microglia network drives microglia polarization towards M1-type, with iNOS induction and arginase down-regulation [30]. Another intracellular pathogen, *Salmonella typhimurium* recruits the host cell cationic amino acid transporter (mCAT1) to the *Salmonella*-containing vacuole to gain access to the cytosolic arginine reservoir. Subsequently, the pathogen imports arginine from the vacuole by overexpressing the arginine transporter (ArgT) in order to support its growth [9] (Figure 1). Apart from intracellular bacteria, extracellular bacteria like *Streptococcus pneumonia* also modulate host arginase. *S. pneumonia* infection of alveolar macrophages induces arginase I expression in an IL-13-dependent manner, resulting in attenuated host defense

against this pathogen during lung infection [31]. Similarly, *Pseudomonas*-infected lungs demonstrate a ~10-fold increase in arginase activity and a decrease in iNOS activity, leading to decreased production of NO [29].

The gastric pathogen *H. pylori* causes chronic active inflammation of the stomach and can lead to either peptic ulcer disease or gastric adenocarcinoma. It primarily interacts with the gastric epithelium as an extracellular pathogen, and it incites an innate and adaptive immune response. While it induces iNOS, it also induces host arginase II expression in mouse and human gastric tissue. *Arg2*^{-/-} mice show lower bacterial burden and increased gastritis pathology as compared to WT mice, which is associated with an increased Th1/Th17 response [32]. *H. pylori* also causes apoptosis of host macrophages in order to evade host immune response; this apoptosis has been attributed to arginase activity, but also to downstream oxidation of polyamines, as the catabolism of spermine by the enzyme spermine oxidase generates H₂O₂ [33]. Additionally, the polyamine spermine not only inhibits expression of proinflammatory genes, but also results in reduction of iNOS protein expression in infected macrophages [34–36]. However, during *H. pylori* infection, inhibition of polyamine synthesis with α -difluoromethylornithine (DFMO) reduces gastric inflammation and bacterial load in the mouse model [19], suggesting that this is a potential therapeutic agent.

Giardia lamblia is the etiological agent responsible for giardiasis. NO produced by iNOS is both cytostatic and cytopathic during *Giardia* infection [37,38]. Treatment with a *Giardia* extract induces arginase activity in host small intestine and in macrophages. However, infection of epithelial cells shows the reverse phenotype [39]. Interestingly, during infection by *Giardia*, macrophages expressing both arginase I and iNOS are recruited to the lamina propria. These double-positive cells were already reported to have an anti-inflammatory function in various infections [40]. In the case of *Schistosoma mansoni* infection, the eggs induce expression of IL-4 and IL-13, subsequently increasing arginase expression in lung and peritoneal macrophages [41].

Arginine - A therapeutic approach

Agmatine, an intermediate metabolite in arginine metabolism, can activate α -1 adrenoreceptors and imidazolguanidine receptors. It has been shown to increase glomerular filtration and tubular reabsorption. This property of agmatine is being exploited to treat disorders related to renal dysfunction. These include chronic kidney disease (CKD), acute renal failure (ARF) and pre-eclampsia. In CKD, renal NO production decreases with declining renal function leading to infections. In ARF, changes in iNOS expression, along with increased levels of superoxide anion can result in increased peroxynitrite and nitrosative stress. Pre-eclampsia is reported to occur in approximately 5 to 10% of all pregnancies in the United States. It is major contributor to maternal and fetal morbidity and mortality. Gestational vasodilation is caused by elevated NO production. Exogenous administration of arginine in all these conditions can significantly reduce symptoms, improve renal function, and regulate NO production [42].

During *Plasmodium* infection, Th1 response is critical for controlling parasite burden. Low arginine levels and endothelial dysfunction are common occurrences in malaria. Supplementation of L-arginine enhances NO production and decreases zygotes and ookinetes significantly [43•]. Notably, dietary arginine supplementation is a common practice as a preventive measure against sepsis in newborns [21]. Furthermore, arginine supplementation in mice has been reported to reduce experimental colitis in mice induced by either *Citrobacter rodentium* infection [44] or by an agent that causes epithelial injury, dextran sulfate sodium [45].

Conclusion

In this review article, the importance of arginine metabolism with respect to the host and pathogen has been discussed. The uptake of arginine is by cationic amino acid transporters (CATs), which are differentially expressed in different cell types. Following uptake, arginine is metabolized by the arginine deaminase pathway, wherein agmatine, an intermediate metabolite, serves as a connecting link between energy requirements and signaling. Moreover, the balance between arginase and iNOS expression dictates pro-inflammatory and anti-inflammatory responses. Hence, different pathogens employ strategies to counteract immune responses by interfering with host arginine metabolism. A fine balance between arginase and iNOS determines the host susceptibility to certain pathogens. Thus, arginine is shown to have potential in therapeutics, which involves the regulation of NO levels.

Arginine-tagged drug delivery systems can be engineered to target specific subcellular locations like *Salmonella*-containing vacuoles inside host cells. In the era of increasing antibiotic resistance, arginine may be a potent approach towards a next generation antimicrobial therapy.

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Highlights

- Arginine as an energy source in the host and pathogen
- Arginine-dependent NO production
- Modulation of arginine metabolism- Strategy for immune evasion by pathogens
- Bioengineered arginine tagged particles – Next generation antimicrobial therapy

Figure 1. Overview of arginine metabolism and its regulation

Arginine is transported via cationic amino acid transporter (CAT2) proteins in the host macrophages. Subsequently it is utilized in iNOS and arginase pathways. In the response to pathogens, iNOS is frequently upregulated and converts arginine to NO and citrulline. Further, citrulline can be utilized in arginine synthesis. NO and peroxynitrite exhibit antimicrobial activity. Arginase converts arginine to urea and ornithine. Ornithine contributes to polyamine synthesis, which is essential for tissue repair, serves as an energy source for various parasites, and can also modulate inflammation. Pro-inflammatory cytokines induce iNOS and repress arginase. Anti-inflammatory cytokines generally reverse the regulation of these enzymes. Arginine may have benefit as a therapeutic in conditions like acute kidney disorders and sepsis, as well as inflammatory bowel disease. The intracellular pathogen *Salmonella* recruits host arginine transporter (CAT1) to the *Salmonella* containing vacuole (SCV) to access the host cytosolic arginine pool. The bacterial arginine transporter (ArgT) imports arginine from the SCV lumen to the bacterial cytosol.