Narrative Review

Arginine metabolism regulates the pathogenesis of inflammatory bowel disease

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The pathogenesis of inflammatory bowel disease (IBD) is related to genetic susceptibility, enteric dysbiosis, and uncontrolled, chronic inflammatory responses that lead to colonic tissue damage and impaired intestinal absorption. As a consequence, patients with IBD are prone to nutrition deficits after each episode of disease resurgence. Nutritional supplementation, especially for protein components, is often implemented during the remission phase of IBD. Notably, ingested nutrients could affect the progression of IBD and the prognostic outcome of patients; therefore, they should be cautiously evaluated prior to being used for IBD intervention. Arginine (Arg) is a semi-essential amino acid required for protein synthesis and intimately associated with gut pathophysiology. To help optimize arginine-based nutritional intervention strategies, the present work summarizes that during the process of IBD, patients manifest colonic Arg deficiency and the turbulence of Arg metabolic pathways. The roles of Arg–nitric oxide (catalyzed by inducible nitric oxide synthase) and Arg–urea (catalyzed by arginases) pathways in IBD are debatable; the Arg–polyamine and Arg–creatine pathways are mainly protective. Overall, supplementation with Arg is a promising therapeutic strategy for IBD; however, the dosage of Arg may need to be carefully tailored for different individuals at different disease stages. Additionally, the combination of Arg supplementation with inhibitors of Arg metabolic pathways as well as other treatment options is worthy of further exploration.

INTRODUCTION

Inflammatory bowel disease (IBD), consisting of ulcerative colitis (UC) and Crohn's disease (CD), is a collection of chronic gut inflammatory disorders known to be caused by genetic or environmental factors, immune intolerance, and enteric dysbiosis.[1–4] According to the latest epidemiological survey, the prevalence of IBD among the

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total population exceeded 0.3% in Canada, Denmark, Germany, Hungary, Australia, New Zealand, Sweden, the United Kingdom, and the United States.[5] Although IBD has long been regarded as a common autoimmune disease in the Western world, newly industrialized countries have witnessed an increasing incidence of IBD in recent years.[6] IBD is relapse prone with a prolonged disease course, which places a huge economic burden on patients. In addition, symptoms of IBD, including abdominal distension, abdominal pain, diarrhea, and mucous blood/pus stool, are also unbearable for some patients. The conventional treatment for IBD relies on the use of biologic agents (eg, anti–tumor necrosis factors [TNFs], anti–IL-12, anti–IL-23, $\alpha 4\beta 7$-integrin antagonist), 5-aminosalicylic acid, glucocorticoids, and immunosuppressants, which only exhibit limited efficacy.

Many studies have proven that nutritional intervention is a promising strategy for alleviating IBD-related symptoms, and a good nutritional status is pivotal for successful IBD treatment.[7–9] Supplementation with specific dietary ingredients, such as vitamin D and vegetable fiber, has demonstrated beneficial effects, whereas diets high in salt are often detrimental.[10–12] In general, patients with IBD require nutrition support during the recovery phase, especially for those protein components. As a semi-essential amino acid, Arg plays an important role in human physiological activities, participating in the synthesis of protein, urea, creatine, creatinine, nitric oxide (NO), glutamine, and pyrimidine.[13] Adults are normally able to synthetize Arg by themselves or obtain it from food; however, under in IBD, the body does not acquire enough Arg to meet metabolic needs. Arginine supplementation has been extensively explored in IBD treatment, yet a comprehensive understanding of the therapeutic mechanisms of supplemented Arg is lacking. Recently, researchers have reported on the crucial involvement of Arg metabolism in IBD from divergent standpoints. To rationalize Arg-based nutritional intervention strategies, we endeavored, in the present work, to provide a panorama of how Arg affects IBD pathogenesis through distinct downstream metabolic pathways. Importantly, Arg supplementation exhibits a net anti-IBD effect, but the dosage of Arg may need to be tailored for different individuals at different IBD stages. In addition, inhibitors targeting Arg metabolic pathways and the metabolic intermediates (polyamines, in particular) of Arg are also good candidates for IBD treatment.

METHODS

The search terms "arginine," "arginine supplementation," "arginine metabolites," "arginine metabolism" AND "colitis" OR "IBD" OR "inflammatory bowel disease" were used to retrieve research articles, guidelines, and clinical trials in the PubMed, Web of Science, Cochrane, and Google databases. The Boolean operators "AND" and "OR" were used to combine the terms, and publications in English were searched. Three authors (H.F.-Z., T.-T.Y., and Y.-C.G.) performed the literature mining independently, and duplicates were excluded from the pooled search results. Titles and abstracts were then screened to sort out the eligible studies.

Biochemical properties and sources of free Arg

Arginine ($C_6H_{14}N_4O_2$; molecular weight: 174.20 Da) is the strongest alkaline amino acid, with a pH range of 10.56 to 12.5. It contains 2 basic groups, existing in the isoform of either D-arginine or L-arginine (L-Arg). Lyophilized Arg presents as an odorless white crystal with a bitter taste, and is soluble in water, very slightly soluble in ethanol, and insoluble in ether. Studies have reported that the average Arg intake is estimated to be 3 to ≈5 g/d in adults, and the observed safe dose for oral administration of Arg is ∼20 g/d.[14,15] Approximately 40% of dietary Arg is degraded during absorption in the small intestinal mucosa, and the remainder is delivered to the liver, where 10% of Arg is sequestered in the form of protein-bound Arg.[15,16] Finally, ∼50% of free Arg enters the systemic circulation, and the elimination half-life of Arg is ∼79.5 ± 9.3 min.[17] However, the bioavailability of Arg could vary from 20% to 87% for complicated reasons, including the concentration of ingested Arg, compliance of research participants, and the biological differences among individuals.[15,17,18]

As a semi-essential amino acid, Arg could also be derived from de novo synthesis and protein turnover.[19,20] In humans, the synthesis of Arg mainly occurs through the collaboration between intestine and kidney, which is termed the intestine–renal axis. The enzymes carbamyl phosphate synthetase I and ornithine transcarbamylase in the small intestine catalyze the production of citrulline from glutamine, proline, or ornithine. Citrulline is then taken up by the proximal tubules of the kidney and efficiently converted into Arg by the sequential action of Arg-succinate synthetase and Arg-succinate lyase.[19] Therefore, the intestinal tract also contributes to the de novo generation of free Arg, which, in turn, serves as a crucial metabolite modulating gut homeostasis.

Role of Arg uptake in IBD pathogenesis

At the cellular level, the uptake of Arg primarily depends on the cationic amino acid transporter (CAT) SLC7A) family of proteins.[21,22] There are 4 isoforms of

CAT: CAT1, CAT2, CAT3, and CAT4. CAT1 is constitutively expressed and involved in the uptake of L-Arg to satisfy basic metabolic needs. CAT2 (SLC7A2) is recognized as the inducible form. SLC7A2A is a low-affinity transporter predominantly present in the liver, and SLC7A2B is a high-affinity transporter abundant in macrophages. CAT3 mainly exists in the brain and thymus, and the function of CAT4 is still unknown.[23] Among the 4 transporters, SLC7A2 plays the most important role in IBD pathogenesis. Using primary colonic epithelial cells isolated from Slc7a2$^{-/-}$ mice and short hairpin RNA knockdown of SLC7A2 in the young adult mouse colonic cell line, researchers found that colonic epithelial restitution is largely dependent on SLC7A2.[22] Mice lacking SLC7A2 are more susceptible to dextran sulfate (DSS)–induced colitis, with increased weight loss, higher mortality rate, and more severe tissue damage.[24] Consistently, the expression of SLC7A2 is reduced in the colonic mucosa of patients with active UC or CD, which might contribute to mucosal injury.[25] Loss of SLC7A2 also leads to exaggerated chemokine production with a shift from the Th1 to Th17 response in DSS-treated mice.[22,24] Moreover, reduced SLC7A2 expression in a chronic IBD model contributes to the risk of developing colitis-associated colon cancer.[26] In general, diminished SLC7A2 is a biomarker of IBD pathogenesis, which implies the impairment of Arg uptake and a potentially beneficial role of Arg.

Arg–NO pathway in IBD pathogenesis

Using Arg as the substrate, NOS2 (the inducible form of nitric oxide synthase [iNOS]) metabolizes L-Arg to NO and L-citrulline. Expression of iNOS and the production of NO are increased in patients with UC and those with CD.[22] However, the role of NO in IBD remains a subject of controversy. Studies have found that NO can cause diarrhea and exacerbate the severity of colitis.[27,28] Mechanistically, NO elevates TNF-α levels in the middle and distal colon to induce the expression of P-selectin and ICAM-1, which promote the infiltration of activated neutrophils and cause colon damage. Administration of a nitric oxide synthase inhibitor lowers oxidative injury,[29] and the effect is relevant to the interference of HIF-1α–mediated hypoxia signaling.[30] Paradoxically, NO can also enhance the expression of peroxisome proliferator-activated receptor γ, which, in turn, alleviates the inflammatory response and oxidative stress.[31] Thus, the effector function of NO in IBD is more complex than previously thought.

Several models have been proposed to reconcile the controversy. First, NO from different sources may exert distinct functions. Enterocyte-derived NO alleviates colitis by decreasing tissue damage and promoting mucosal repair, whereas immune cell–derived NO is associated with macrophage activation and a heightened inflammatory response.[32] Second, the amount of local NO content might be decisive. Small (picomolar) amounts of NO are thought to be physiologic and protective, whereas large (micromolar) amounts of NO produced by significantly overexpressed iNOS are likely to be proinflammatory.[33] Third, inhibition of iNOS shunts Arg flux into other metabolic pathways (covered in the following sections), and the protective effect would come from the accumulation of their corresponding products.[34] Nonetheless, suppressing iNOS displays a net protective effect and is a good therapeutic option for IBD treatment (Figure 1).

Arg–urea pathway in IBD pathogenesis

This process is under the control of arginases, which are binuclear manganese metalloenzymes catalyzing Arg into urea and ornithine. There are 2 subtypes of arginases: arginase I (Arg1) and arginase II (Arg2). Arg1 is a cytosolic protein predominantly expressed in hepatocytes and macrophages,[7] and Arg2 is a mitochondrial protein expressed in the kidney, small intestine, brain, monocytes, and macrophages.[8] The expression of colonic arginases is altered during the progression of IBD, and differential patterns have been observed. In *Citrobacter rodentium* infection–induced colitis, Arg1 is upregulated in colon tissue, whereas Arg2 remains unchanged.[35] The expression of Arg1 positively correlates with the degree of inflammation in intestinal tissues of patients with IBD, and Arg1 is upregulated in both intestinal epithelial cells and myeloid cells in a DSS-induced mouse colitis model.[36] However, there was also a study reporting that SLC7A2 and Arg1 mRNA levels were decreased, whereas Arg2 and NOS2 levels were increased in the colon of patients with UC.[22] Given the complementary function between Arg1 and Arg2, it is difficult to conclude whether the Arg–urea pathway is accelerated or decelerated in the setting of IBD.

The role of arginases in IBD pathogenesis is also complicated by host–microbiota interactions. Arginases, as well-identified markers for anti-inflammatory macrophages, are deemed to decrease the synthesis of NO and deprive cells of environmental Arg, thus suppressing T-cell activation.[37] However, surprisingly, only limited evidence indicates that arginase is protective in IBD by enhancing the generation of polyamines and the competitive inhibition of iNOS.[35] The majority of studies have demonstrated its deteriorative role, which is possibly attributed to the pathogenicity of the pathobiont. Fecal transplantation experiments showed that the stool of arginase-deficient mice

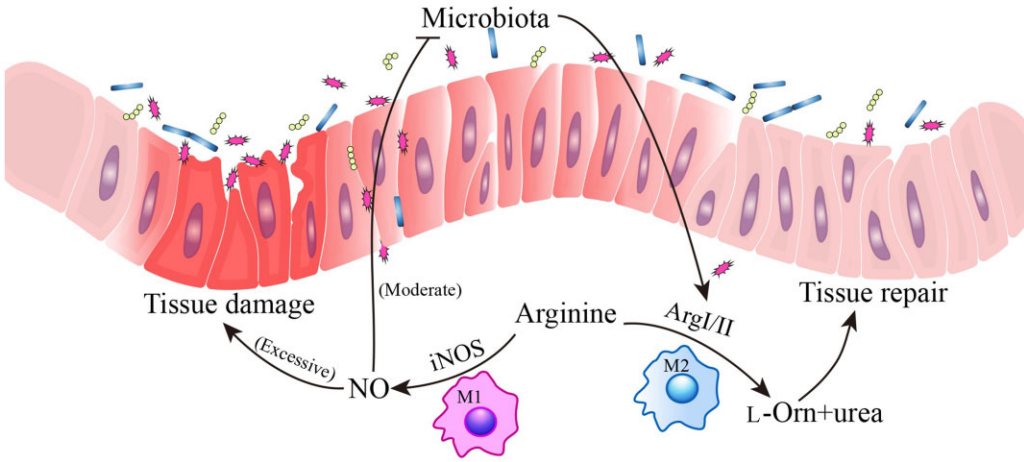

Figure 1 **A fine balance between the arginine–urea and arginine–nitric oxide (NO) pathways is required to exert optimal anti–inflammatory bowel disease effects.** Moderate activation of induced nitric oxide synthase (iNOS) produces NO, which functions as an antimicrobial agent; however, overactive iNOS accompanied by excessive NO production is detrimental to elicit colonic tissue damage. Upregulation of arginases could be induced by microbial stimulation, which competes with the arginine–NO pathway and favors the tissue reparative program but bears the risk of microbial penetration. L-Orn, L-ornithine; M, macrophage.

ameliorates the severity of IBD symptoms in recipients.[36] Consistently, *Helicobacter pylori* infection upregulated the expression level of Arg2, which exhausts the NO substrate L-Arg and impedes NO-dependent bactericidal activity.[38] The harmful role of arginase was also confirmed in the DSS-induced colitis model, where arginase inhibition is effective for colitis treatment.[39] The apparent functional duality of arginase reflects a dilemma in IBD, where Arg–NO and Arg–urea pathways are required to reach the fine balance to satisfy the antibacterial need while avoiding inflammatory self-destruction (Figure 1).

Protective effect of Arg–polyamine and Arg–creatine pathways in IBD pathogenesis

Arginine-derived L-ornithine is catalyzed by ornithine decarboxylase (ODC) into putrescine. Subsequently, putrescine is transformed into spermidine by spermidine synthase and then spermine by spermine synthase. This process is termed the polyamine pathway, which is an acknowledged protective pathway in IBD. Polyamines (namely, putrescine, spermidine, and spermine) stimulate colonic epithelial cell growth and modulate epithelial apoptosis, with both antiapoptotic and proapoptotic effects reported.[33] In particular, spermidine facilitates M2 macrophage polarization, inhibits dendritic cell activation, and favors the differentiation of regulatory T cells.[40–42] Supplementation with spermidine promotes the homeostasis of intestine resident regulatory T cells and alleviates intestinal pathology in rats with T-cell adoption–induced colitis.[42] Additionally, the provision of spermidine also prevents the colitis-associated colon cancer model induced by azoxymethane-DSS, indicating its potential as an adjunctive treatment for colon carcinogenesis.[43] However, the alteration of the polyamine pathway is also questionable in patients with IBD. One study revealed greater ODC activity in pediatric patients with IBD, and ODC activity was associated with enhanced mucosal inflammation and a heightened risk of colorectal carcinoma.[44] Authors of a different study reported that ODC was significantly decreased in the colonic mucosa of patients with moderate or severe CD and UC.[45] The age difference and small sample size are probably responsible for the observed discrepancy, but larger, population-based investigations are still lacking.

Another protective metabolic pathway of Arg is creatine synthesis. Creatine is generated from Arg by serial catalysis of L-Arg glycine amidino-transferase and guanidinoacetate *N*-methyltransferase. Creatine maintains intestinal homeostasis and protects against colitis.[46,47] A study revealed that loss of guanidinoacetate *N*-methyltransferase increases intestinal metabolic stress and intestinal injury. This deficiency can be rescued by creatine supplementation, which enhances adenosine triphosphate supply and provides the energy needed for intestinal epithelial repair.[48] Thus, unlike the controversial roles of the Arg–NO and Arg–urea pathways, Arg–polyamine and Arg–creatine pathways generally exert protective effects during IBD pathogenesis.

Rationale for Arg supplementation in IBD treatment

Dietary Arg uptake and serum L-Arg levels were comparable in a study of patients with UC versus healthy

Table 1 **Arginine supplementation in inflammatory bowel disease treatment**

Subject	Sample size	Model	Delivery route	Duration of treatment	Effects of Arg supplementation	Reference
Rats	50	TNBS-induced colitis	Oral administration	7 d	Colitis amelioration; decreased TNF-α level	Al-Drees et al (2016)[50]
Mice	12	DSS-induced colitis	1% arginine in drinking water	4 d	Increased capacity for wound repair	Coburn et al (2012)[52]
Mice	11	*Citrobacter rodentium*–induced colitis	1% arginine in drinking water	14 d	Reduced intestinal inflammation	Gobert et al (2004)[35]
Mouse cell line	NA	YAMCs	Added in culture medium	6–24 h	Improved colonic epithelial cell restitution	Singh et al (2012)[23]
Human	31	Active Crohn's disease	Enteral supplement	9 wk	Improved nutritional status (combined with other supplements)	Nielsen et al (2007)[49]
Human	8	Healthy volunteers	Enteral infusion	2 wk	Enhanced NO level; unaffected cytokine production	Lecleire et al (2005)[51]

Abbreviations: DSS, dextran sulfate; NO, nitric oxide; TNBS, trinitro-benzene-sulfonic acid; YAMC, young adult mouse cell.

control participants; however, in active UC, tissue levels of L-Arg were decreased, whereas L-citrulline levels and the L-citrulline to L-Arg ratio were increased.[22] It is plausible to deduce that local Arg deficiency is mainly turbocharged by enhanced iNOS activity and impaired Arg uptake. Considering the promiscuous roles of the downstream Arg metabolic pathways, the overall effect of Arg supplementation is thus worth exploring. In general, supplementation with Arg exhibits a beneficial effect, and the mechanistic explanations vary (Table 1).[23,35,49–52] Supplementation with Arg could reduce the release of proinflammatory factors, normalize DSS-induced gene upregulation, and enhance intestinal epithelial cell migration.[52] Arginine also mediates intestinal mucosal repair, accelerates gastrointestinal wound healing, and reduces cell damage via the Arg–NO pathway.[51,53–55] In addition, Arg exerts antioxidant effects to protect intestinal epithelial cells from oxidative stress via the arginase-mediated signaling pathway and the potential antiinflammatory effect via the polyamine pathway.[50,56–58] Arg supplementation also was reported to regulate the severity of experimental colitis by affecting the colonic microbiome.[14] Supplementation with Arg increases the diversity of intestinal microbiota, notably those in the phylum Bacteroidetes, which alleviate enteritis by releasing lipopolysaccharide A to inhibit the Th17 response.[14] Nonetheless, supplementation with high doses of Arg may also be deleterious due to collagen deposition, tissue damage elicited by excessive NO production,[59] and the risk of developing and/or accelerating certain malignancies.[15] Indeed, dosage is a matter of concern. An in vitro study showed that the protein synthesis–promoting effect of Arg peaked at 0.1 mM, and a higher concentration did not further boost protein translation.[23] This might be a similar case for in vivo Arg supplementation, in which a proper dosage of Arg for patients with IBD is required to provide the utmost protection while avoiding the "spillover" side effects.

CONCLUSION AND DISCUSSION

In summary, 5 important Arg metabolic pathways—namely, Arg uptake, the Arg–NO pathway, the Arg–urea pathway, the Arg–polyamine pathway, and the Arg–creatine pathway—and their respective roles in IBD pathogenesis were introduced. Overall, patients with IBD have colonic Arg deficiency and turbulence of Arg metabolic pathways (Figure 2, Table 2).[22,26,27,35,44,52,58,60,61] Two messages can be taken from this study. First, changes in Arg metabolic enzymes and/or metabolic intermediates are potential biomarkers for IBD progression. Although many studies have revealed the disease-indicative role of Arg metabolism, those studies primarily were performed in animal models or with small numbers of human patients. Considering the accessibility of colon biopsy and peripheral blood samples, it would be interesting to see whether good correlations exist between Arg metabolic genes or products and the disease activity indices of IBD in future studies with larger cohorts. Second, cautious supplementation with Arg and the modulation of Arg metabolic pathways represent promising strategies for IBD treatment. Critically, supplementation with a high dose of Arg bears the risk of accelerating certain malignancies and causing colon damage by promoting NO production.[15] Thus, similar to many other nutritional interventions, Arg-targeted therapies also need to be customized to fit different patients at distinct IBD stages by giving a tailored dose.

Arg metabolism influences IBD pathophysiology in a diverse manner, which is complicated by host–

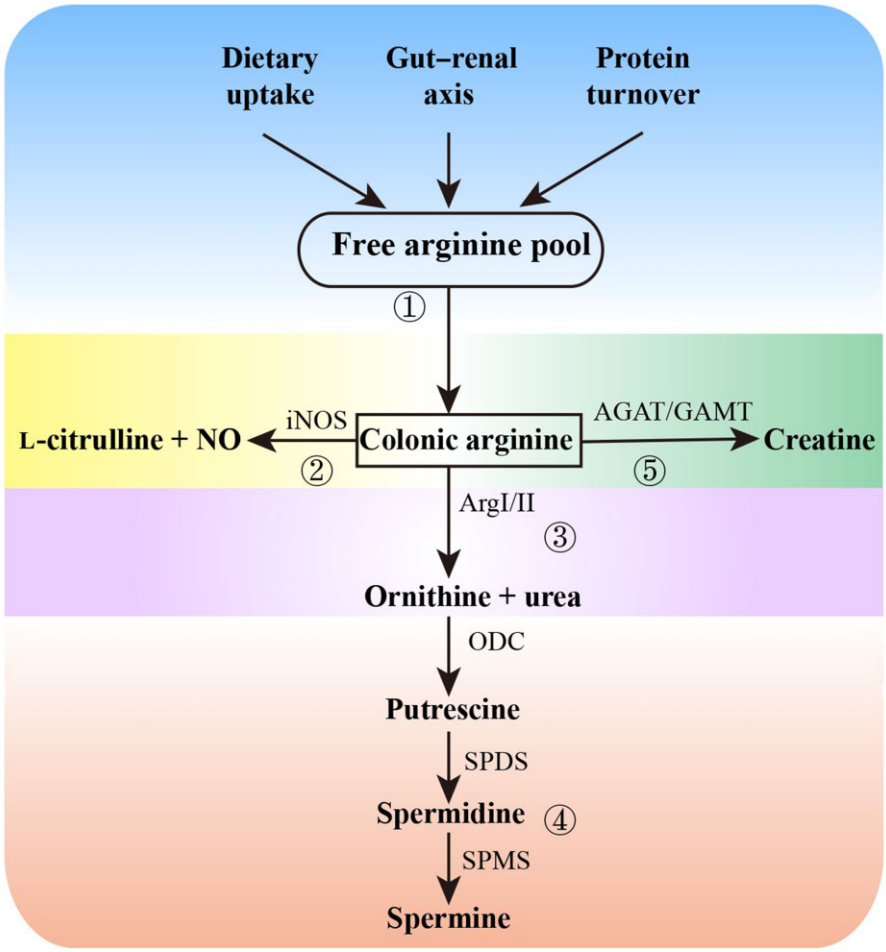

Figure 2 **Arginine metabolic pathways are differentially involved in inflammatory bowel disease (IBD) pathogenesis.** Step 1: Arginine uptake is compromised in the colon, and deficiency of SLC7A2 renders the host more susceptible to IBD. Step 2: The arginine–nitric oxide (NO) pathway works as a double-edged sword, the effect of which depends on the cell type and the amount of NO being released. Nonetheless, suppressing induced nitric oxide synthase (iNOS) has a net protective effect and is a good therapeutic option for IBD treatment. Step 3: The functional duality of the arginine–urea pathway is complicated by host–microbiota interactions and competition with the arginine–NO pathway. Steps 4 and 5: The polyamine pathway and creatine pathway generally exert protective effects during IBD pathogenesis. AGAT, L-Arg glycine amidino-transferase; GAMT, guanidinoacetate *N*-methyltransferase; ODC, ornithine decarboxylase; SPDS, spermidine synthase; SPMS, spermine synthase.

microbiota crosstalk. In the early phase of IBD, Arg deficiency modulated by myeloid cell arginase suppresses the T-cell response and plays a fundamental role in inflammation-associated immunosuppression. However, the competition between Arg and iNOS may lead to decreased NO production, thus undermining the antimicrobial capacity of the host. On the other hand, hyperactive iNOS is detrimental for inducing tissue damage, especially hyperactive iNOS expressed in macrophages. The ideal scenario is that the supplemented Arg could be finely controlled and optimally shunted into each metabolic flux to sustain host defense, prevent unwanted immune responses, and promote tissue repair as needed. The combination of Arg supplementation with iNOS inhibitors, arginase inhibitors, or gut-protective probiotics is a feasible approach worth investigating.

The "metabolism" of the non–free form Arg, mainly through posttranslational modification, is another interesting topic in the field of IBD research. Specific Arg residues within proteins can be methylated by a family of protein Arg methyl transferases or transformed into citrulline by protein Arg deiminases. Moreover, Arg can be incorporated into protein by arginylation, a mechanism whereby Arg is covalently attached to specific amino acid residues. These unusual Arg metabolic processes are involved in IBD progression. Three common methylated Args—asymmetric dimethylarginine, symmetric dimethylarginine, and N^G-mono-methyl-L-arginine—are released when

Table 2 **Arg metabolic enzymes in IBD pathogenesis**

Metabolic enzyme	Tissues and cells	Subject	Expression/activity	Function	Reference
SLC7A2	Colon tissues	Patients with UC	Decreased	Contribute to reduced Arg uptake	Coburn et al (2016)[22]
SLC7A2	Colon tissues	DSS-induced mice	Upregulated	Compensatory response to enhance Arg uptake	Coburn et al (2012)[52]
SLC7A2	Colon tissues	DSS-induced mice	Decreased	Contribute to reduced Arg uptake	Coburn et al (2019)[26]
Arg1/2	Intestinal tissues, IECs, myeloid cells	Patients with IBD and DSS-induced mice	Upregulated	Impede the resolution of colitis by altering the microbiome and metabolome	Baier et al (2020)[36]
Arg1/2	Gut tissues and HIMECs	Patients with IBD	Upregulated	Competitively inhibit the generation of NO, which is bad for vascular homeostasis	Horowitz et al (2007)[58]
Arg1	Colon tissues	Patients with IBD	Upregulated in acute UC	Serve as biomarker for diagnosis and prognosis of patients with IBD	Christophi et al (2012)[60]
Arg1/2	Colon tissues	*Citrobacter rodentium*–induced colitis	Upregulated Arg1; unaltered Arg2	Protective in *C. rodentium* colitis by enhancing the generation of polyamines	Gobert et al (2004)[35]
Arg1/2	Colon tissues	Patients with UC	Decreased Arg1; upregulated Arg2	Indicate a pattern of dysregulated Arg metabolism in UC	Coburn et al (2016)[22]
iNOS	Colon tissues	*C. rodentium*–induced colitis	Upregulated	Cause tissue damage	Gobert et al (2004)[35]
iNOS	Colon tissues	Patients with IBD	Upregulated	Contribute to the diarrhea observed in "minimal colitis"	Perner et al (2005)[27]
ODC	Colon tissues	*C. rodentium*–induced colitis	Upregulated	Compensatory response to promote polyamine pathway	Gobert et al (2004)[35]
ODC	Colon tissues	Patients with IBD	Upregulated in regenerating area	Possibly promote tissue regeneration	Allgayer et al (2007)[61]
ODC	Colonic mucosa	Patients with IBD (children)	Upregulated	Indicate a higher colonic mucosal proliferative state	Pillai et al (1999)[44]

Abbreviations: Arg, arginine; DSS, dextran sulfate; HIMEC, human intestinal microvascular endothelial cell; IBD, inflammatory bowel disease; IEC, intestinal epithelial cell; iNOS, inducible nitric oxide synthase; NO, nitric oxide; ODC, ornithine decarboxylase; SLC7A2, solute carrier family 7 member 2; UC, ulcerative colitis.

proteins containing methylated Arg residues are degraded. Studies have found that plasma asymmetric dimethylarginine and symmetric dimethylarginine levels are elevated in patients with IBD, and the concentration of asymmetric dimethylarginine is even higher in the active IBD stage, indicating its role as a potential disease marker.[62,63] Protein Arg deiminases, a unique family of enzymes that catalyze the hydrolysis of peptidyl-Arg to form peptidyl-citrulline on histones, fibrinogen, and other biologically relevant proteins, were found to promote the severity of colitis. Inhibition of PAD4 blocks the formation of neutrophil extracellular traps and is efficacious for IBD treatment.[64] However, the detailed roles of protein citrullination and protein arginylation in IBD pathogenesis remain largely elusive and warrant study.

DATA AVAILABILITY

All data needed to evaluate the conclusions in this article are included in the article. Additional data related to this article may be requested from the authors.

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Author contributions. J.Y.-L. and F.S. proposed the article and wrote the manuscript. H.F.-Z., T.-T.Y. and Y.-C.G. collected and analyzed the information. F.S., W.-Z.W. and F.-X.W. supervised the study conception and writing of the article. All authors read and approved the final version of the manuscript.

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Declaration of interest. The authors have no relevant interests to declare.

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