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REVIEW

Role of polyamines in intestinal mucosal barrier function

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Abstract
The intestinal epithelium is a rapidly self-renewing tissue; the rapid turnover prevents the invasion of pathogens and harmful components from the intestinal lumen, preventing inflammation and infectious diseases. Intestinal epithelial barrier function depends on the epithelial cell proliferation and junctions, as well as the state of the immune system in the lamina propria. Polyamines, particularly putrescine, spermidine, and spermine, are essential for many cell functions and play a crucial role in mammalian cellular homeostasis, such as that of cell growth, proliferation, differentiation, and maintenance, through multiple biological processes, including translation, transcription, and autophagy. Although the vital role of polyamines in normal intestinal epithelial cell growth and barrier function has been known since the 1980s, recent studies have provided new insights into this topic at the molecular level, such as eukaryotic initiation factor-5A hypusination and autophagy, with rapid advances in polyamine biology in normal cells using biological technologies. This review summarizes recent advances in our understanding of the role of polyamines in regulating normal, non-cancerous, intestinal epithelial barrier function, with a particular focus on intestinal epithelial renewal, cell junctions, and immune cell differentiation in the lamina propria.

Keywords Polyamines · Intestinal mucosal barrier · Cell proliferation · Inflammation · Intestinal microbiome

Introduction

The intestinal epithelium is one of the most rapidly self-renewing tissues in adult mammals and is characterized by cell turnover every 3–5 days [1]. This turnover is significantly influenced by microbial colonization, which induces rapid epithelial turnover in the intestines [2, 3]. Given the constant exposure of intestinal epithelial cells to pathogens and harmful components from diets or the microbiota, this rapid turnover eliminates infected and damaged cells [4–6]. However, the disruption or loosening of the intestinal barrier increases paracellular permeability, allowing the entry of pathogens and harmful components from diets and the intestinal microbiome. Consequently, this invasion induces inflammation and contributes to the onset or exacerbation of inflammatory and autoimmune diseases, such as type 1 diabetes, rheumatoid arthritis, systemic lupus erythematosus, and allergies [7–10]. Therefore, maintaining the normal turnover of intestinal epithelial cells is essential for ensuring robust intestinal barrier function, with cell growth factors playing a vital role in this process. Among these, polyamines stand out. Polyamines, widely distributed among prokaryotes and eukaryotes, including humans, are essential for many cell functions and play a crucial role in normal cell growth, proliferation, and differentiation [11–15]. The vital role of polyamines in intestinal epithelial renewal and barrier function has been known since the 1980s [16–18]. Most of these findings were obtained through experiments in the 1980s and 1990s, and limited progress has been made in recent decades. However, several reports since 2020 have updated the molecular mechanisms by which polyamines regulate intestinal epithelial barrier function; for example, the involvement of eukaryotic initiation factor-5A (EIF5A) hypusination in intestinal barrier functions has been reported [19, 20]. In recent years, although several excellent reviews on the functions of polyamines have been published, introducing a wide range of functions with respect to disease prevention and anti-aging [14, 21], there are only a few new reviews on intestinal epithelial barrier function. In addition, intestinal epithelial barrier function depends on the epithelial cell proliferation and junctions and the state of the immune system in the lamina propria. However, recent

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reviews on this topic have been limited to explanations of either [22, 23]. Therefore, this review highlights the roles of polyamines in regulating normal intestinal epithelial barrier function, including both intestinal epithelial renewal and mucosal immune system, from historical data to the latest molecular mechanisms.

Polyamines are essential bioactive molecules

Polyamines, encompassing putrescine (PUT), spermidine (SPD), and spermine (SPM), are cationic molecules containing two or more amino groups and are ubiquitously present in all cell types, including those of prokaryotes, higher plants, and mammals (some researchers classify PUT as a diamine). Cellular polyamines perform various important functions, including cellular growth, proliferation, differentiation, and maintenance, through multiple biological processes, including the regulation of RNA, DNA, protein synthesis, ion channels, cell–cell interactions, the cytoskeleton, and signaling via phosphorylation [11, 24, 25]. Particularly, in a post-translational modification termed EIF5A hypusination, SPD emerges as the sole substrate among the compounds present in living organisms and is essential for EIF5A-dependent protein synthesis [26]. There are two isoforms of EIF5A: EIF5A1, expressed ubiquitously, and EIF5A2, expressed in the testes, colorectal adenoma, and brain [27]. In this review, we use EIF5A to represent EIF5A1. Moreover, SPD promotes autophagy and the recycling of cellular organelle proteins to maintain normal cellular function [14, 28].

Ornithine is the precursor of PUT synthesis in mammalian cells, a process catalyzed by the rate-limiting enzyme ornithine decarboxylase (ODC), and its production is followed by SPD and SPM production. Cellular polyamine levels, including polyamine uptake and biosynthesis, are tightly controlled. Both processes are highly regulated by a unique class of small, inhibitory proteins called antizymes. Antizymes bind to ODC with high affinity and form ODC-antizyme heterodimers, thereby preventing the formation of the enzymatically active ODC homodimer [29]. In addition, reverse degradation pathways, including spermidine/spermine-N1-acetyltransferase and polyamine oxidase, are also present (Fig. 1a). The enzyme deoxyhypusine synthase transfers the N-terminal moiety of SPD to the lysine-50 residue of the EIF5A protein to form the intermediate deoxyhypusine residue. Then, deoxyhypusine hydroxylase catalyzes the hydroxylation of this intermediate to complete the synthesis of the nonproteinogenic amino acid hypusine [26] (Fig. 1b).

The intracellular biosynthesis of polyamines, particularly SPD, and their concentrations in many organs, including the heart, liver, thymus, kidney, spleen, brain, and skeletal muscle, decrease with age in rodents [30–32] and humans [33, 34]. Interestingly, whole-blood polyamine levels are higher in individuals aged 90–100 years than in individuals aged 60–80 years, bearing similarities to levels observed in individuals aged 30–50 years [34]. This observation suggests that individuals with high blood polyamine levels may have an increased likelihood of longevity, potentially becoming centenarians. Considering these findings, the extension of healthy life expectancy, including disease prevention, could be achieved by providing individuals with supplementary exogenous polyamines as their endogenous polyamine synthesis declines. For instance, the extension of lifespan via oral administration of polyamines, particularly SPD and SPM, in model organisms, such as *Caenorhabditis elegans* [28], *Drosophila* [28], and mice [35], has been reported. Upregulation of intestinal bacterial polyamine production was also observed to promote longevity in mice [36, 37]. Studies investigating the mechanisms underlying polyamine functions have recently intensified, focusing on various organs and diseases. For instance, experiments using mouse models have demonstrated cardioprotection [38], as well as the prevention of liver fibrosis and hepatocellular carcinoma [39], via autophagy activation, and improvement of antitumor immunity via cytotoxic functions of $CD8^+$ T cells achieved through enhancing mitochondrial fatty acid oxidation [40], induced by the administration of SPD.

Polyamines and intestinal epithelial cell proliferation

In 1980, Luk et al. [41] demonstrated that the polyamine content of the intestinal mucosa and ODC activity increased during the maximum growth period of the intestinal mucosa in newborn rats, as observed in the third week after birth. They also found that treatment with DL-α-difluoromethylornithine (DFMO), which selectively inhibits ODC (Fig. 1a), delayed both intestinal mucosal maturation and recovery from injury. To the best of our knowledge, this report is credited with initiating the exploration of the relationship between polyamines and intestinal barrier function. Subsequently, accumulating evidence has underscored the significance of polyamines in the proliferation of intestinal epithelial cells [18, 42]. For instance, suppressing polyamine biosynthesis through oral DFMO administration reduces the total thickness and villous height of the small intestinal mucosa in weanling rats [43], impacting intestinal mucosal adaptation [44]. Porter et al. also demonstrated that polyamine pools were distributed uniformly along the gradient corresponding to villus length and increased appreciably in the crypt region, which serves as a proliferative zone [45]. Several studies using mucosal injury models and DFMO

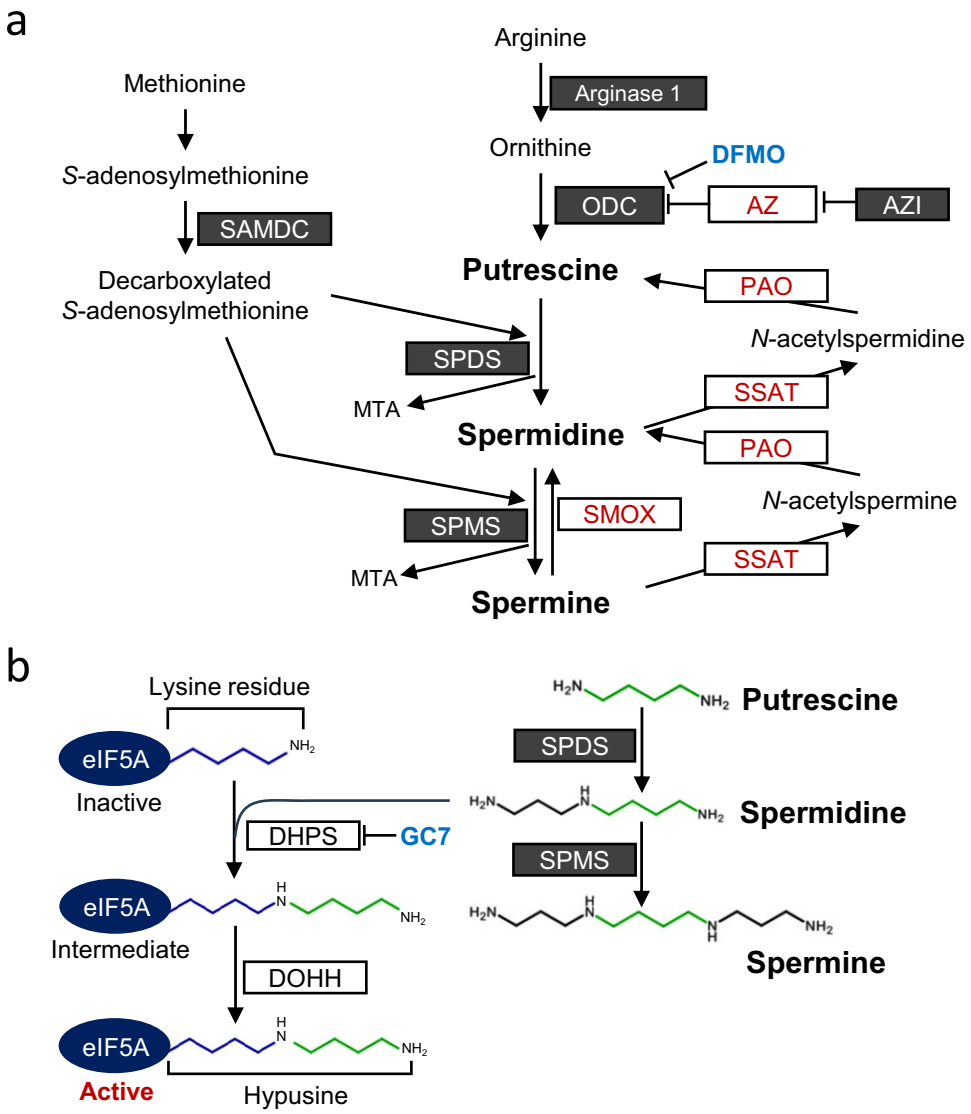

Fig. 1 Polyamine biosynthesis and EIF5A hypusination pathway in mammals. **a** Polyamine biosynthesis pathway. Enzymes and proteins are denoted by squares, and those related to synthesis and degradation/inhibition are shown by white text in black boxes and red text in white boxes, respectively. Sadenosylmethionine decarboxylase (SAMDC) and ornithine decarboxylase (ODC) are rate-limiting enzymes involved in polyamine synthesis. SAMDC decarboxylates S-adenosylmethionine to decarboxylated S-adenosylmethionine (dcSAM), such that dcSAM can provide aminopropyl groups to putrescine to produce spermidine using spermidine synthase (SPDS) and is added to spermidine to generate spermine by spermine synthase (SPMS). Spermine can be directly recycled into spermidine by spermine oxidase (SMOX). Spermine and spermidine can be recycled to spermidine and putrescine, respectively, by spermidine/spermine-N1-acetyltransferase (SSAT), followed by oxidation by polyamine oxidase (PAO) through N-acetylspermine and N-acetylspermidine, respectively. Antizymes (AZ) function as ODC inhibitors under the negative feedback regulation of polyamines. AZ is regulated by AZ inhibitors (AZI). DFMO (Difluoromethylornithine) is an irreversible suicide inhibitor of the ODC. MTA: methylthioadenosine. **b** The mammalian EIF5A hypusination pathway. Hypusine modification of the lysine residue of EIF5A occurs by adding spermidine via two enzymatic reactions. First, deoxyhypusine synthase (DHPS) transfers the aminobutyl group of spermidine to the amino group of lysine, generating an intermediate substrate. Second, deoxyhypusine hydroxylase (DOHH) adds a hydroxyl group and forms the hypusine residue of EIF5A. EIF5A is active in this hypusination form. GC7 (N1-guanyl-1,7diaminoheptane) is a potent inhibitor of DHPS. Enzymes are denoted by squares

have further elucidated the essential role of polyamines in cell proliferation [46–49]. Oral intake of polyamines and de novo synthesis promote intestinal mucosal growth. For instance, administering a polyamine-deficient diet to rats for an extended period (26 weeks) decreased DNA content per tissue weight in the small intestinal and colonic mucosa but not in the liver. However, this effect was reversed by supplementing the diet with polyamines, demonstrating the

impact of orally administered polyamines on intestinal cell proliferation [50]. Oral administration of PUT during the suckling period in piglets also increased the percentage of cells expressing proliferating cell nuclear antigen (a key factor in DNA replication) in the jejunal mucosa following early weaning [51]. Subsequent investigations revealed the molecular mechanism underlying polyamine-induced intestinal epithelial cell proliferation, which involves the regulation of numerous cell growth-associated genes. Experiments using IEC-6 cells demonstrated that polyamines upregulate the transcription of growth-promoting genes, such as *Fos*, *Jun*, and *Myc* [52–55].

Conversely, polyamines downregulate the expression of growth-inhibitory proteins, such as p53, N-Myc downregulated 1 (NDRG1), nucleophosmin, and the TGFβ/TGFβ receptor at the post-transcriptional level [56–61]. Additionally, polyamines induce cell proliferation by promoting cyclin-dependent kinase (CDK) 4 expression, which is essential for the progression of the G1 phase of the cell cycle. Polyamines promote CDK4 transcription by suppressing the expression of JUND, an activator protein-1 (AP-1) transcription factor responsible for inhibiting CDK4 transcription [62]. Polyamines suppress miR-222 and CUG-binding protein 1 expression, thereby regulating post-transcriptional gene expression, and both molecules synergistically suppress CDK4 translation [63]. Polyamines downregulate miR-29b expression by suppressing JUND levels, reducing proliferation [64]. Moreover, SPM treatment promotes the repair of damaged porcine intestinal epithelium by accelerating Rac1/PLC-γ1 signaling-mediated cell proliferation and migration [65].

Using a gnotobiotic mouse model, we demonstrated the effect of gut bacteria-derived PUT, the most abundant polyamine in the human intestinal lumen [66, 67], on colonic epithelial cell proliferation [19]. This model involved two strains of *Escherichia coli*: a PUT-synthesizing wild-type strain (WT) and a PUT synthesis gene-deficient strain. Intracellular levels of PUT and SPD in colonic epithelial cells in WT strain-associated mice were significantly higher than those in PUT-deficient strain-associated mice. Correspondingly, colonic epithelial cell proliferation was significantly enhanced in WT strain-associated mice compared to that in PUT-deficient strain-associated mice. Additionally, the intracellular levels of hypusinated EIF5A (hyp-EIF5A) in WT strain-associated mice were higher than those in PUT-deficient strain-associated mice.

Furthermore, the administration of N1-mono-guanylated 1,7-diaminoheptane (GC7), a deoxyhypusine synthase inhibitor, to specific pathogen-free mice reduced hyp-EIF5A and inhibited colonic epithelial proliferation. In experiments using mouse colonic organoids, PUT in the culture medium was actively absorbed by cells and converted to SPD, and treatment with trans-4-methylcyclohexylamine, an SPD synthase inhibitor, suppressed organoid proliferation. Similarly, GC7 treatment of colonic organoids suppressed proliferation and decreased hyp-EIF5A levels. These findings suggest that epithelial proliferation likely requires exogenous PUT as a substrate for SPD synthesis, and SPD is presumed to be involved in proliferation through EIF5A hypusination.

Polyamines and cell junctions in the intestinal epithelium

Adherens junctions

Adherens junctions (AJs) primarily comprise the cadherin-catenin complex, associated with the actin and microtubule cytoskeletons. In epithelial cells, the transmembrane protein E-cadherin serves as the adhesive molecule responsible for AJ formation [68–70]. E-cadherin initiates intercellular contact by forming calcium-dependent homophilic interactions with those on neighboring cells [71]. E-cadherin binds to β-catenin, which binds to α-catenin, linking to the actin cytoskeleton, thereby providing structural support. Experiments involving E-cadherin inhibitory antibody-treated cells and α-catenin-deficient cells have demonstrated the inhibition of the formation of not only AJs but also tight junctions (TJs), indicating the essential role of AJs in TJ formation [72, 73] (Fig. 2).

The initial discovery demonstrating the importance of polyamines in maintaining cell adhesion complexes was their association with E-cadherin expression. This study revealed that DFMO-induced reduction in intracellular PUT and SPD levels decreased E-cadherin expression and increased paracellular permeability. The underlying mechanism is attributed to the decline in SPD, which reduced Ca^{2+} influx into cells via voltage-dependent potassium channels, leading to the decreased concentration of intracellular free Ca^{2+} responsible for inducing E-cadherin degradation [74, 75]. Furthermore, polyamines are essential during the transcription and translation of c-MYC, which promotes E-cadherin transcription by binding to the E-Pal box in the proximal region of the E-cadherin promoter [76]. Subsequently, PUT has been demonstrated to upregulate c-MYC translation through CHK2-dependent phosphorylation of the RNA-binding protein HuR [77, 78].

Tight junctions

TJs comprise transmembrane proteins, such as occludin and the claudin family, along with intracellular scaffold proteins, such as the zonula occludens (ZO) family, which establish connections between these transmembrane proteins and the actin cytoskeleton [79, 80]. Polyamines play a role in regulating and stabilizing the expression of these TJ components

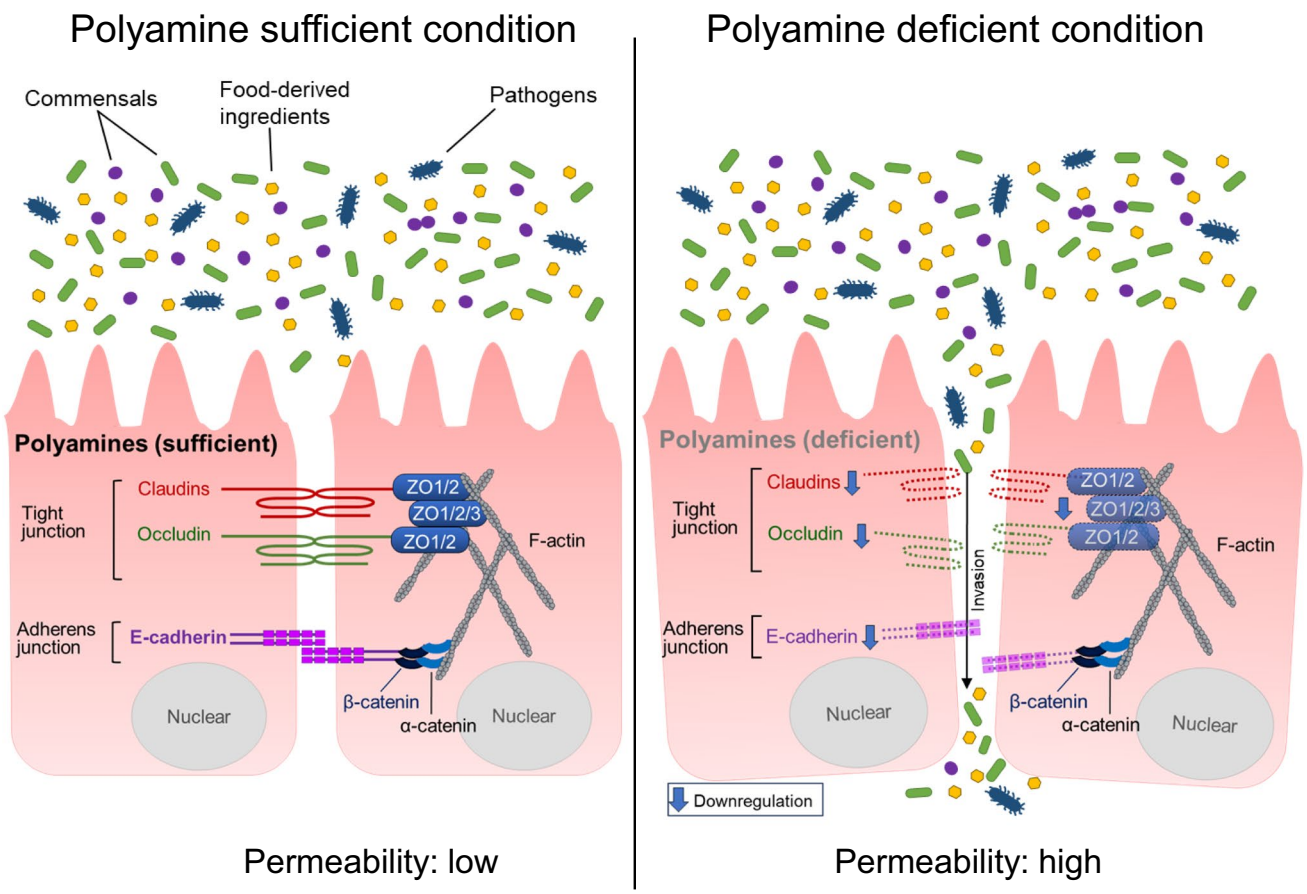

Fig. 2 Polyamines and cell junctions in the intestinal epithelium. Decreased polyamine levels disrupt the intestinal barrier by reducing the proteins that comprise the tight junctions and adherens junctions of the intestine. Subsequently, it increases permeability, allowing molecular components derived from diet and intestinal bacteria to invade the host body

(Fig. 2). Specifically, polyamines induce CHK2(checkpoint kinase 2)-dependent phosphorylation of the RNA-binding protein HuR, leading to enhanced translation through p-HuR binding to *Ocln* mRNA [78]. Additionally, the DFMO-induced depletion of intracellular PUT and SPD promotes occludin degradation. Conversely, supplementing the culture medium with SPD inhibits this degradation, confirming that SPD contributes to occludin stability [81]. In experiments involving Caco-2 cells, lipopolysaccharide treatment reduced the gene expression of *TJP1*, encoding *ZO-1, CLDN1*, *CLDN3*, *CLDN4*, and *OCLN*; however, SPD supplementation restored the reduced gene expression and protein levels of claudin-1 and occludin [82].

Moreover, DFMO treatment-induced reduction of intracellular PUT levels increased JUND levels, which in turn upregulated the expression of the RNA-binding protein TIAR. TIAR binds to the CREB site in the 3′ untranslated region of *TJP1*, inhibiting its translation and reducing ZO-1 (*TJP1*) mRNA expression and protein levels [83]. In addition, DFMO-induced inhibition of polyamine synthesis increased paracellular permeability by decreasing TLR2 mRNA and protein expression [84]. These studies demonstrate the significant role of polyamines in the expression and stabilization of major components of intestinal epithelial junctions, including AJs and TJs. To the best of our knowledge, the relationship between polyamines and desmosomes, another type of cell junction system, is yet to be reported.

Polyamines and intestinal permeability

Evidence suggests that inhibiting polyamine synthesis or administering polyamines in vivo can modulate intestinal permeability through TJs. In experiments involving mice subjected to cecal ligation and puncture, oral administration of DFMO resulted in decreased *Ocln* expression and delayed recovery of the intestinal barrier, indicating the role of polyamines in TJ regulation in vivo [78]. Mice fed a high-fat diet exhibited decreased claudin-1 and occludin levels, resulting in increased permeability, compared to mice fed a control diet; notably, oral administration of SPD restored these levels [82]. However, the effects of SPD administration were

attenuated by antibiotic treatment, leaving the possibility of an influence through SPD administration-induced changes in the gut microbiome unexplored. Oral administration of PUT during the suckling period in piglets also increased the protein levels of ZO-1, occludin, claudin-1, and claudin-3 in the jejunum after early weaning.

Conversely, oral administration of SPM-containing formula to 12-day-old piglets increased the gene expression of ZO-1, ZO-2, occludin, claudin-2, claudin-3, claudin-12, claudin-14, and claudin-16 in the ileum compared to that in the control group [85]. Furthermore, SPM administration downregulated the gene expression of TNF-α and myosin light chain kinase, which induced TJ barrier loosening and increased permeability. In mouse models of dextran sodium sulfate (DSS)- or trinitrobenzene sulfonic acid (TNBS)-induced colitis, the decrease in claudin-1 and occludin levels was inhibited by the oral administration of SPD, leading to improved symptom scores and inflammatory markers associated with colitis [86].

Polyamines and immune cells in intestinal lamina propria

In the intestinal lamina propria, various myeloid and lymphoid cells are present and play a secondary barrier function [87]. Macrophages belong to the group of mononuclear phagocytes and are key players in the maintenance of intestinal homeostasis [88]. Innate lymphoid cells (ILCs) have been highlighted for their role in intestinal mucosal homeostasis and inflammatory bowel disease (IBD) [89]. Recent studies have revealed that polyamines participate in the differentiation and function of macrophages and lymphocytes.

Role of polyamines in macrophage differentiation

Based on their functional differences, macrophages can be classified into two main subsets: classically activated macrophages (M1) and alternatively activated macrophages (M2). M1 macrophages are activated by Th1 responses and are characterized by high levels of pro-inflammatory cytokines, chemokines, and nitric oxide (NO) production, leading to antimicrobial and anti-tumoral activity [90]. In contrast, M2 macrophages are involved in tissue repair, immunosuppression, inflammatory response resolution, tumor promotion, and efficient phagocytosis [90] (Fig. 3).

Experiments have been conducted to elucidate the effects of polyamines on macrophages using bone marrow-specific *Odc* gene knockout mice ($Odc^{\Delta mye}$). $Odc^{\Delta mye}$ mice infected with *Helicobacter pylori* or *Citrobacter rodentium* exhibited increased levels of H3K9ac, a euchromatin marker of transcriptional activation, and decreased levels of H3K9me2/3 compared to those in control mice. Additionally, increased levels of inflammatory cytokines, chemokines, and NO produced by M1 and elevated disease scores were observed [91]. Similarly, DSS-induced colitis $Odc^{\Delta mye}$ mice exhibited increased M1 macrophage-induced production of pro-inflammatory cytokines and chemokines and upregulation of iNos gene expression compared to those in the control group [92]. These observations align with the findings from *H. pylori* and *C. rodentium* infections. However, the disease scores in DSS-induced colitis $Odc^{\Delta mye}$ mice were reduced compared to those of the control group, suggesting that the DSS-induced injury may be impaired owing to the lack of ODC [92]. In contrast, M2 macrophages characteristically express arginase 1 (Arg1), which generates ornithine from arginine (Arg), rather than iNOS, which is involved in NO production [90]. The expression of M2-specific genes, including *Arg1*, relies on polyamines, and stimulation with IL-4, which induces differentiation into M2 macrophages, enhances polyamine synthesis [86, 93, 94] (Fig. 3). Additionally, SPD promotes M2 polarization through the activation of mitochondria-dependent AMPK, stabilization of Hif-1α, and induction of autophagy in macrophages [95]. SPD treatment also reportedly suppresses DSS-induced colitis; however, pretreatment of macrophages with SPD resulted in an M2-like phenotype, and adoptive transfer of these macrophages alleviated the symptoms [95].

The polarization of M1/M2 macrophages involves metabolic reprogramming. In M1 macrophages, aerobic glycolysis induces activation, which involves increasing glucose uptake and converting pyruvate to lactate. The pentose phosphate pathway is also induced in M1 macrophages. This pathway is key for the generation of NADPH for the NADPH oxidase, which is important for reactive-oxygen species and NO production. These metabolic events can rapidly provide the cell with energy and reducing equivalents, which are required for bactericidal activity.

In contrast, M2 macrophages obtain much of their energy from fatty acid oxidation and oxidative metabolism, which can be sustained for longer-term functions. Following activation, M2 macrophages can induce the expression of constituents of the electron transport chain, which performs oxidative phosphorylation (OXPHOS) [96]. A recent study showed that polyamines play a role in this metabolic reprogramming. IL-4 stimulation increases hyp-EIF5A, and inhibition of hypusination reduces glucose uptake into the tricarboxylic acid cycle. Inhibition of hypusination by an inhibitor or gene silencing leads to dysregulation of mitochondrial metabolism and reduction of OXPHOS. Part of these mechanisms involve mitochondrial targeting sequences, which increase dependence on hyp-EIF5A [94]. A study in gnotobiotic mice using PUT-producing or PUT-deficient strain showed that the expression of the OXPHOS complex proteins CI, CII, and CIV was upregulated in macrophages stimulated with IL-4, but not in those stimulated

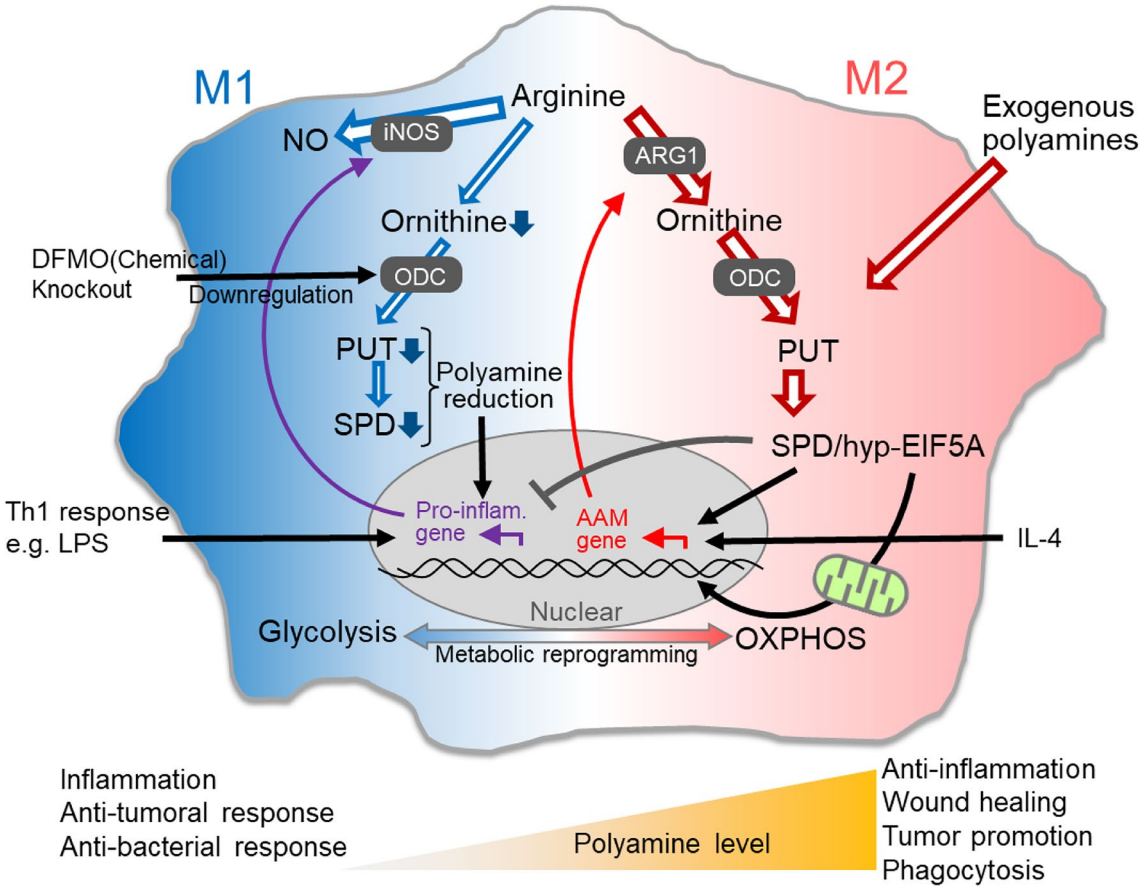

Fig. 3 The role of polyamines in polarization and function of macrophage. The expression of alternatively activated macrophage (AAM) genes, including ARG1, is dependent on polyamines, and stimulation with IL-4, which induces differentiation into M2 macrophages, enhances polyamine synthesis. In contrast, M1 macrophages are activated by Th1 responses and are characterized by high levels of proinflammatory cytokines and nitric oxide (NO) production. A part of arginine is consumed for the production of NO in M1 microphages. The polarization of M1/M2 macrophages involves the metabolic reprogramming of mitochondria. Hyp-EIF5A regulates the expression of oxidative phosphorylationrelated mitochondrial proteins and induces M2 activation. Exogenous-polyamines are taken up and drive the M2 phenotype. Conversely, the absence of ODC by genetic deletion or inhibition of ODC by chemicals reduces polyamines and enhances the M1 phenotype. Open arrows represent metabolic pathways, red and purple arrows represent gene expression, and black arrows and T bars represent activated and inhibitory interactions, respectively

with LPS + IFN-γ. Additionally, CI, CII, and CIV expression was decreased in DFMO-treated macrophages, but exogenous PUT restored this suppression. OXPHOS complex protein expression in macrophages treated only with PUT was consistent with that in macrophages stimulated with IL-4 [19].

Effects of intestinal bacteria-derived polyamine on macrophage differentiation

A study has focused on the effects of polyamines derived from intestinal bacteria on macrophage differentiation. This study investigated the effect of intestinal bacteria-derived PUT on macrophages using gnotobiotic mice inoculated with either wild-type *E. coli* capable of PUT synthesis (WT) or a PUT synthesis gene-deficient strain of germ-free (GF) mice. The results revealed that intestinal bacteria-derived PUT regulated macrophage balance in the colon mucosa lamina propria (cLP). Specifically, the levels of the CX_3CR1^{high} $Ly6C^{-}$ macrophage subset, which exhibits anti-inflammatory properties, increased in WT strain-associated mice compared to those in PUT-deficient strain-associated mice [19]. Additionally, $Arg1^{+}$ M2-like subset levels were significantly increased in the cLP of WT strain-associated mice compared to that in PUT-deficient strain-associated mice.

Conversely, the frequency of $iNOS^{+}$ M1-like macrophages in the cLP of PUT-deficient strain-associated mice was significantly higher than that in WT strain-associated mice, thus augmenting the M1/M2 ratio in the cLP. Furthermore, the uptake of luminal PUT and its conversion to SPD in macrophages were demonstrated

using the stable isotope PUT-^{15}N. Therefore, intestinal bacteria-derived PUT is converted to SPD, and SPD may contribute to these effects via bioactive functions, such as EIF5a hypusination.

Role of polyamines in the function and differentiation of lymphocytes

In recent years, research on the anti-inflammatory effects of polyamines through lymphocytes has seen significant advancements. Group 3 ILCs (ILC3s), located in the intestine, participate in antibacterial infections and autoimmune responses. ILC3s exhibit higher expression of polyamine metabolism-related genes, including ODC, than other ILCs and significantly higher intracellular PUT levels than ILC2s. PUT supplementation enhances IL-22 production in ILC3s in vitro and in vivo. Conversely, conditional knockout of ODC1 significantly reduces IL-22 production in ILC3s, impairing antibacterial defense during *C. rodentium* infection and markedly reduced colitis severity in an anti-CD40 autoimmunity-induced colitis model [97].

Moreover, the addition of SPD to naïve T cells under Th17 differentiation conditions dose-dependently inhibited IL-17 production and enhanced the expression of Foxp3, the master transcription factor for regulatory T cells (Tregs). Furthermore, oral administration of SPD to mice promotes the constant differentiation of Tregs in the gut, thereby alleviating the pathology of T cell transfer-induced colitis models [98]. The polarization effect of SPD on Tregs requires the autophagy mechanism, as T cells lacking the autophagy gene *Atg5* exhibit reduced Foxp3 expression in response to SPD [98]. Polyamines also play a role in the differentiation and functional expression of Th cells through EIF5A hypusination. Adoptive transfer of naïve T cells into recombination-activating gene (Rag), consisting of Rag1 and Rag2, knockout mice results in the development of colitis. Adoptive transfer of naïve T cells from mice lacking T cell-specific *Odc* or deoxyhypusine hydroxylase (*Dohh*), which is involved in EIF5A hypusination, into Rag1 knockout mice resulted in exacerbation of colitis caused by the dysregulation of Th subsets and cytokine disruption [99]. The observed dysregulation resulting from the loss of polyamine or hypusine synthesis was attributed to disturbances in the tricarboxylic acid cycle and histone acetylation. In another report, polyamine depletion promoted Th9 cell differentiation [100]. Th9 cells enhance DSS- and TNBS-induced disruption of epithelial barrier function and are involved in the exacerbation of IBD [101]; therefore, polyamines may also contribute to colitis suppression by regulating differentiation toward Th9 cells.

Polyamines and IBD

Although it remains unclear whether intestinal barrier dysfunction precedes disease onset or results from active inflammation, studies have demonstrated increased intestinal TJ destruction and associated disease progression in patients with IBD [102, 103]. Therefore, restoring intestinal barrier integrity is considered an effective therapeutic strategy. Polyamines have also been associated with IBD, prompting investigations into polyamine concentrations and metabolism in colonic tissues of patients with IBD and colitis mouse models.

Polyamine metabolism in IBD

A decrease in ODC activity in inflammatory regions compared to that in non-inflammatory regions has been reported in patients with ulcerative colitis (UC) and Crohn's disease (CD) [104]. Conversely, a positive correlation exists between ODC activity and mucosal inflammation in child patients with UC and CD [105], with increased expression of the ODC gene observed in quiescent regions of the colonic mucosa compared to that in inflamed regions in patients with CD [106]. Regarding polyamine levels, patients with UC exhibited significantly lower concentrations of SPM in colonic epithelial cells than healthy individuals. Similarly, a DSS-induced chronic colitis mouse model exhibited lower SPM concentration than control mice [107]. However, the same study reported a positive correlation among the concentrations of SPD, N^8-Acetylspermidine, and N^1-Acetylspermine in colonic epithelial cells of patients with IBD and the inflammation index. An increase in SPD levels in the colonic epithelium was also observed in a DSS-induced acute colitis mouse model, leading to the hypothesis that elevated levels of SPD and acetylated polyamine metabolites may reflect the proliferation and regeneration of colonic epithelial cells [107]. Studies have demonstrated a reduction in the gene expression levels of spermine oxidase (SMOX), the enzyme responsible for degrading SPM for the regulation of intracellular SPD concentrations, in the colonic tissues of patients with UC, with this expression correlating negatively with symptom scores [108]. SPD levels decreased in the colonic tissue of DSS-induced colitis *Smox*$^{-/-}$ mice, thereby exacerbating colitis.

Conversely, the administration of SPD improved colitis indicators [108, 109]. However, SPD levels in the colonic tissue of *Smox*$^{-/-}$ mice with *C. rodentium*-infected enteritis were reduced. At the same time, symptoms improved compared to those in the controls, showing opposite results to those observed in DSS-induced colitis [109].

These studies underscore the involvement of polyamines in colitis; however, polyamine metabolism and levels in intestinal tissues during colitis should be carefully considered, given that polyamines play complex roles depending on colitis type, inflammation stage, and the distance from the site of inflammation.

Polyamines and immune cells in IBDs

Monocytes and macrophages play a significant role in IBD. Inflammatory mucosal tissues from patients with IBD exhibit prominent infiltration of immature macrophages [110, 111], leading to the excessive production of inflammatory mediators, such as IL-6, TNFα, and NO, which negatively impact intestinal barrier function [111–113]. Infiltrating monocytes and M1 macrophages in intestinal tissues induce epithelial barrier destruction in IBD through TJ protein deregulation and induction of epithelial cell apoptosis [114]. In this context, the role of polyamines in IBD, particularly through the immune system and macrophages, has been extensively studied. Macrophages participate in various stages of colitis, from pathogenesis and inflammation to resolution and tissue repair. Evidence suggests that polyamines influence colitis by modulating macrophage differentiation and function.

In colitis, an increase in M1, accompanied by a decrease in M2, leads to inflammation [90]. These findings highlight the significance of macrophage polarization in IBD, suggesting macrophage polarization as a potential therapeutic target for IBD treatment [115, 116]. In DSS- or TNBS-induced colitis mouse models, oral administration of SPD suppressed colitis. This suppression occurred through the reduction of the expression of the transcription factors NF-κB and MAPK involved in inflammatory responses, as well as the decrease and increase in the expression of M1 macrophage- and M2 macrophage-related genes in colonic tissues, respectively [86]. In PUT-producing or deficient *E. coli*-mono-associated gnotobiotic mouse experiment, WT PUT-synthesis *E. coli* strain-associated mice exhibited more resistance to DSS-induced colitis than PUT-deficient strain-associated mice, as evidenced by the significant amelioration of disease symptoms and increased survival rates in the WT strain-associated mice. This result indicates that intestinal bacteria-derived PUT shifts the M1/M2 balance toward M2 polarization, thereby mitigating colitis [19].

Genome-wide studies involving patients with IBD have identified tyrosine phosphatase non-receptor type 2 (PTPN2) as a susceptibility locus associated with IBD. SPD increases the expression and activity of PTPN2 and decreases IFN-γ-induced phosphorylation of signal transduction and activator of transcription (STAT)1, STAT3, and MAPKs in a PTPN2-dependent manner [117]. Furthermore, SPD dose-dependently alleviates colitis symptoms in adoptive T-cell transfer experiments in Rag2 knockout mice, a model of colitis [118]. These effects of SPD are attributed to its inhibition of dysbiosis in the gut microbiome induced by T-cell transfer and PTPN2 expression induction in intestinal epithelial and mononuclear bone marrow cells [118]. Furthermore, specific deletion of PTPN2 in bone marrow cells was observed to suppress the polarization of anti-inflammatory M2 macrophages. Co-culture experiments with macrophages and Caco-2 cells revealed that the barrier-protective and anti-inflammatory effects of SPD were lost in macrophages obtained from patients with IBD characterized by SNP mutations in PTPN2 [118].

Application of polyamines for preventing and treating intestinal barrier function-related diseases

As endogenous polyamine synthesis declines with age, exogenous polyamines can serve as a complement to cellular polyamines. Exogenous polyamines encompass dietary and intestinal microbiome-derived polyamines. Most dietary polyamines are absorbed by the small intestine [19, 119]. Analysis of polyamine concentrations in the colonic contents of GF mice and intestinal microbiota-colonized ex-GF mice confirmed that most PUT and SPD in the colonic lumen are produced by the intestinal microbiome [120]. Moreover, PUT is the most abundant polyamine in the human intestinal lumen. Fecal polyamine levels in older individuals and patients with atopic dermatitis are lower than those in healthy adults, depending on the intestinal microbiome composition [66, 67]. For example, the abundance of bacterial species belonging to *Clostridium* subcluster XIVa, including *Roseburia intestinalis*, *Roseburia cecicola*, *Blautia* (*Ruminococcus*) *obeum*, etc., was higher in healthy adults with high fecal polyamine levels than in elderly people with low fecal polyamine levels. However, these data were obtained by terminal restriction fragment length polymorphism analysis, whose ability to identify bacterial species is inferior to that of the 16SrRNA gene amplicon sequencing and shotgun sequencing metagenomics currently being performed. Therefore, in the colon, which is faced with a risk of invasion by intestinal microbiome-derived pathogens, enrichment of intestinal microbiome-derived polyamines (particularly PUT) is a useful strategy for maintaining intestinal barrier function. For instance, previous experiments using PUT-producing *E. coli* or PUT-deficient *E. coli*-associated gnotobiotic mice have demonstrated that PUT is transported into host cells, including colon epithelium and immune cells. Subsequently, it is exchanged for SPD, promoting intestinal epithelial cell proliferation and shifting the M1/M2 balance toward M2 polarization, thereby mitigating colitis [19]. Our group developed a novel biomedical strategy involving the

simultaneous intake of *Bifidobacterium animalis* subsp. *lactis* LKM512 and Arg. This system upregulates PUT production in the colonic lumen by controlling intestinal bacterial metabolism [37].

The mechanism by which the intestinal bacterial biosynthetic pathway produces and releases PUT from Arg has been elucidated. Analysis of extracellular polyamines and polyamine intermediates in fecal cultures grown in the presence of isotope-labeled Arg demonstrated that PUT is produced and released through multiple pathways in the microbiome, with extracellular intermediates exchanged among bacterial species [121]. Further investigation into the collective metabolic pathways of the intestinal microbial community for PUT production from Arg revealed a hybrid PUT biosynthesis system through many experiments using genetically engineered bacteria. This system is a sequential reaction involving three bacterial groups: *E. coli*, *Enterococcus faecalis*, and *B. animalis* subsp. *lactis* (acid-producing bacteria) [122]; it is triggered by environmental acidification by *B. animalis* subsp. *lactis*. Initially, the acid resistance system (using *adiA* and *adiC*) of *E. coli* uses Arg and releases agmatine as an extracellular byproduct. Subsequently, the energy (ATP) production system (using *aguA* and *aguD*) of *En faecalis* uses agmatine and releases PUT as an extracellular byproduct, resulting in induced PUT production (Fig. 4). The application of this technology was demonstrated through the oral administration of a mixture of *B. animalis* subsp. *lactis* and Arg in aged mice in a long-term in vivo study (for 12 months from 14-month-old to 26-month-old). This intervention resulted in suppressed inflammation and extended longevity [37]. In a human clinical trial, oral consumption of this mixture increased fecal PUT and serum PUT, and serum SPD levels [123]. These results suggest that this technology holds promise for developing new therapies to maintain intestinal barrier function via polyamine-associated maintenance of intestinal epithelial cells and promote anti-inflammatory macrophage differentiation in the lamina propria in the near future.

Polyamines and cancer

Although this review focuses on the role of polyamines in normal cells in intestinal mucosa, we briefly discuss their role in cancer in this section. Polyamine metabolism is often dysregulated in various cancers, including colorectal cancer, in which both ODC activity and polyamine levels are elevated [124–126]. Additionally, polyamine transport, which contributes to the intracellular polyamine levels, is upregulated in cancer cells including colorectal cancer cells [126–128]. This escalation of polyamine synthesis and transport in cancer cells support the demand for their

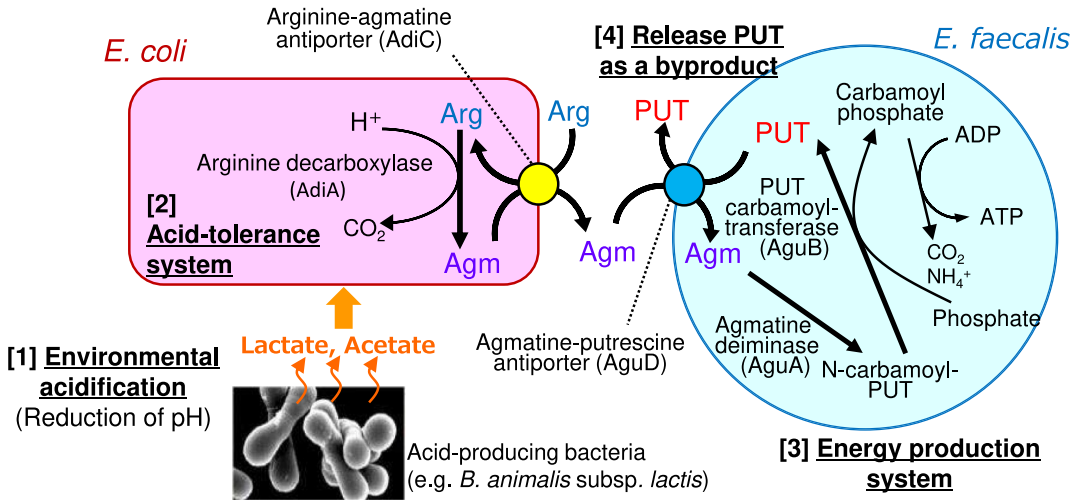

Fig. 4 Hybrid putrescine biosynthesis system in the intestinal microbiome. A mechanistic model of a pathway for putrescine production from arginine through agmatine involving the collaboration of three different bacterial species. (1) This pathway is triggered by environmental acidification due to acetate and lactate roduced by acid-producing bacteria, represented by *B. animalis subsp. lactis* (strain LKM512). (2) In the second step, the acid-tolerance system of *Escherichia coli* [Arg-dependent acid resistance system consisting of arginine decarboxylase (AdiA) and an arginine-agmatine antiporter (AdiC)] is activated by acidic stress. Arg is taken up from the environment into *E. coli* cells by AdiC and converted to agmatine (Agm) by AdiA. The generated Agm is then exported from the *E. coli* cells to the environment via AdiC. (3) In the third step, the ATP synthesis system of *Enterococcus faecalis* consisting of agmatine deiminase (AguA), putrescine carbamoyltransferase (AguB), and agmatine-putrescine antiporter (AguD) is activated. *En. faecalis* takes up the Agm derived from *E. coli* using AguD. Agm is then converted to PUT by the sequential actions of AguA and AguB in the process of ATP production. (4) In the final step, the generated PUT is exported from *E. faecalis* cells via AguD as a byproduct of the collaboration between these different bacterial species

continuous proliferation. In addition, tumor-associated macrophages (TAMs) reside in the tumor microenvironment and are closely connected with polyamines. Within the tumor microenvironment, M2 macrophages, commonly deemed TAMs, are contributors to many pro-tumorigenic outcomes in cancer through angiogenic and lymphangiogenic regulation, immune suppression, hypoxia induction, tumor cell proliferation, and metastasis [129]. Therefore, TMAs in tumor microenvironment have emerged as therapeutic targets in cancer therapy [130]. Polyamine synthesis is enhanced in M2 macrophage [94] and PUT derived from intestinal bacteria promotes M2 macrophage polarization in cLP [19]. Against this background, polyamine blockade therapy, which targets both polyamine synthesis and transport, has been investigated as a cancer therapeutic approach for long time [126, 131, 132]. However, to the best of our knowledge, there are no reports of efficacy in clinical trials, although inhibition of polyamine synthesis and uptake reduces tumor progression and prolongs survival in mouse models [133]. Conversely, recent study suggests that SPD enhances antitumor responses in the context of PD-1-checkpoint blockade by boosting of fatty acid oxidation in activated $CD8^+$ T cells trough binding to mitochondrial trifunctional protein [40]. Thus, polyamines have both cancer-promoting and cancer-inhibiting properties that must be carefully considered when discussing their role in cancer.

Conclusions

As described in this review, polyamines are potentially useful in preventing IBD by enriching the renewal of intestinal epithelial cells and regulating the differentiation of monocytes into anti-inflammatory-type macrophages in the lamina propria (Fig. 5). The accuracy of this theory has been strengthened by experimental data from DSS-induced colitis models [19]. Furthermore, since colonic barrier function is involved in many diseases through systemic (chronic) inflammation [134], enhancing the intestinal barrier function using polyamines is highly beneficial for preventing many diseases, i.e., healthy life expectancy extension. There is a report that oral SPD supplementation induces weight loss and improves insulin resistance by enhancing intestinal barrier function in diet-induced obese mice [135]. In addition, most papers report that polyamines positively affect intestinal barrier function, but a report suggests a negative effect [136]. Therefore, clarifying the molecular mechanisms of the difference between positive and negative data is also

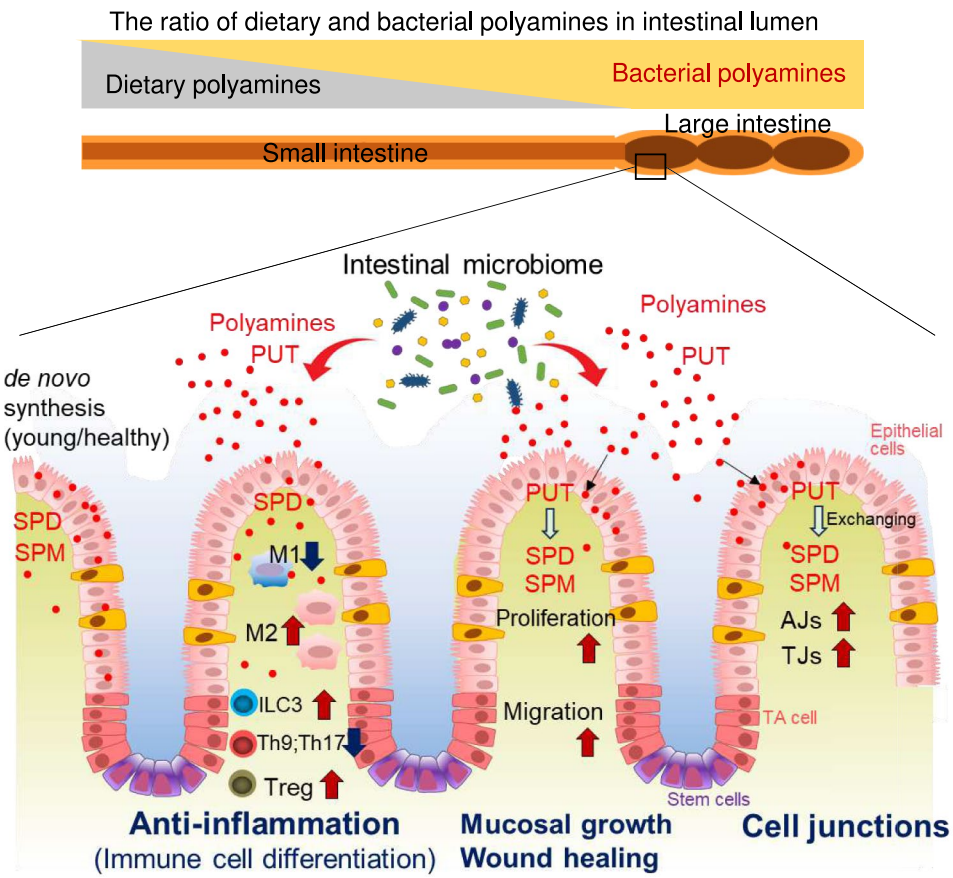

Fig. 5 Overview of polyamine sources in the intestinal lumen and effects of polyamines on intestinal barrier function. Bacterial polyamines, i.e., PUT and SPD, are the primary source of polyamines in the lower intestinal tract because almost all dietary polyamines are absorbed in the small intestine. Bacterial PUT, the most abundant in the human intestinal lumen, is produced by intestinal microbial metabolism systems, such as the hybrid biosynthetic system of multiple bacteria (Figure 4). Absorbed PUT is converted to SPD, which is involved in many biological processes, including EIF5a hypusination, autophagy, and mitochondrial fatty acid oxidation, in intestinal epithelial cells. In the intestinal lamina propria, polyamines contribute to healthy intestinal barrier function, mainly playing roles in intestinal epithelial renewal promoted by AJs and TJs (Figure 2) and in the reduction of inflammation induced by the regulation of macrophage differentiation (Figure 3)

necessary to optimize this treatment. Furthermore, it has been suggested that polyamine uptake by intestinal epithelial cells is regulated by multiple mechanisms, including transcellular transporters, co-transporters, and passive diffusion [16, 137, 138]; hence, identifying the critical path/transporter for exogenous polyamines is important for the development of novel strategies to maintain intestinal barrier function.

Intestinal barrier function is important in preventing many non-gut-related diseases [135, 139–141]. Since most dietary polyamines are absorbed in the small intestine [119], PUT or SPD production by regulating intestinal microbial metabolism using probiotics, prebiotics, and synbiotics is a useful strategy for colonic epithelial barrier functions. Human clinical trials using a mixture of *B. animalis* subsp. *lactis* and Arg, which have already yielded results, should be conducted. In parallel, research should be conducted to identify the unknown complex polyamine biosynthetic system of the intestinal microbiome. Further understanding of the molecular mechanisms by which polyamines participate in intestinal barrier function, particularly autophagy, EIF5A hypusination, M1/M2 macrophage differentiation, and mitochondrial function enhancement, may lead to potential therapeutic targets.

Author contributions A.N. drafted the manuscript and prepared the figures; M.M. edited, revised, and finalized the manuscript and figures. All authors read and approved the final manuscript.

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Declarations

Ethics approval No human and animal experiment data were generated for this review article.

Competing Interests The authors declare no competing interests.

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