

REVIEW



L-arginine metabolism as pivotal interface of mutual host–microbe interactions in the gut

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ABSTRACT

L-arginine (L-arg) is a versatile amino acid and a central intestinal metabolite in mammalian and microbial organisms. Thus, L-arg participates as precursor of multiple metabolic pathways in the regulation of cell division and growth. It also serves as a source of carbon, nitrogen, and energy or as a substrate for protein synthesis. Consequently, L-arg can simultaneously modify mammalian immune functions, intraluminal metabolism, intestinal microbiota, and microbial pathogenesis. While dietary intake, protein turnover or de novo synthesis usually supply L-arg in sufficient amounts, the expression of several key enzymes of L-arg metabolism can change rapidly and dramatically following inflammation, sepsis, or injury. Consequently, the availability of L-arg can be restricted due to increased catabolism, transforming L-arg into an essential amino acid. Here, we review the enzymatic pathways of L-arg metabolism in microbial and mammalian cells and their role in immune function, intraluminal metabolism, colonization resistance, and microbial pathogenesis in the gut.

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Introduction

L-arginine (L-arg) exhibits remarkable metabolic and regulatory versatility in and among many organisms. It occurs universally across all kingdoms of life and plays a key role in host–microbe interactions.¹ Thus, L-arg metabolism is of central importance for multiple biological processes and mutual interactions of mammals, microbes, and plants.^{2–6}

Furthermore, L-arg is a semi-essential or conditionally essential amino acid in many species.^{7,8} Thus, endogenous synthesis and dietary intake of L-arg usually meet the metabolic demands of the respective organism. However, in conditions of catabolic stress or intestinal-renal dysfunction, the interorgan axis is pivotal for endogenous L-arg synthesis,^{9–11} the levels of available L-arg might not sufficiently meet metabolic needs anymore.^{12,13} Accordingly, L-arg needs to be supplemented by diet.⁷

L-arg is also a central intestinal metabolite.¹⁴ Thus, L-arg serves as a substrate for intestinal and

microbial cells that colonize the largest interface at which our body crosstalks to its microbiota. The mutual interactions between intestinal tissues and microbiota that might even outnumber our own cells play a pivotal role for the digestion and metabolism of ingested food particles, for the intestinal circulation and vessel permeability as well as for the control of inflammation and colonization resistance.^{15,16} Thus, intestinal microbiota signal to local and distant tissues of the host body and influence multiple physiologic interactions and pathophysiologic processes, on the one hand,^{17,18} On the other hand, the immune system of the host prevents the translocation of harmful signals and substances from the gut into the tissue and balances the homeostasis between the internal and external environments of the intestinal tract.¹⁹

The human gut microbiota also modulates immunity through the release of ligands and metabolites that translocate from the gut into the local and systemic circulation.²⁰ A disruption of the

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symbiotic interactions between intestinal tissues and the microbiota can simultaneously alter the immune response of the host and the composition of the intestinal microbiota. These alterations consequently lead to a disrupted intraluminal metabolism and an increased intestinal permeability and thus, can trigger the development of inflammatory or infectious disease. Intestinal dysbiosis and the leaky gut syndrome indeed accompany many immune-mediated disorders including inflammatory bowel disease (IBD).²¹ Alterations in microbial metabolite pools can even predict IBD types.^{22,23}

Several mutual interactions between gut microbiota and body tissues also affect the metabolism of L-arg. Thus, a disrupted L-arg metabolism is associated with immune-mediated or infectious diseases.²⁴ Intraluminal L-arg levels might not even sufficiently fulfill metabolic demands in both disorders.¹⁴ This is particularly important since the fractional synthesis rate of proteins within the intestinal metabolism depends on the accessibility of the metabolic precursor pool in the gut.²⁵ This intraluminal synthesis rate is indeed higher than in other major metabolically active tissues, such as the liver or muscle.¹⁴ Infection- or inflammation-associated L-arg deficiency contributes to immunopathology (Table 1), and clinical trials involving L-arg supplementation have shown a substantial contribution of L-arg in decreasing complications of inflammation and infection.^{64,65} Actually, the depletion of L-arg is one of the strategies used throughout nature to control the growth of organisms competing for the same biological niche.⁶⁶

Moreover, invading pathogens exploit L-arg starvation as a survival strategy.^{34,66,67}

While studies have focussed preferentially on the immune defense of the host in the past, information on the influence of metabolic alterations in L-arg metabolism on the composition of the intestinal microbiota and on microbial pathogenesis are limited. The most exciting studies in this area over the past years indicated novel roles for L-arg – converting enzymes in health and disease, as a result of their effects to limit the availability of free L-arg and altering consequently intraluminal metabolism and the composition of intestinal microbiota. Furthermore, L-arg affects the stress response of pathogenic bacteria and parasites and the expression of virulence factors that we will review and discuss here as well.

Mammalian L-arg metabolism

L-arg metabolism in mammals underlies the production of a diverse range of products, including agmatine, creatine, glutamate, homoarginine, nitric oxide (NO), polyamines, proline, and urea.⁶ Furthermore, L-arg is pivotal for the synthesis and the modification of proteins.³ Consequently, methylated arginines such as asymmetric (ADMA) or symmetric dimethylarginine (SDMA) can be released upon degradation of proteins.³ Interestingly, the combined ratios of ADMA, L-arg and SDMA as well as the availability of NO have been suggested as markers for endothelial dysfunction, oxidative stress, or survival of patients

Table 1. Overview over selected diseases with disruptions of L-arg metabolism.

Disease	Alterations in L-arg metabolism and functional consequences	Ref
Sepsis	depletion of plasma L-arginine levels → systemic L-arg – deficiency	13,26–28
	→ decreased arginine : ornithine ratio/endothelial dysfunction, decreased NO production/availability	29–33
	→ dysregulated immune responses/immunosuppression → myeloid suppressor cell expansion, T cell exhaustion	35–37
	→ enhanced gut permeability and bacterial translocation	38–39
NEC	decreased plasma L-arg levels at time of diagnosis	40–43
	decreased expression of L-arg synthesizing enzymes; increased expression of catabolic enzymes	44
Infections	depletion of L-arg as immune evasion mechanism	45–49
IBD	decrease availability of NO synthesis and increase ornithine production by increased ADI activity in bacteria	45–50,51
	altered availability of L-arg in feces and serum → compartmentalized L-arg – deficiency	52–56
	→ alterations in microbiota composition and microbiota-mediated immune responses	52–57,113
	→ alterations in L-arg transport	53–54,58
	→ endothelial dysfunction	52–59
Covid-19	→ decreased L-arg biosynthesis	58
	arginine depletion → enhanced arginase activity and endothelial dysfunction, hypercoagulability, immune dysfunction	60–63

in a variety of disorders including IBD, necrotizing enterocolitis (NEC), a devastating intestinal disease affecting premature or very low birth weight infants, and sepsis.^{13,26–28,43–56,68–71} Thus, the bioavailability of L-arg and its metabolic products is critical for the maintenance of proper organ homeostasis.

Consequently, the respective tissue levels of L-arg and its metabolites are tightly monitored. Indeed, there are several cellular components that sense and react to changes in the concentrations of amino acids such as L-arg; among these biosensors are the mechanistic target of rapamycin complex 1 (mTORC1) and some G-protein-coupled receptors (GPCRs) (Figure 1) that regulate cellular growth, metabolism, and signal integration.^{3,72,73} mTORC1 and GPCRs are both activated once L-arg is present in sufficient amounts. Vice versa, cellular stresses such as amino acid starvation activates the general control nonderepressible 2 (GCN2) stress response kinase that downregulates protein synthesis, consequently affects the phenotype of immune cells, and inversely is able to inhibit mTORC1 again.^{74,75} Thus, L-arg can also regulate cellular growth independent of the production of polyamines.

In mammals, the availability of L-arg depends on dietary uptake, catabolic degradation, regeneration of L-arg from citrulline and protein turnover. Actually, there exists a complex network of different enzymes that utilize L-arg as a substrate or

synthesize it as a product.⁶ These enzymes often interact or compete with each other and can influence immune responses in multiple and even opposing ways.⁵ The key enzymatic pathways for the degradation of L-arg in mammals are the nitric oxide synthases (NOS) and the arginases (Arg) (Figure 1). Of immunologic relevance are in particular the cytosolic arginase isoform type 1 (Arg1) and the inducible isoform 2 of the three known NOS (NOS₂). Moreover, cells may contain multiple intracellular L-arg pools that are not equally accessible to all L-arg metabolizing enzymes.³ Finally, the availability of L-arg is influenced by the expression, efficiency and capacity of L-arg transporters. These consist mainly of members of the solute carrier 7 family (SLC7) or other cationic amino acid transporters (CATs) (Figure 1) that transport next to L-arg a broad range of other metabolites into and out of cells.⁷⁶

Enterocytes of the small intestine also synthesize citrulline from glutamine, proline, or ornithine (Figure 1) and thus, provide a local L-arg supply to the gut.⁷⁷ This local L-arg supply impacts intestinal cell physiology and immune homeostasis in many ways, similarly as a dietary L-arg supplementation as discussed below. However, being a major source of endogenous L-arg synthesis, enterocytes are also pivotal for the maintenance of L-arg homeostasis in other tissues of the body and for inter- and intra-organ

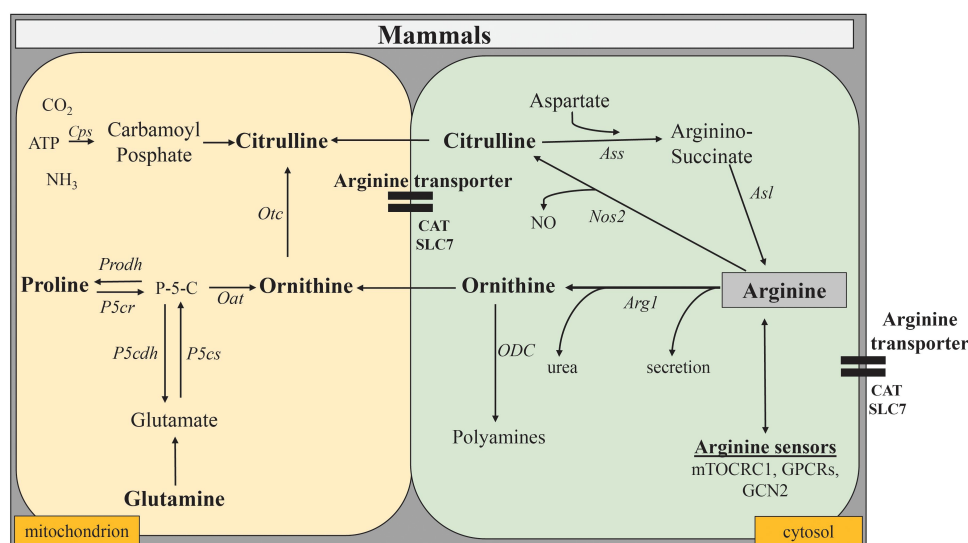


Figure 1. Anabolic and catabolic pathways of L-arg metabolism in mammalian cells. The key enzymatic pathways for the degradation of L-arg in mammals are *Arg1* and *Nos2*. Both are cytosolic enzymes that utilize L-arg as substrate. While *Nos2* catalyzes the formation of NO and citrulline from L-arg, *Arg1* converts L-arg into ornithine and urea. Once transported into mitochondria, the ornithine transcarbamylase (*Otc*) converts ornithine into citrulline. The ornithine aminotransferase (*Oat*), another mitochondrial enzyme, can build ornithine from glutamate and proline in the gut, whereas in other tissues, conversely, glutamate and proline are the products of this enzymatic reaction. Conversely, the combined action of the cytosolic enzymes argininosuccinate synthetase (*Ass*) and argininosuccinate lyase (*Asl*) convert citrulline again into L-arg.

L-arg exchange.¹² Consequently, supplementation of L-arg and/or inhibition of L-arg consumption can be a key issue in situations in which the gut is compromised.^{12,78}

Indeed, intestinal microbiota and the hypoxic microenvironment of the gut trigger a constitutive expression of L-arg converting enzymes such as Arg1 in intestinal tissues.^{52,79} Importantly, during inflammation or infection the expression and/or function of multiple L-arg converting and/or depriving enzymes can be enhanced emptying L-arg supplies and turning L-arg into a nutritionally essential amino acid. Consequently, patients that suffer from catabolic stress might profit from dietary L-arg supplementation, as studied intensively in the past.⁸⁰ While these studies focused on the host's metabolism, less attention had been paid to the effects of L-arg supply on the intestinal microbiota or gastrointestinal pathogens and their consequences for metabolic interactions with the host.

Microbial L-arg metabolism

Similar to in mammals, L-arg plays a pivotal role in multiple biological processes of microbes. Thus, L-arg is a precursor of polyamine synthesis and serves as a building block of proteins. It is

also pivotal for microbial growth and differentiation, and acts as a microbial energy source.⁴ Consequently, multiple anabolic and catabolic enzymatic pathways regulate L-arg availability and metabolism in microbes as well.

There exist several routes for the biosynthesis of L-arg. Two of them proceed from L-glutamate or glutamine in bacteria (Figure 2).⁴ *Enterobacteriaceae* that contain several species causing gastrointestinal diseases, use thereby the so-called linear arginine pathway in which the acetyl group removed from N-acetyl-L-ornithine (NAO) is lost to the environment during the enzymatic reaction (Figure 2). Another striking feature of bacterial L-arg biosynthesis is that L-ornithine can be formed by several non-orthologous enzymes.⁸¹ Moreover, arginine sensors such as ArgR (Figure 2), regulate the expression of bacterial virulence genes.⁸² Thus, L-arg is an important substrate for microbial metabolism and virulence.

L-arg can also be a source of carbon, nitrogen, and energy through a variety of catabolic pathways in bacteria, fungi, and protozoan parasites. These catabolic pathways include the arginine deiminase pathway (ADI) (Figure 2), the arginase (Arg) pathway, the arginine succinyltransferase pathway (AST) and the arginine oxidase (AO) pathway.⁴ While ADI and Arg contribute to establish infections, the role of AO and AST in microbial pathogenesis is unknown.

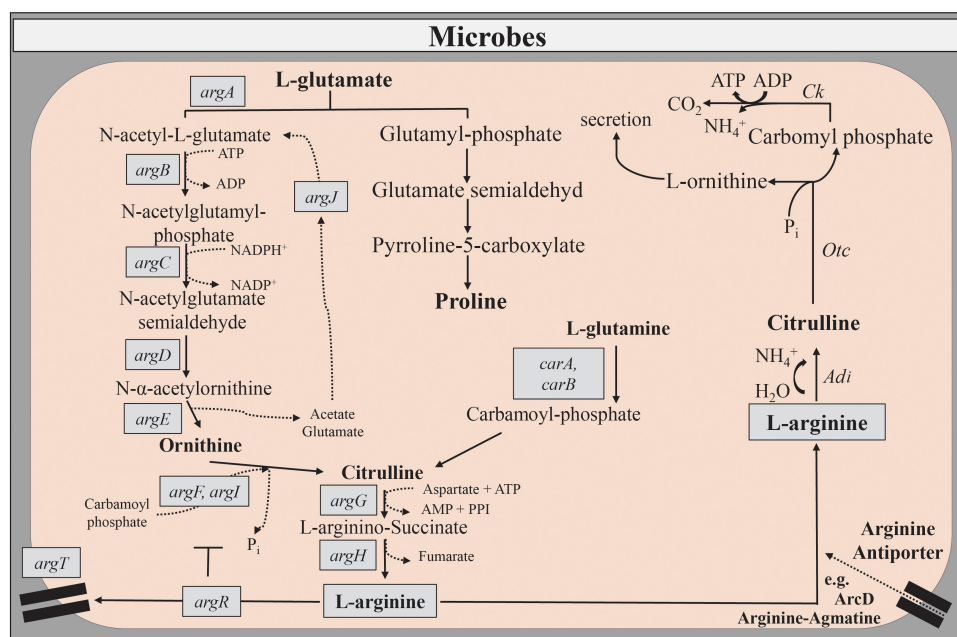


Figure 2. Anabolic and catabolic pathways of L-arg metabolism in microbial cells.

The ADI system (Figure 2) supplies energy and/or acid tolerance to a variety of bacteria and parasites.^{83,84} It enables *Enterobacteriaceae* to overcome oxygen limitations in the gastrointestinal tract.⁸⁵ This arginine-dependent acid resistance system decarboxylates L-arg to L-ornithine or alternatively to agmatine, thereby consuming one proton from the cytoplasm.⁸⁶ In protozoan parasites, ADI also acts as a virulence factor and suppresses local immune responses due to the restriction of L-arg availability.^{47–49} Next to its impact on the virulence and immune escape of gastrointestinal pathogens, ADI of probiotic bacteria can also beneficially modulate immune responses of the host and alleviate symptoms of intestinal inflammation.⁸⁷ Importantly, microbial ADI moved also into the focus of interest because of its therapeutic potential against auxotrophic tumors.⁸⁸

Arginase occurs in many bacterial genera and species. It contributes to basic nitrogen metabolism and redistribution, stress resistance and bacterial pathogenesis.⁸¹ Some bacteria even utilize L-arg as the sole source of carbon and nitrogen.⁴ However, not all bacteria such as *Escherichia coli* (*E. coli*) express the arginase pathway.⁴⁵ In contrast, other bacteria belonging to the *Burkholderia cepacia* complex that encompass opportunistic human pathogens encode even more than one arginase gene.⁸¹ Furthermore, pathogenic bacteria including

Helicobacter pylori strongly induce the arginase pathway to evade the immune response of the host. The resulting depletion of L-arg lowers the substrate availability for anti-microbial acting enzymes of the host (Figure 3), such as NO synthases and is thus, beneficial for bacterial survival following invasion of host tissues.⁵⁰

In fungi, the arginase enzyme represents a major catabolic path for L-arg.⁸⁹ With a few exceptions, most fungi do not express an arginine decarboxylase (ADC). Instead, the majority of fungi produce the polyamine putrescine via decarboxylation of ornithine, a product of the arginase reaction.⁹⁰ Thus, fungi possess arginase-dependent and arginase-independent routes of polyamine production that do not require the production of agmatine.¹ Importantly, the intraluminal polyamine pool is filled by collective biosynthetic pathways of different intestinal microbiota.⁹¹ Next to their usual functions in mammalian and microbial cell growth and differentiation, polyamines suppress specifically chronic inflammatory processes in the gut and contribute to the maintenance of intestinal barrier function (Figure 3).⁹²

Role of L-arg metabolism in microbial pathogenesis and immune evasion in the gut

As outlined above, L-arg and its products are central for multiple biological processes in mammals and

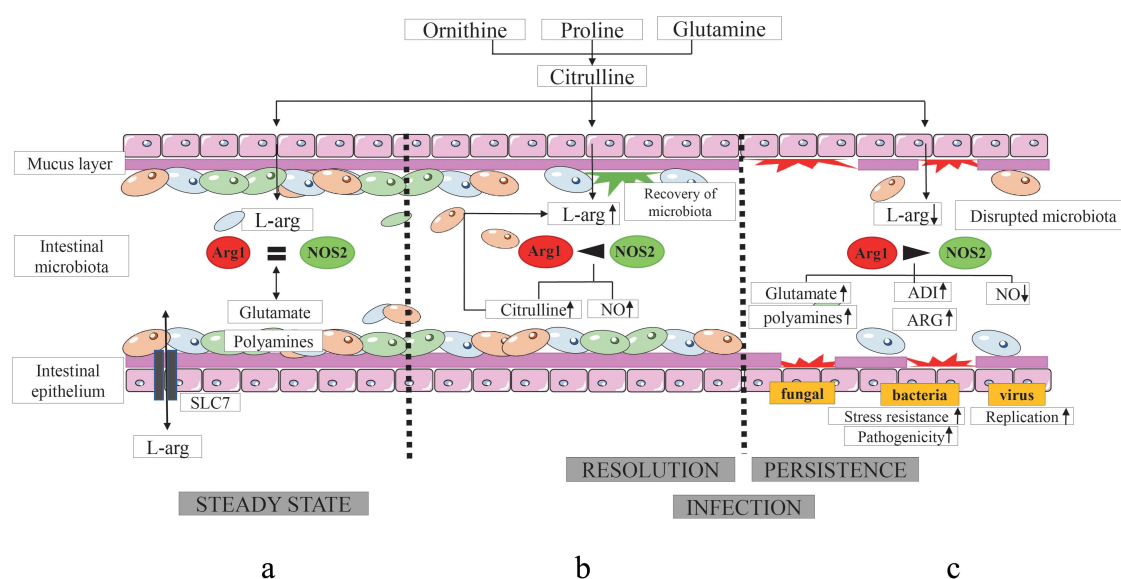


Figure 3. Mutual interactions of L-arg with host tissues, intestinal microbiota and pathogens and their consequences for the outcome of infection.

microbes and play a key role in host–microbe interactions.^{1–6} However, while L-arg metabolism modulates also immune responses and mucosal barrier functions in mammals,³⁴ L-arg is crucial for the growth, development, virulence, and/or (sexual) reproduction of bacteria, fungi, and parasites and is a key metabolite for viral replication.^{1–6,93} The competition for L-arg between mammalian and microbial cell needs to be therefore tightly controlled in order to maintain homeostatic host–microbe interactions, particularly at interfaces, where many microbes mutually interact with the host. Thus, an availability of L-arg in sufficient amounts balances the equilibrium between metabolic demands of microbial and host cells in the gut (Figure 3a). While sufficient amounts of intraluminal L-arg foster also the recovery of intestinal microbiota and the resolution of inflammation or infection (Figure 3b), L-arg deprivation prolongs bacterial persistence and perpetuates chronic inflammation (Figure 3c). By sensing environmental L-arg concentrations, microbes can adapt their metabolism from steady state conditions to various different stress situations. Moreover, pathogens can deplete L-arg from the environment thereby restricting substrate access for host enzymes converting L-arg into anti-microbial compounds. Finally, L-arg deprivation can disrupt intestinal microbiota and consequently impair colonization resistance allowing the outgrowth of pathogenic and pathobiontic

microbial organisms (Figure 3c). Thus, disruptions of L-arg metabolism have been associated with a variety of disorders affecting intestinal permeability and the outgrowth of pathogenic/pathobiontic microorganisms, including IBD, NEC, severe infections, or sepsis (Table 1).^{13,26–28,43–56,68–71} However, L-arg is not only an integral component of the host defense and a crucial modulator of immune responses, but also directly affects bacterial virulence and pathogenesis.⁹⁴ Not only free L-arg, but also arginine-residues in proteins play fundamental roles in these latter processes. Indeed, arginine residues modify many biological functions of proteins. Thus, we will discuss here selected examples of bacteria, parasites, viruses, and fungi that can cause intestinal infections and exploit L-arg metabolism for immune evasion or as virulence and/or survival factor.

Bacterial pathogens

Bacterial secretion systems, particularly the syringe-like type III secretion systems (T3SSs) are fundamental tools for the interaction between some Gram negative bacteria and their hosts (Figure 4a,b). T3SSs span the inner and outer bacterial membranes and form injection nanomachines that deliver different effector proteins into target cells of their hosts in order to modulate their functions and to establish colonization and/or

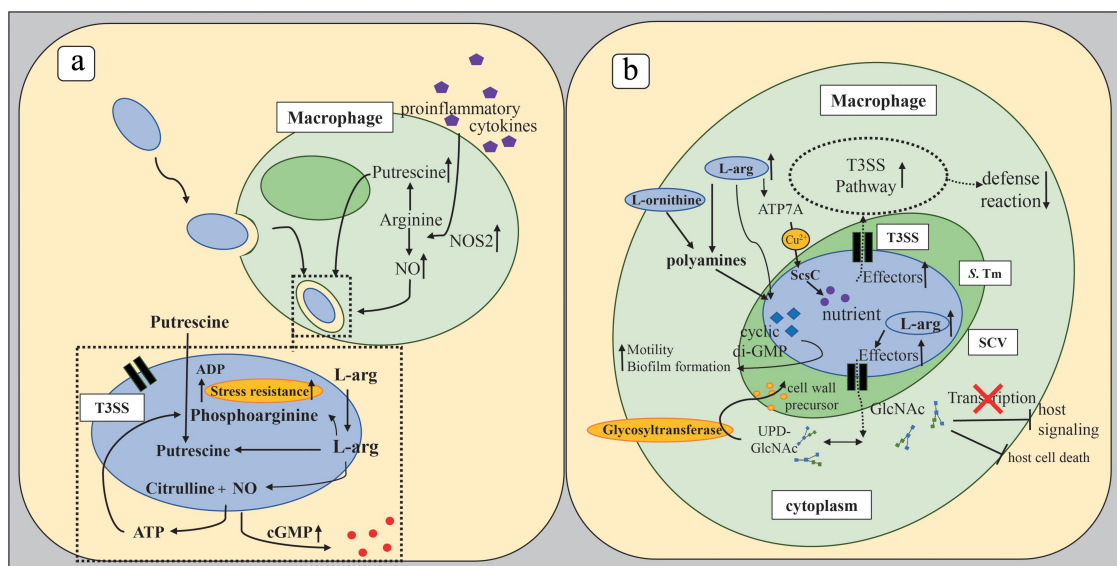


Figure 4. Effects of L-arg on microbial pathogenesis.

disease.^{95,96} Many of these bacterial effector proteins have arginine residues and share catalytic activities that promote post-translational modifications of host proteins. One family of effector proteins, for example, exhibits glycosyltransferase activity that catalyzes the addition of N-acetyl-d-glucosamine to specific arginine residues in target proteins, leading to a reduced NF- κ B pathway activation and impaired host cell death and thus, providing a niche for intracellular bacteria to survive.⁹⁷ Although L-arg metabolism interferes with many bacterial pathogens, we will focus here on three gastrointestinal pathogens, namely, *Clostridioides difficile* (*C. difficile*), *Citrobacter rodentium* (*C. rodentium*) and *Salmonella enterica* serovar Typhimurium (*S. Tm*).

- (A) *difficile* is leading cause of antibiotic-associated diarrhea worldwide.⁹⁸ This anaerobic and spore-forming bacterium produces two toxins, toxin A (TcdA) and toxin B (TcdB) that mediate disease. There is also epidemiologic evidence that *C. difficile* infections (CDI) occur more frequently and are more severe in IBD patients compared to the general population.^{99–101} Furthermore, asymptomatic colonization with *C. difficile* is also more frequent in the IBD population.¹⁰² Interestingly, L-arg metabolism is involved in the non-inflammatory colonization of intestinal surfaces with *C. difficile* as well as in inflammatory CDI. For example, mice humanized with stool samples from patients with diarrhea that still contained a healthy-like microbiota composition were recalcitrant to CDI and inflammation compared to mice humanized with feces from dysbiotic donors.¹⁰³ Utilizing gut microbiome metatranscriptomic analysis, mice recalcitrant to CDI and inflammation exhibited an increased community-wide expression of L-arg, ornithine, and polyamine metabolic pathways.¹⁰⁴ Thus, the increased availability of L-arg and its inter-related metabolic pathways enhance gut barrier function, lower the inflammatory responses of immune cells and thus, contribute indirectly to asymptomatic carriage.¹⁴ Furthermore, L-arg might directly inhibit

the production of the two-disease mediating toxins.¹⁰⁵ Vice versa, Enterococci provides fermentable amino acids, including leucine and ornithine, which increase the fitness of *C. difficile* in the antibiotic-perturbed gut. The parallel depletion of L-arg by enterococci through arginine catabolism provides thereby a metabolic cue for *C. difficile* that facilitates increased virulence.¹⁰⁶ Interestingly, IBD patients suffering from concomitant CDI revealed a more pronounced dysbiosis with higher levels of *Enterococcus* operational taxonomic units (OTUs).¹⁰⁷

- (B) *C. rodentium* is a murine pathogen utilized as a surrogate animal model to study enteropathogenic *E. coli* (EPEC) and enterohemorrhagic *E. coli* (EHEC) infections *in vivo*.¹⁰⁸ *C. rodentium* and both *E. coli* pathotypes share respective pathogenic mechanisms. This also includes the expression of genes encoding the T3SS upon sensing fluctuations of L-arg concentrations (Figure 4a).¹⁰⁹ Moreover, *C. rodentium* might share the enzymatic pathways of *E. coli* that allow the production phosphoarginine, which functions as a short-term energy buffer in the recovery from and adaptation to pH-induced stress (Figure 4a).¹¹⁰ At the peak of *C. rodentium* infection, for example, an increased concentration of L-arg in the colon is correlated with a downregulation of the inducible SLC7A2 transporter of the host that transports cationic amino acids such as L-arg, lysine and ornithine into host cells and is thus, a critical regulator of inflammatory processes in the gastrointestinal tract.^{111–113} This increase in intraluminal L-arg concentrations promotes the expression of virulence genes in *C. rodentium*.⁸² Interestingly, the source of L-arg sensed by *C. rodentium* was rather endogenous than dietary. In contrast, another study reported that Slc7a2^{-/-} mice exhibited an improved survival, a reduced adherence of *C. rodentium* to the intestinal lining and a decreased histopathologic injury of the gut. An inhibition of the L-arg uptake with a competitive inhibitor also prevented the

attachment of *C. rodentium* to intestinal cells and the expression of chemokines.¹¹⁴ Consequently, the authors concluded that *C. rodentium* enhances its own pathogenicity by inducing the expression of SLC7A2 to favor its attachment to the epithelium and to create its ecological niche. A notable difference underlying the discrepant results of these studies is that one investigated the role of L-arg in *C. rodentium* pathogenesis at the peak of infection in a very susceptible host, while the other one assessed these parameters at the onset of disease resolution, in a less susceptible host. Thus, the genetic background, the accessibility of individual cells and of cellular compartments to L-arg as well as the intraluminal availability of L-arg for intestinal microbiota might contribute to an altered outcome in different animal models.

Bacterial transport systems involving arginine residues also influence the virulence and fitness of *C. rodentium*. For example, the twin-arginine translocation (Tat) system, that transports folded proteins across energy-transducing cytoplasmic membranes, promotes the colonization of the gut by *C. rodentium*.¹¹⁵ Substitution of both arginines in the nearly invariant twin-arginine dipeptide blocks the export of physiologic Tat substrate proteins and thus impairs microbial pathogenesis.¹¹⁶ Tat-exported peptidoglycan amidase-dependent cell division also contributed to the fitness of *S. Tm* in the inflamed gut.¹¹⁷

S. Tm has emerged as a model pathogen that manipulates host cells in a complex fashion. In humans, *S. Tm* causes acute intestinal inflammation similar to that in mice following pretreatment with streptomycin.¹¹⁸ Intriguingly, T3SS secreted virulence proteins also exhibit a central role in *S. Tm* pathogenesis and the induction of acute colitis.¹¹⁹ *S. Tm* encodes two specific T3SSs within the *Salmonella* pathogenicity islands 1 and 2 (SPI-1 and SPI-2) that display various important functions during host invasion and infection (Figure 4b).

Post-translational modifications of arginine residues on bacterial T3SS effectors and/or host proteins play an important role in both, physiology

and pathogenesis of *S. Tm*. Similar as many other *Enterobacteriaceae*, *S. Tm* also use arginine residues for the regulation of lipopolysaccharide (LPS) biogenesis.¹²⁰ Glycosylation of arginine residues is another characteristic feature of *S. Tm* to modify proteins post-translationally. T3SS effectors of *S. Tm* glycosylate proteins of the host and of the bacterium itself during infection of specific arginine residues with N-acetyl glucosamine (GlcNAc).^{121,122} Subsequently, the DNA binding capacity of these proteins is affected and host signaling disrupted.¹²³ Furthermore, bacterial targets are modified. The functional consequences of these glycosylation processes have remained largely unclear. However, arginine-glycosylates might antagonize apoptosis-induced host cell death or might contribute to the maintenance of sufficient levels of uridine diphosphate N-acetylglucosamine (UDP-GlcNAc) which is required by glycosyltransferases as coenzyme for the synthesis of bacterial cell wall precursors.^{124–126}

Similar as *C. rodentium*, *S. Tm* also senses periplasmic, free L-arg. L-arg induces a rapid and translation-independent increase of cyclic-di-GMP in *S. Tm* (Figure 4b), a second messenger, which regulates bacterial motility and biofilm formation.¹²⁷ Furthermore, periplasmic L-arg regulates also the (stress) response of *S. Tm* to copper,¹²⁸ an important micronutrient, but also toxic component when present in excess. Opposite to *C. rodentium*, L-arg does not appear to affect the expression of T3SS genes in *S. Tm* directly. However, metabolic products of L-arg such as polyamines might exhibit similar effects.¹²⁹ Importantly, the depletion of polyamine biosynthesis led to a down-regulation of genes encoding structural components of the T3SS 1 and its secreted effectors. Thus, L-arg might be indirectly involved in the regulation of T3SS in *S. Tm* as well.

The metabolism of L-arg also contributes to the adaption of enteric pathogens such as *S. Tm* to a hostile environment. Thus, *S. Tm* can colonize the gut despite the required stomach passage with its lethal acidic pH environment (pH < 2.5) due to the activation of inducible acid tolerance response (ATR) systems. The biodegradative arginine decarboxylase (ADC) of *S. Tm* is a pivotal component of this ATR system.¹³⁰ The enzyme consumes cytoplasmic protons in the process of L-arg degradation

to agmatine.⁸⁶ Consequently, the arginine-agmatine antiporter (AdiC) exchanges the product agmatine for L-arg again. Thus, the ADC pathway in *S. Tm* permits survival under acidic conditions as low as pH 2.5.¹³¹

The ADI system is another L-arg dependent pathway that contributes to the virulence of *S. Tm* (Figure 1). The expression of ADI pathway genes is induced inside macrophages. Enzymes of the ADI pathway promote next to their metabolic functions the intracellular replication of *S. Tm*. and the virulence of this gastrointestinal pathogen during infection of mice.¹³² However, the deletion of genes in the ADI pathway did not affect the production of NO by macrophages.

Parasitic pathogens

There are also several parasites, which primarily infect the intestinal tract. These include a variety of protozoan parasites and a panoply of helminths. We will focus here exemplarily on two protozoan parasites, namely *Giardia* (*G.*) *lamblia* and *Cryptosporidium* (*C.*) *parvum* and discuss the role of the L-arg metabolism on their pathogenesis. Since L-arg exhibits a myriad of biological roles, we will also discuss its role as a substrate of different enzymatic reactions.

The protozoan parasite, *G. lamblia* is the causative agent of giardiasis, a frequent cause of diarrhea worldwide. It primarily interacts with the local microbiota, the mucus and the epithelial cell layer in the gut.¹³³ Indeed, the composition of the intestinal microbiota is known to affect the outcome of *G. lamblia* infection.¹³⁴ Vice versa, *G. lamblia* infection also alters the microbial diversity of the gut microbiota.¹³⁵

Although an infection usually induces a minor inflammatory response, giardiasis is associated with enterocyte apoptosis, hypermobility, intestinal barrier dysfunction, and villus shortening.^{136–138} However, in genetically susceptible hosts even a transient infection with this pathogen can trigger colitis.¹³⁹ Despite extensive *in vitro* investigations, the dynamics of infection between the host and the parasite *in vivo* underlying acute or chronic giardiasis are only poorly understood. A metabolite that might influence the clinical outcome is L-arg, as it can simultaneously affect the intestinal

microbiota, the parasite itself as well as the immune response of the host.

Indeed, *G. lamblia* can affect L-arg metabolism in many ways. First, it is able to degrade L-arg directly as energy source via the arginine dihydrolase pathway.⁸⁴ *G. lamblia* release also two enzymes of this pathway (Figure 3), the arginine deiminase (ADI) and the ornithine carbamoyltransferase (OCT) following interactions with intestinal epithelial cells (IECs).¹⁴⁰ The resulting diminished availability of L-arg for the host reduces the proliferation of IECs and of T lymphocytes.^{47,48} Second, this protozoan parasite also indirectly influences the availability of L-arg due to the induction of host enzymes utilizing L-arg as substrate. Thus, Arg1- and NOS2-expressing macrophages accumulate in the gut following *G. lamblia* infection.¹⁴¹ As both enzymes compete for L-arg as common substrate, Arg1 expression could limit the availability of L-arg for NOS2 and thus promote the growth of *G. lamblia*, since NO acts cytostatic on the trophozoites of *G. lamblia in vitro* and limits encystation and excystation *in vivo*.¹⁴² Therefore, a reduction of the NO response favors the growth of *G. lamblia* and the parasite could utilize the induction of Arg1 as immune evasion strategy. Indeed, an addition of L-arg or of citrulline that converts into L-arg once having entered intestinal tissues reverses many of the adverse effects of L-arg depletion. Thus, dietary L-arg substitution could be a beneficial supplement in oral rehydration therapy of giardiasis.

C. parvum is the leading cause of human cryptosporidiosis, which can manifest with intestinal or respiratory tract symptoms such as diarrhea or cough.¹⁴³ Similar as *G. lamblia*, *C. parvum* can infect humans and a wide range of animals.^{143,144} Furthermore, the gut microbiota and/or intraluminal metabolites affect the outcome of *C. parvum* infection as well.^{145–148} Vice versa, commensal strains of *Cryptosporidia* such as *Cryptosporidium tyzzeri* protect against *C. rodentium* infection due to a modulation of intestinal immune responses.¹⁴⁹ Thus, multiple microbial genera and pathways interfere in multiple ways with each other.

The protective effects of L-arg metabolism on the clearance of *C. parvum* have been primarily associated with the NOS isoforms.^{150–153} In contrast, the expression of Arg1 is correlated with an

enhanced inflammation of the gut following cryptosporidial infection.¹⁵⁴ Vice versa, the expression of Arg2 by the intestinal epithelium promoted the uptake of L-arg from the intestinal lumen following *C. parvum* infection, which might initiate the synthesis of polyamines that are required for the repair of damaged mucosal tissues.¹⁵⁵

Other indirect effects of L-arg were linked to diamine oxidase (DAO), a polyamine-degrading enzyme whose expression positively correlates with the growth of mucosal cells in the small intestine.¹⁵⁶ Low serum or plasma activities of DAO predict intestinal mucosal damage in human and veterinary medicine.^{157–159} Interestingly, plasma concentrations of L-arg as precursor substrate of polyamines are also significantly decreased in diarrheic calves compared to controls.¹⁶⁰ Thus, these data indicate a dysfunction of L-arg metabolism upon *C. parvum* infection and subsequently suggest L-arg and its metabolites as biomarkers for mucosal damage in humans or animals suffering from cryptosporidiosis.

Viral pathogens

The role of L-arg on viral replication is controversially discussed in the literature. On the one hand, L-arg can inactivate some viruses due to interactions with their lipid membranes.^{161,162} Moreover, L-arg produced by intestinal microbiota can enhance mucosal $\gamma\delta$ T cell responses to viral infections.¹⁶³ On the other hand, being a key metabolite for viral replication, L-arg depletion has been suggested as potent antiviral strategy against several viruses (summarized in⁹³). Unfortunately, only limited data on the effects of L-arg on intestinal viral infections or on the intestinal virome are available that has been associated with IBD pathogenesis.^{164–166}

However, several studies addressed the role of L-arg metabolism in the pandemic COVID-19 disease, caused by SARS-CoV2. Next to respiratory disease, this novel beta coronavirus can also cause gastrointestinal symptoms.^{167,168} Indeed, angiotensin-converting enzyme 2 (ACE2) the receptor through which SARS-CoV2 enters the host cells^{169,170} is not only found in the airways, but also on enterocytes.^{171,172}^{173–182} Following infection, SARS-CoV2 significantly alters the metabolism of L-arg. For example, COVID-19 patients had significantly lower plasma L-Arg

concentrations compared to healthy controls.⁶⁰ Vice versa, methylated arginine products such as ADMA, SDMA, or n-monomethyl-L-arginine (L-NMMA) were significantly higher in patients with severe Covid-19.⁶² Importantly, the variations in COVID-19 severity and the fluctuating involvement of different organ systems might be a result of phenotypic variations in L-arg metabolism to which heritable metabolic pathways in erythrocytes contribute.⁶³ Indeed, adding oral L-arg to standard therapy can decrease the length of hospitalization and reduce respiratory support in defined patient cohorts (Table 2).^{183,184} Furthermore, L-arg supplementation contributes to the reduction of oxidative stress and of endothelial dysfunction in long-Covid-19 sequelae.¹⁸⁵

However, no data are available on the role of L-arg metabolism and/or supplementation on Covid-19-mediated intestinal disease. Nonetheless, intraluminal L-arg metabolism and microbiota might affect obesity or hamper the intestinal barrier and thus promote the subsequent formation of neutrophil extracellular traps (NETs) due to the translocation of microbial products,^{186–188} with obesity and NETs being risk factors for severe COVID-19 disease.^{189–193} Furthermore, as L-arg modulates intestinal microbiota^{14,24,52,194,195} and as microbiota can affect immune responses in the lung, as discussed below also for bacterial and fungal infections,^{196–199} dietary L-arg supplementation and subsequent alterations in intestinal microbiota composition/function might indirectly improve the outcome of pulmonary SARS-CoV2 infection.

Moreover, SARS-CoV-2-induced endothelial dysfunction leads to endotheliitis and thrombosis due to endothelial nitric oxide (NO) inhibition with subsequent vasoconstriction and tissue hypoxia. Thus, being a precursor of NO L-arg could improve endothelial function due to the prevention of SARS-CoV2 induced coagulopathy and/or the NO-mediated inhibition of viral replication.²⁰⁰ In contrast, as L-arg is a key metabolite in the life cycle of many viruses, L-arg depletion might be also a promising therapeutic approach for patients with Covid-19.⁹³

In summary, L-arg interferes with various aspects of viral infection and virus associated complications, including viral replication, virus-triggered immune responses, coagulation, and endotheliitis. Thus, viruses can simultaneously

Table 2. Clinical trials assessing the effects of L-arg supplementation on selected infectious agents, sepsis, IBD and NEC.

Disease	Study design	Adminis-tration	Concen-tration	Dura-tion	Clinical effect	Ref
Sepsis	n = 390 prospective, randomized double-blinded clinical trial	within 72 hours after intensive care unit (ICU) admission enteral nutrition	1,25 g L-arg/100 ml (total volume 2.5 L/day) → 31,25 g/day	until ICU discharge	reduced morbidity rate, no effect on mortality in critically ill patients	173
NEC	n = 11 prospective clinical study	infusion of the NO synthesis inhibitor NG-nitro-L-arginine methyl ester (L-name) enteral nutrition	1 mg L-name/kg/h	12 hours	increased systemic vascular resistance; no impact on inflammatory cytokine or NO reduced mortality	174
	n = 237 randomized multicentre clinical trial		6.8 g/L	28 days		175,176
	n = 152 randomized placebo-controlled study	oral	1.5 mmol/kg per day as parenteral nutrition	28 days	reduced incidence of all stages of NEC in premature infants	177
Bacterial infection review of evidence → summary of randomized trials	n = 285 Cochrane Neonatal Review → summary of (quasi-) randomized controlled trials	oral or enteral	1.5 mmol/kg/d, 0.75 mmol/kg/d	at least 7 days	reduced risk for development of NEC; reduced death rate related to NEC	178
	n = 912 (summary of 8 studies)	enteral and/or oral nutrition pre-operative	n.d.	5–7 days before surgery	reduction of postoperative infections, reduced length of hospital stay	64
	n = 1483 (summary of 13 studies)	enteral and/or oral nutrition peri-operative	3–12.5 g	from 10 days before until 14 days after surgery	reduction of postoperative infections, reduced length of hospital stay	64
Fungal infection	n = 1483 (summary of 17 studies)	enteral and/or oral nutrition post-operative	1–25 g	1–11 days after surgery	reduction of postoperative infections, reduced length of hospital stay	64
	n = 120 randomized clinical trial	nutritional support intervention	8.5 g/L containing enteral nutrient solution	14 days	alleviation of malnutrition promotion of immune functions and wound healing recovery of intestinal motility and barrier function	179
IBD	CD: n = 31 randomized controlled trial	nutritional isocaloric supplements	3.8 g/2x per day	9 weeks	improved nutritional status	180
Covid-19	n = 80 parallel randomized study	oral	3 g/day	21–30 days	reduction in ventilation days decreased muscle reduction	181
	n = 1390 nationwide survey	oral	1.6 g/twice per day	30 days	reduction of long-Covid symptoms	185
	n = 74 randomized controlled trial	oral	3 g/day	max. 10 days	no significant advantages	184
	n = 50 randomized controlled trial	oral	1.6 g/twice per day	28 days	improved physical performance, endothelial function and less persistent fatigue in Long Covid	182

affect compartmentalized and systemic L-arg metabolism.

Fungal pathogens

Fungi are an integral part of the commensal gut microbiota in humans and mice.^{201–205} Similarly to bacteria, environmental, and mother-to-infant transfers of fungi occur perinatally, resulting in the rapid colonization of different body sites.²⁰³ There, the mycobiota influences the assembly and function of the commensal microbiota and the development of the immune system.^{203,206,207} Later on, the diet primarily influences the colonization of the intestinal tract by fungi and thus, the composition of the mycobiome.^{205,207} Presence of *Candida spp.*, for example, is positively associated with dietary carbohydrates and correlates inversely with dietary amino acids, proteins, and fatty acids.²⁰⁵ Thus, the gut mycobiome appears less stable than the bacterial microbiome, and is even more likely subject to environmental factors.²⁰⁴ Interestingly, fungal and bacterial abundances in the gut appear to negatively correlate to each other.²⁰⁸

Similarly, as described for the outgrowth of *C. difficile*²⁰⁹ a disruption of the physiologic commensal microbiota is also a prerequisite for the overgrowth of fungi in the gut.^{207,208} Importantly, dysbiosis also affects intestinal fungi is associated with invasive infections and IBD.^{205,210} Thus, most fungi are intestinal commensals and contribute to the maintenance of mucosal immune homeostasis and colonization resistance. Using the common mucosal surface commensal *Candida (C.) albicans* as an example, we will discuss here briefly some aspects of this double-edged function of fungi in health and disease.

For example, *C. albicans* is a potent inducer of Th17 responses that can exhibit beneficial functions in the gut and can contribute to colonization resistance.²¹¹ Indeed, the commensal *C. albicans* pool generates protective immunity against a wide range of opportunistic fungal and obligate bacterial pathogens.^{212–214} Vice versa, a *C. albicans* mediated, systemic expansion of Th17 cells that cross-react to antigens of other fungi, such as *Aspergillus fumigatus* or to antigens of house dust mite can cause immunopathology of the lungs.^{198,199} Moreover, *C. albicans* might contribute to the accumulation of Th17 cells in intestinal tissues

of IBD patients. Indeed, *Candida* is the most prevalent fungal genus consistently increased in several IBD cohorts based on fecal sequencing.^{215–218}

All *Candida spp.* can employ amino acid metabolism. However, there exist metabolic differences between individual *Candida spp.*²¹⁹ L-arg, for example, is crucial for fungal growth, development, pathogenicity and survival.¹ Moreover, phagocytosed *C. albicans* rapidly upregulate the biosynthesis of L-arg upon exposure to reactive oxygen species.²²⁰ The subsequent increased availability of L-arg resulted in a switch from yeast to hyphae and enabled *C. albicans* to escape macrophage-mediated host defense.²²¹ In addition, *C. albicans* induces the expression of Arg1 in human macrophages and thus, limits the availability of L-arg for NOS2. This resulted in a reduced NO release and subsequent improved fungal survival.²²² Vice versa, L-arg inhibits the formation of biofilms in fungi.²²³ Furthermore, dietary L-arg substitution might not only exhibit anti-colitogenic effects, but also limit the adverse effects of systemic Th17 responses that are inversely correlated with the availability of L-arg.^{52,57}

Influence of L-arg on gut microbiota, mucosal immune responses, and the outcome of intestinal disease

Dietary proteins modulate the composition and the metabolic activity of the gut microbiota, which in turn influences human health. Vice versa, the microbiota also affect protein metabolism and thus, the bioavailability and distribution of free and protein-bound L-arg.²²⁴ These mutual interactions influence the epithelial and the endothelial barrier of the gut, affect colonization resistance, and control the translocation of intraluminal contents into the portal circulation, potentially leading to a variety of metabolic or immune-mediated disorders.^{225–227} However, the role of specific microbiota and/or microbial pathways in these complex interactions is just begun to be understood.

The interplay of intestinal microbiota and L-arg-metabolizing enzymes is involved in the pathogenesis of intestinal and extra-intestinal disorders, including autoimmunity, cancer, and infectious

other *Enterobacteriaceae* markedly expand in IBD patients compared to healthy controls.²³⁶ Indeed, NO derived from dysbiotic nitrate respiration is involved in the pathogenesis of IBD and alters colon motility.^{239,240} In contrast, the bioactivation of dietary nitrate by certain commensal microbiota might still promote favorable metabolic effects, even under inflammatory conditions.²⁴¹ Therefore, the ability of selected bacteria to reduce nitrate certainly contributes to the changes in the microbial community structure observed during intestinal infection or chronic inflammation. These changes included the depletion of obligate anaerobic bacteria and an increase of facultative anaerobic pathobionts from the family of *Enterobacteriaceae*. Thus, in summary, L-arg and its products promote or impair colonization resistance in a context-dependent manner. Consequently, further studies need to identify the microbiota that selectively profit from L-arg supply. Moreover, the individual beneficial functions of selected microbiota against intestinal infection and inflammation as well as the microbial pathways underlying protection in the respective intestinal disorders need to be characterized.

Effects of dietary L-arg on intestinal immune responses

Intestinal microbiota as targets for L-arg metabolism has become a focus of research within recent years as well.²⁴² For example, dietary L-arg supplementation ameliorated and resolved faster a dextran sulfate sodium- (DSS-) induced colitis in pre-clinical models.⁵² Protection from severe intestinal pathology was associated with an altered composition of intestinal microbiota and an accumulation of bacterial genera associated with human health. Furthermore, endothelial cell functions improved and less inflammatory cells were extravasated into intestinal tissues following L-arg application. Thus, oral L-arg substitution is an attractive target for clinical intervention in IBD.²⁴³

Dietary L-arg supplementation restores also the diversity of intestinal microbiota and protected from intestinal injury and inflammation following *C. rodentium* infection.²⁴ L-arg-mediated protection was associated with an enhanced abundance of *Bacteroidetes* and a decrease of *Verrucomicrobia*.

Furthermore, dietary L-arg inhibited the activation of colitogenic Th17 cells and the induction of experimental colitis by *Eggerthella lenta*,⁵⁷ a human gut actinobacterium enriched in patients with immune-mediated diseases.^{244–247} Finally, L-arg supplementation enhances secretory immunoglobulin A (sIgA) production as well as the release of cytokines and anti-microbial peptides (Figure 4).^{228,229} This effect also depends on intestinal microbiota, as the application of antibiotics abrogated the influence of L-arg supplementation on sIgA secretion. L-arg reduces bacterial loads in mouse mesenteric lymph nodes and decreases bacterial invasion into the mouse ileal wall as well. Next to T- and B-lymphocytes, L-arg also influences the phenotypes and functions of other immune cells including macrophages, granulocytes, myeloid-derived suppressor cells (MDSCs), natural killer (NK), innate lymphoid cells (ILCs) and dendritic cells (DCs).^{194,230} Interestingly, oral administration of L-arg and the subsequent remodeling of gut microbiota enhances the anti-microbial immune defense even in extra-intestinal tissues, such as the lung, against non-tuberculous and tuberculous mycobacterial infection.^{196,197}

As L-arg is a precursor of many metabolites, it also influences the function and phenotype of non-hematopoietic cells. Consequently, L-arg contributes to the maintenance and restoration of intestinal immune homeostasis.⁴⁵ Thus, L-arg promotes an expansion of intestinal stem cells (ISCs) (Figure 5).^{248,249} An increased expression of Wnt2b in CD90⁺ stromal cells, a ligand of the Wnt/ β -catenin signaling pathway, mediated the effects of L-arg on ISCs function.²⁴⁸ Paneth cells, a critical component of the ISCs niche, also augmented ISCs function in response to L-arg.²⁴⁹ Furthermore, intraluminal available L-arg protected the gut against 5-fluorouracil- (5-FU-) mediated tissue injury, one of the most commonly used drugs to treat cancer and a well-known agent for the destruction of the small intestinal epithelium.²⁵⁰ In contrast, L-arg supplementation of fibroblasts might have adverse effects on disease outcome as it promotes fibrosis.²⁵¹ Thus, the cellular compartments and subsets that can be accessible to L-arg need to be characterized before a dietary supplementation of this semi-essential amino acid is initiated.

Dietary L-arg supplementation as therapeutic option for intestinal pathologies

As a supplement, L-arg can be administered intravenously, orally or topically. Due to its broad physiologic effects and its potential benefits on endothelial and vascular dysfunction, hypertension, immune cell physiology, metabolic pathways, or wound repair,^{3,65} L-arg supplementation was evaluated in a broad range of various different diseases.^{9–11,64,65,252,253} A few clinical trials also assessed the effects of L-arg in decreasing complications of IBD, NEC, infection, or sepsis (Table 2).^{28,56,68–70} However, previous studies analyzed primarily the systemic or nutritional and less the local effects of L-arg supplementation. Thus, with the exception of animal studies,^{14,24,52,113} there are hardly any data of dietary L-arg alimentation on intestinal physiology and the composition of gut microbiota in humans available. Moreover, there exists only limited information regarding the safety and efficacy of L-arg supplementation in patients with different diseases.^{252,253} Thus, further studies need to characterize the intraluminal (adverse) effects of L-arg supplementation on colonization resistance and immune modulation, particularly with respect to its potential use in the correction of intestinal dysbiosis preceding *C. difficile* infections or IBD symptoms as alimentary adjuvant.

Furthermore, the route of application and the dose of L-arg supplied are pivotal for the anti-colitogenic or the richness and diversity of microbiota promoting the effects of L-arg. As patients suffering from ulcerative colitis (UC), one of the two main clinical entities of IBD, for example, exhibit increased L-arg levels in their sera,⁵³ systemic L-arg infusion might be even detrimental in this patient cohort. Furthermore, intravenous infusion does not change the composition of the intestinal microbiota, which mediates the observed beneficial effects of dietary L-arg alimentation.^{24,52} Thus, pathologic alterations in the availability of L-arg in different host tissue and/or microbiota compartments might completely disrupt the entire L-arg metabolism. Consequently, L-arg formulations and therapeutic regimens need to aim to replenish only the compartment lacking L-arg. Therefore, the dose of dietarily supplied L-arg needs to be

optimally suited to allow beneficial changes in the composition of intestinal microbiota and/or intraluminal microbial metabolites without causing systemic spillover effects into other host tissues. Preparation of a retarded and tissue-targeted L-arg release in the gut might be advantageous in this context. In contrast, to overcome the general L-arg – deficiency as observed during sepsis or NEC, for example, a systemic reconstitution of L-arg appears to be preferable that can also ameliorate endothelial dysfunction and severe catabolism.^{26–28,69} Thus, L-arg needs to be prepared, dosed, and applied in a way that only the appropriate, L-arg deficient compartment(s) are fed.

Furthermore, alterations in the composition of microbiota can affect many other disorders including colorectal carcinogenesis.²⁵⁴ Thus, for example, an upregulation of the expression of the argininosuccinate lyase (ASL), the only enzyme able to produce L-arg, correlated with an improved epithelial integrity and alleviation of colitis of inflammation-associated colon cancer.^{255,256} Epithelial argininosuccinate synthetase, in contrast, was dispensable for intestinal regeneration and tumorigenesis.²⁵⁷ Therefore, additional studies on the effects of L-arg expanded microbiota or L-arg mediated alterations in microbiota functions on other intestinal and extra-intestinal diseases have to be carried out.

Importantly, several bacterial, fungal, and parasitic pathogens and pathobionts also sense L-arg levels and might expand following L-arg supplementation and thus, adversely affect the outcome of disease. For example, the exclusive colonization of mice with commensal *C. albicans* reduces the susceptibility to DSS colitis or subsequent *C. difficile* infection.^{206,258} Vice versa, bacterial and fungal co-colonization or oral application of *C. albicans* into B6 mice kept under SPF conditions increased colonic inflammation.^{206,259} Moreover, *C. albicans* induced mucosal dysbiosis can also promote invasive infections.²⁶⁰ Thus, fungi influence microbial ecology in the gut in a context-dependent manner and can influence inflammation and colonization resistance in opposing ways. Consequently, explicit attention has to be paid to fungi when translating pre-clinical studies into human disease, since the diverse microbiota of free-living mammals

significantly differ from the restricted microbiota of lab animals.^{85,261} In particular, fungi have been shown to promote a more human-like immunity and physiology, microbiome assembly, and inter-kingdom interactions between bacterial and fungal communities, affecting also the exchange of amino acids.^{206–264} Thus, the microbial composition of the gut, the niches in which microbes reside in as well as the accessible cellular compartments of the host and metabolic pathways need to be characterized. As L-arg is an important modulator of microbial virulence, we suggest to screen intestinal microbiota for the presence of pathogenic microbial organisms and pathobionts before dietary L-arg supplementation is initiated. Moreover, pre-clinical and clinical studies need to address also the role of L-arg metabolism on the intestinal mycobiome and virome and its implications in the pathogenesis of inflammatory and infectious diseases.

Conclusion and future directions

There exist multiple lines of evidence that mammalian and microbial L-arg metabolisms interfere with each other. While the influence of L-arg on the immune response of the host and on the pathogenesis of gastrointestinal pathogens is relatively well established, little to nothing is known about the effects of L-arg on beneficial commensal microbiota and colonization resistance in the gut. Specifically, it will be interesting to study which pathways specific microbiota engage and how microbial diversity increases following dietary L-arg supplementation. Furthermore, future studies need to evaluate whether and to which extent an altered microbiota composition and/or metabolism affects intestinal, extra-intestinal and systemic symptoms of gastrointestinal pathogens, NEC or IBD. Moreover, only limited information is available for parasitic infections that profit from L-arg supplementation in pre-clinical models.²⁶⁵ In this context, it will be important to understand how alterations in the microbiota enhance intestinal and extra-intestinal immune responses and maintain mucosal and systemic immune homeostases. Thus, L-arg supplementation might be beneficial for the outcome of many infectious and/or inflammatory diseases. Moreover, as intestinal dysbiosis and the leaky gut syndrome accompany many

immune-mediated disorders beyond IBD,²¹ L-arg-mediated correction of intestinal permeability and/or microbiota composition and function might be beneficial in a variety of other immune-mediated disorders as well and could be considered as adjuvant alimentary therapy.

Cationic amino acid transport systems of the SLC7 or CAT families transport L-arg across intestinal cellular membranes in mammals. Both transporter systems can interfere with signaling in L-arg biosensor systems. Cellular components that sense and react to changes in the concentrations of L-arg are the mechanistic target of rapamycin complex 1 (mTORC1) and some G-protein-coupled receptors (GPCRs). mTORC1 and GPCRs are both activated once L-arg is present in sufficient amounts. Vice versa, cellular stress such as amino acid starvation activates the general control nonderepressible 2 (GCN2) stress response kinase that downregulates protein synthesis, consequently affects the phenotype of immune cells, and inversely inhibits mTORC1.

Abbreviations: ATP, adenosine triphosphate; CAT, cationic amino acid transporter; CO₂, carbon dioxide; *Cps*, Carbamoyl phosphate synthetase; NH₃, ammonia; NO, nitric oxide; *Nos2*, inducible nitric oxide synthase; *Oat*, ornithine aminotransferase; ODC, ornithine decarboxylase; *Otc*, ornithine transcarbamylase; *Prodh*, Proline dehydrogenase; *P-5-C*, Pyrroline-5-carboxylate; *P5cdh*, Pyrroline-5-carboxylate dehydrogenase; *P5cr*, Pyrroline-5-carboxylate reductase 1; *P5cs*, Pyrroline-5-carboxylate synthase; SLC7, solute carrier 7

A major pathway of arginine biosynthesis consists of a multi-enzymatic process network that the acetylation of the amino group of glutamate initiates. Shown here are the most pivotal steps of this so-called linear arginine pathway that is in detail described elsewhere.²⁶⁶ Conversely, a major catabolic pathway in microbial cells is the arginine deiminase pathway (ADI). The ADI system is an arginine-dependent acid resistance system to foster microbial pathogenesis and virulence. Furthermore, ADI generates cellular energy in different bacteria and parasites. Three enzymes, arginine deiminase (*Adi*), carbamate kinase (*Ck*), and ornithine transcarbamylase (*Otc*) constitute the ADI system. The respective enzymatic reactions catalyze the conversion of L-arg into ornithine,

ammonia, and carbon dioxide along with the concomitant formation of ATP. The arginine-ornithine antiporter (ArcD), as part of the ADI, mediates the uptake of L-arg and the concomitant export of ornithine in an ATP-independent manner. To acquire arginine from the host intestinal pathogens such as *S. Tm* exploit also the arginine-arginine antiporter or the lysine-arginine-ornithine-binding periplasmic protein ArgT. The transcriptional regulator and arginine sensor ArgR controls arginine metabolism and transport, for example, due to the regulation of ArgT expression or the activation of catabolic pathways.

Abbreviations: *Adi*, arginine deiminase; ADP, adenosine diphosphate; ArcD, arginine-ornithine antiporter; *argA*, N-acetylglutamate synthase; *argB*, N-acetylglutamate kinase; *argC*, N-acetyl-γ-glutamyl-phosphate reductase; *argD*, acetylornithine aminotransferase; *argE*, acetylornithine deacetylase; *argF*, *argI*, ornithine transcarbamylase; *argG*, argininosuccinate synthetase; *argH*, argininosuccinate lyase; *argJ*, ornithine acetyltransferase; *argR*, arginine deiminase system associated receptor; ATP, adenosine triphosphate; *CarA*, *CarB*, carbamoyl phosphate synthase; CO₂, carbon dioxide; *Ck*, carbamate kinase; NH₄, ammonium

Bacterial, and mammalian enzymes compete for L-arg as common substrate and convert it into various metabolites that exhibit diverse and even opposing effects on the immune response, colonization resistance or microbial virulence. Both enterocytes and microbiota can be a cellular source of local L-arg in the gut. While host and microbial enzymes balance L-arg metabolism under steady state conditions (A), infection/inflammation disrupts this homeostasis resulting in an enhanced L-arg consumption and/or decreased L-arg production (C). While sufficient amounts of L-arg foster the resolution of inflammation/infection and the recovery of microbiota (B), L-arg deprivation prolongs bacterial persistence and/or perpetuates chronic inflammation (C). Microbial pathogens frequently utilize L-arg to induce their ADI system, which helps them to survive within hostile environments. Furthermore, microbial pathogens exploit the arginase system to evade the immune response of the host. The subsequent depletion of L-arg from the environment hampers the immune defense of the host and promotes the

survival of bacteria and parasites inside host cells in addition. Furthermore, L-arg deprivation disrupts the functions and diversity of intestinal microbiota subsequently hampering colonization resistance.

Abbreviations: ADI, arginine deiminase; ARG, microbial arginase; Arg1, arginase isoform 1; NO, nitric oxide; NOS2, inducible nitric oxide synthase; SLC7, solute carrier 7

Arginine can affect microbial pathogenesis and the anti-microbial immune defense in multiple ways.

- (A) Arginine can be a source of polyamines, such as putrescine that promote microbial growth. Moreover, L-arg derived phosphoarginine functions as a short-term energy buffer in the recovery from and adaptation to pH-induced stress. Vice versa, L-arg can be a source for anti-microbial NO, generated by host NOS2.
- (B) Arginine residues of bacteria or host cell-derived proteins are targets for modification by glycosylation. These modifications affect either the functions of effector proteins transported through bacterial T3SSs or the biology of host proteins. Thus, proteins from both sources can be glycosylated with consequent diverse biologic effects, which include the inhibition of host cell death or the promotion of intracellular bacterial survival. Glycosylation might also maintain sufficient levels of uridine diphosphate N-acetylglucosamine (UDP-GlcNAc) which is required by glycosyltransferases as coenzyme for the synthesis of bacterial cell wall precursors. Bacterial motility and biofilm formation increase due to the accumulation of secondary bacterial messengers such as cyclic di-GMP. Importantly, many pathogenic bacteria sense L-arg concentrations and consequently induce the expression of T3SS genes or other virulence factors that disrupt the immune defense of the host.

Abbreviations: ADP, adenosine diphosphate; ATP, adenosine triphosphate; ATP7A, copper transporting ATPase; Cu²⁺, copper ions; di-GMP, dimeric guanosine monophosphate; GlcNAc, N-acetylglucosamine; NO, nitric oxide; NOS₂, inducible nitric

oxide synthase; ScsC, periplasmic suppressor protein of copper sensitivity; SCV, *Salmonella* containing vacuole; S. Tm, *Salmonella* Typhimurium; T3SS, type 3 secretion system; UDP-GlcNAc, uridine diphosphate N-acetylglucosamine

The local endogenous L-arg supply by enterocytes as well as dietary L-arg supplementation exhibit various beneficial effects on intestinal physiology and immune homeostasis. First, both enhance the richness and diversity of intestinal microbiota. Second, both promote the release of sIgA, antimicrobial peptides and cytokines that reciprocally shape the composition of intestinal microbiota. Third, both inhibit the expansion and differentiation of colitogenic Th17 cells, at least partially due to the induction of NOS₂. Finally, L-arg promotes the expansion and renewal of intestinal stem cells (ISCs). Paneth cells and Wnt2b signaling of CD90⁺ stromal cells contribute to these ISCs promoting their effects. Vice versa, intestinal parasites, such as *G. lamblia* utilize their ADI system to deplete L-arg from the environment of the host and to hamper intestinal immune defense.

Abbreviations: ADI, arginine deiminase; Arg1, arginase isoform 1; IEC, intestinal epithelial cell; ISCs, intestinal stem cells; NOS₂, inducible nitric oxide synthase; OTC, ornithine transcarbamylase; P-mTor, phosphorylated mammalian target of rapamycin; sIgA, secretory immunoglobulin A;

Abbreviations

5-FU-	5-fluoruracil
ACE2	angiotensin-converting enzyme 2
ADC	arginine decarboxylase
ADI	arginine deiminase
AdiC	arginine-agsmatine antiporter
ADMA	asymmetric dimethylarginine
ADP	adenosine diphosphate
AO	arginine oxidase
ArcD	arginine-ornithine antiporter
Arg	arginase
Arg1	arginase isoform 1
argA	N-acetylglutamate synthase
argB	N-acetylglutamate kinase
argC	acetyl-γ-glutamyl-phosphate reductase
argD	acetylornithine aminotransferase
argE	acetylornithine deacetylase

argF, argI	ornithine transcarbamylase
argG	Argininosuccinate synthetase
argH	Argininosuccinate lyase
argJ	N-acetylglutamate synthetase
argR	arginine deiminase system associated receptor
argT	lysine-arginine-ornithine-binding periplasmic protein=
ASL	argininosuccinate lyase
Asl	argininosuccinate lyase
Ass	argininosuccinate synthase
AST	arginine succinyltransferase pathway
ATP	adenosine triphosphate
ATP7A	copper transporting ATPase
ATR	acid tolerance response
<i>C. albicans</i>	<i>Candida albicans</i>
<i>C. difficile</i>	<i>Clostridioides difficile</i>
<i>C. parvum</i>	<i>Cryptosporidium parvum</i>
<i>C. rodentium</i>	<i>Citrobacter rodentium</i>
CarA	Carbamoylphosphate synthase
CATs	cationic amino acid transporters
CDI	<i>Clostridioides difficile</i> infection
CK	carbamate kinase
CO ₂	carbondioxide
Cps	carbamoylphosphate synthase
Cu ²⁺	copper
DAO	diamine oxidase
DC	dendritic cell
di-GMP	dimeric guanosine monophosphate
DSS	dextran sodium sulfate
<i>E. coli</i>	<i>Escherichia coli</i>
EHEC	enterohemorrhagic <i>E. coli</i>
EPEC	enteropathogenic <i>E. coli</i>
<i>G. lamblia</i>	<i>Giardia lamblia</i>
GCN2	general control nonderepressible 2
GlcNAc	N-acetyl glucosamine
GPCRs	G-protein-coupled receptors
IBD	inflammatory bowel disease
IEC	intestinal epithelial cell
IL-	interleukin-
ILCs	innate lymphoid cells
ISCs	intestinal stem cells
L-arg	L-arginine
L-NMMA	n-monomethyl-1-arginine
LPS	lipopolysaccharide
MDSC	myeloid derived suppressor cell
mTORC1	mechanistic target of rapamycin complex 1

NAO	N-acetyl-L-ornithine
NEC	necrotizing enterocolitis
NET	neutrophil extracellular trap
NH ₃	ammonia
NH ₄	ammonium
NK	natural killer cell
NO	nitric oxide
NOS	nitric oxide synthase
NOS2	inducible nitric oxide synthase
Oat	ornithine aminotransferase
OCT	ornithine carbamoyltransferase
ODC	ornithine decarboxylase
OTC	ornithine transcarbamoylase
OTU	operational taxonomic units
P-5-C	Pyrroline-5-carboxylate
P5cdh	Pyrroline-5-carboxylate dehydrogenase
P5cr	Pyrroline-5-carboxylate reductase
P5cs	Pyrroline-5-carboxylate synthase
Pi	phosphat inorganic
P-mTor	phosphorylated mechanistic target of rapamycin
Prodh	proline dehydrogenase
S.Tm	<i>Salmonella enterica</i> serovar Typhimurium
ScsC	periplasmic suppressor protein of copper sensitivity
SCV	<i>Salmonella</i> containing vacuole
SDMA	symmetric dimethylarginine
sIgA	secretory immunoglobulin A
T3SS	type 3 secretion system
SLC7	solute carrier 7 family
SPI	<i>Salmonella</i> pathogenicity island
T3SSs	syringe-like type III secretion systems
Tat	twin-arginine translocation
TcdA	toxin A
TcdB	toxin B
UC	ulcerative colitis
UDP-GlcNAc	uridine diphosphate N-acetylglucosamine
Wnt	wingless-type MMTV integration site family member

Disclosure statement

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Data availability statement

All data analyzed during this study are included in this published article.

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