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Dual role of arginine metabolism in establishing pathogenesis

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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.

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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 eIF2α, eukaryotic translation initiation factor which regulates translation [3].

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 upregulation of the arginine decarboxylase pathway in response to LPS and cytokines, resulting in increased agmatine concentrations [5••].

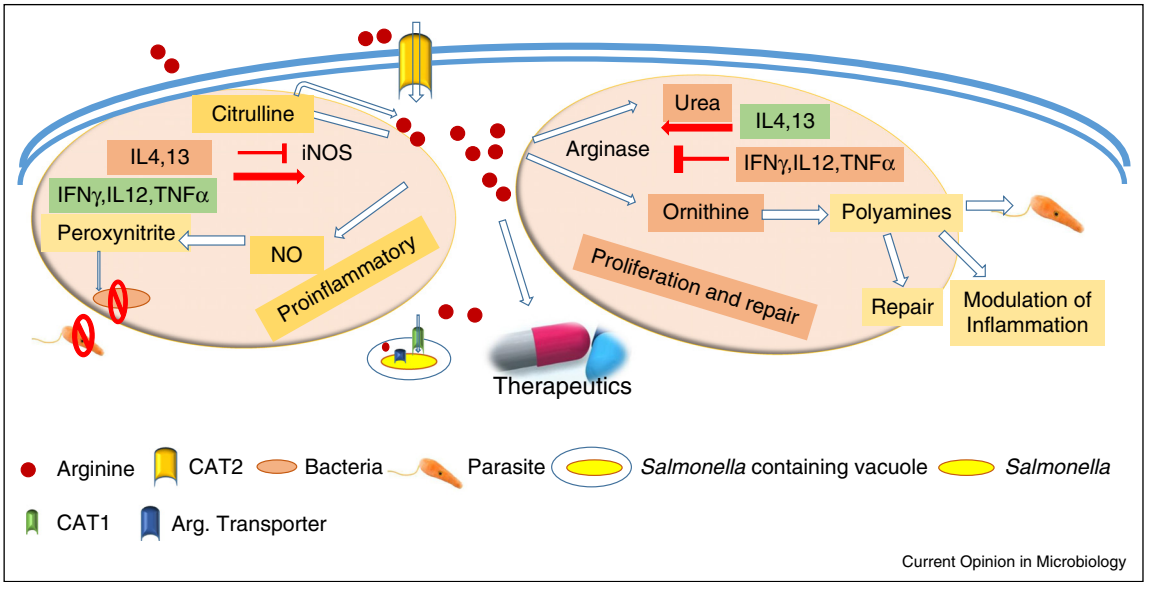
Leishmania genome includes an arginase encoding gene. Arginase-deficient *Leishmania* strain shows compromised intracellular survival in macrophages. In hosts, inhibition of arginase I and depletion of metabolites like agmatine result in decreased survival of *Leishmania* [7•]. These facts highlight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

The importance of arginine metabolism has been reported in other pathogens like *Salmonella* Typhimurium, *Helicobacter pylori* and *M. 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

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.