Epithelial sensing of microbiota-derived signals

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Abstract
The gastrointestinal tract harbors trillions of microbial species, collectively termed the microbiota, which establish a symbiotic relationship with the host. Decades of research have emphasized the necessity of microbial signals in the development, maturation, and function of host physiology. However, changes in the composition or containment of the microbiota have been linked to the development of several chronic inflammatory diseases, including inflammatory bowel diseases. Intestinal epithelial cells (IECs) are in constant contact with the microbiota and are critical for maintaining intestinal homeostasis. Signals from the microbiota are directly sensed by IECs and influence intestinal health by calibrating immune cell responses and fortifying intestinal barrier function. IECs detect commensal microbes through engagement of common pattern recognition receptors or by sensing the production of microbial-derived metabolites. Deficiencies in these microbial-detecting pathways in IECs lead to impaired epithelial barrier function and altered intestinal homeostasis. This Review aims to highlight the pathways by which IECs sense microbiota-derived signals and the necessity of these detection pathways in maintaining epithelial barrier integrity.

Introduction
The mammalian gastrointestinal tract requires a constant balance of power between immune activation and tissue homeostasis. A monolayer of intestinal epithelial cells (IECs) separate the mucosal immune system from the external environment. Remarkably, trillions of bacteria, fungi, archaea, and viruses reside within the intestinal lumen and constantly interact with host mammalian cells. The sheer abundance and proximity of the microbiota, and their foreign antigens, create an immense source of potential immune stimuli. However, during homeostatic conditions host immune cells act in a restrained manner, balancing inflammatory and regulatory responses to prevent aberrant reactions to innocuous commensal antigens. Yet, during pathogenic infections, intestinal immune cells are poised to combat and eliminate invading microbes. Extensive work has been devoted to understanding the mechanisms by which the immune system discriminates between innocuous commensals and invading pathogens and how it mounts the appropriate immune response. Importantly, IECs are uniquely positioned and equipped to play a fundamental role in initial microbial sensing that directs downstream immune responses.

Intestinal epithelium
In addition to providing a physical barrier, IECs coordinate numerous physiological processes including nutrient absorption, pathogen defense, and immune regulation. Epithelial stem cells reside at the base of intestinal crypts and undergo constant proliferation to give rise to diverse differentiated IECs [1]. During homeostatic conditions, it is estimated that the intestinal epithelium is regenerated every 4–5 days [1]. The diversity and constant renewal of IECs allows for their ability to modulate a variety of biological pathways. IECs are broadly separated into absorptive enterocytes, which are responsible for metabolic and digestive processes, or secretory lineages that are specialized to maintain digestive or barrier functions [1, 2]. Secretory lineages include goblet cells that produce mucin glycoprotein and form mucus, Paneth cells which reside at the base of intestinal crypts and secrete antimicrobial
peptides (AMPs), microfold cells which are critical for antigen capture and presentation to immune cells, enterendocrine cells which secrete hormones that aid in digestion and communicate with the nervous system, and tuft cells that promote type 2 immune responses. Recent studies have employed single-cell RNA sequencing to further define the specific characteristics and behaviors of these distinct IEC subtypes [3, 4]. Together these IECs function to maintain intestinal barrier integrity and instruct downstream immune cell functions to regulate tissue homeostasis.

It is well appreciated that the microbiota influence various physiological functions including digestion, cellular metabolism, tissue development, and immune cell education. Germ-free (GF) mouse models, which lack all microbes, have demonstrated the requirement for the microbiota in calibrating IEC differentiation, proliferation, defense mechanisms, and immune cells [5]. Interestingly, changes in the diversity or localization of the microbiota have been associated with several chronic diseases including cancer, diabetes, obesity, and inflammatory bowel diseases (IBD) [6]. Therefore, it remains critical that immune responses to the microbiota be carefully controlled to avoid inappropriate stimulation or inflammatory reaction.

The intestinal epithelium provides both a physical and chemical barrier to separate mucosal immune cells from commensal microbial stimulation and invading pathogens. This complex and dynamic relationship between the host immune system and microbial signals hinges on IEC involvement. IECs must sense and decipher microbial stimulation and instruct immune cells how to respond. IECs recognize microbial stimuli through a number of different mechanisms including engagement of pattern recognition receptors (PRRs) including toll-like receptors (TLRs), NOD-like receptors (NLRs), and inflammasomes (Fig. 1A). In addition, IECs can sense microbial metabolites via receptors and enzymes that can lead to alterations in gene transcription (Fig. 1B).

**Microbe/Pathogen-associated molecular patterns (PAMPs)**

PRRs detect common microbial molecules, termed pathogen-associated molecular patterns (PAMPs), during infection and are critical for coordinating immune responses and protection against invading pathogens [7]. Common PAMPs include bacterial cell walls components such as lipopolysaccharide (LPS), peptidoglycan, muramyl-dipeptide, and D-glutamyl-meso-diaminopimelic acid, as well as flagella, dsRNA, and DNA molecules. However, ligands for PRRs are not exclusive to pathogenic microbes but are abundantly produced by the microbiota. Several studies have revealed that ligands from the microbiota signal through intestinal PRRs to promote healthy development of host tissues and maturation of the immune system [8]. Interestingly, PRRs have been identified in both vertebrates, as well as invertebrates, suggesting these conserved molecules evolved to communicate with commensal microbes to maintain a symbiotic relationship between the microbiota and host cells [8].
TLRs were one of the first PRRs to be identified and TLR signaling has been shown to be critical for maintaining a healthy intestinal barrier. Polymorphisms or variants of TLR2, TLR4, TLR5, or TLR9 have been associated with increased incidence or severity of IBD [9–12]. In mice, loss of TLR2, TLR4, TLR5, or TLR9 or the TLR signaling adapter, MyD88, contributed to intestinal inflammation in murine models of IBD [13–15]. Interestingly, the exacerbated disease observed in these mouse models was not due to altered inflammatory responses, but instead, because of defects in IEC proliferation, survival, distribution of junction proteins, and overall barrier function [13, 16, 17]. IECs are known to express TLR2, TLR3, TLR4, TLR5, and TLR9 [18]. A recent study constructed five TLR fluorescent reporter mice to visualize the expression and localization of different TLRs throughout the gastrointestinal tract [18]. This study revealed low expression of TLR2, TLR4, TLR5, TLR7, and TLR9 in small intestinal IECs but much higher expression in colon IECs [18], suggesting higher expression of TLRs may be associated with the increased abundance of commensal microbes in the colon relative to the small intestine. Given the complex PAMPs found within the microbiota and the high potential for immune stimulation, the anatomical distribution of TLRs within polarized IECs has often been described as a potential mechanism for controlling overt stimulation. Indeed, several studies have reported that the majority of TLR expression is localized to the basolateral membrane, while TLR3 and TLR9 have also been shown at the apical surface [14, 19, 20]. However, the use of fluorescent reporter mice, TLR2, TLR4, and TLR5 were shown on both the apical and basolateral surface of colon IECs, and TLR4 was also observed intracellularly [18]. Therefore, IECs can detect microbial PAMPs located within the lumen as well as the underlying lamina propria through TLR signaling pathways (Fig. 1A).

Once activated by ligand binding, TLR activation initiates a signaling cascade resulting in the nuclear translocation of NF-κB. This leads to the expression and secretion of various cytokines and chemokines including TNF-α, IL-6, IL-8, IL-18, CXCL2, CXCL2, and CCL20, which signal and calibrate underlying immune cells. In addition, TLR signaling and NF-κB activation in IECs can result in induction of innate defense factors including AMPs, mucus production, and iNOS [21–23]. Paneth cells are the main source of AMPs including α-defensins, REG3β, and REG3γ [24–26]. These molecules function to directly inhibit or lyse bacteria and are critical for preserving intestinal homeostasis. Further, disruption to their production is linked to elevated microbial translocation leading to exacerbated intestinal inflammation [25]. Several studies have reported that induction of AMPs depends on TLR signaling downstream of a wide range of TLR agonists. For example, in vivo stimulation of TLR3 and TLR9 initiated rapid Paneth cell degranulation and secretion of AMPs [27]. In addition, β-defensins were upregulated in IECs following TLR2, TLR3, and TLR4 engagement in an NF-κB-dependent manner [23, 28]. Deletion of the TLR signaling adapter molecule, MyD88, resulted in significantly reduced or undetectable levels of AMPs [24, 29–32]. Furthermore, aged transgenic mice that employed an IEC-specific dominant negative MyD88 developed spontaneous intestinal inflammation due to a lack of AMP secretion and constant bombardment of bacterial antigens [32]. However, other studies have not reported the development of spontaneous inflammation in other mouse models with MyD88 specifically deleted in IECs [33, 34]. Nevertheless, these papers each found that loss of MyD88 signaling in IECs resulted in dysfunctional AMP production and impaired barrier function, highlighting the necessity for TLR-MyD88 signaling in IECs. AMP secretion in the intestine is not exclusive to Paneth cells. Enteroendocrine cells, which are the main producer of hormones within the intestine, sense antigens from the microbiota through TLR4, TLR5, and TLR9. Ligand binding to these receptors triggered release of chemokines and β-defensin [35]. In the colon, goblet cells also required TLR/MyD88 signaling to produce MUC2 and other mucin molecules [36, 37]. Separate from the direct effects on NF-κB activation and AMP production, TLR signaling in IECs also increased the expression of canonical and noncanonical inflammasome components [38]. Together numerous studies have illustrated the importance of IEC-intrinsic TLR signaling pathways.

Nucleotide binding and oligomerization domain (NOD)-like receptors

Recognition of microbial PAMPs by TLRs is critical for IEC development and intestinal barrier integrity. However, TLR signaling is usually restricted to external or phagocytic PAMPs. For detection of intracellular or cytosolic PAMPs, a large family of highly conserved proteins called NOD-like receptors (NLRs) have been described. While NLRs have been largely examined for their roles in detection and protection against invading pathogens, these molecules are also required for maintaining tissue homeostasis. NOD2 was identified early in gene association studies for IBD and remains one of the strongest genetic risks in the development of IBD [39–41]. Consistently, in mice, deficiencies in NOD1, NOD2, or both NOD1 and NOD2 rendered mice extremely sensitive to models of IBD [42–46]. In addition, deficiencies in NOD sensing pathways associated with alterations in the microbiota composition in IBD patients [46–48]. NOD1 is constitutively expressed in...
IECs, while NOD2 expression is confined to Paneth cells in the small intestine [49]. Activation of NOD1 and/or NOD2 by peptidoglycans and other bacterial cell wall components triggered downstream signaling cascades that elicit the production of a variety of antimicrobial peptides and pro-inflammatory cytokines and chemokines [48–52]. In contrast to MyD88-deficient mice, animals null for NOD2 displayed normal levels of REG3β, REG3γ, and RELMβ, but exhibited reduced expression of α-defensins [30]. However, deletion of both NOD1 and NOD2 ablated REG3γ expression in these mice thus resulting in elevated intestinal inflammation [45]. Interestingly, administration of peptidoglycan or other NOD ligands in vivo suppressed TLR signaling and protected mice from the development of inflammatory bowel disease (IBD) [58]. NLRP3, which responds to multiple stimuli, including commensal bacteria, as well as microbial products and metabolites [54]. NLRP3 activation has been shown to play a protective role in intestinal homeostasis, as reduction in NLRP3 expression was linked with increased susceptibility to Crohn’s disease [55]. In mouse models of IBD, deficiency in NLRP3 resulted in heightened intestinal inflammation, suggesting a protective role for NLRP3 activation [56, 57]. Mechanisms attributed to this protective role of NLRP3 activation include non-hematopoietic cell production of IL-18 which promoted epithelial barrier integrity [56] and secretion of AMPs including β-defensin [57, 58]. Interestingly, mutations in NLRP3 that induce hyperactivity have been identified in humans with an autoimmune disease [59, 60]. Further, mice with this specific hyperactive NLRP3 mutation were resistant to mouse models of IBD [58]. NLRP3 hyperactivity promoted IL-1β and AMP secretion and improved barrier function to protect mice from intestinal inflammation [58]. Another well-studied inflammasome-forming NLR is NLRP6, which is predominately expressed in mucosal epithelial cells [61–63]. Within the intestine, NLRP6 is preferentially expressed in enterocytes and goblet cells and is critical for regulating intestinal homeostasis and defense against invading pathogens. Deletion of NLRP6 disrupted secretion of mucin by goblet cells and rendered mice more susceptible to enteric infection [64]. Furthermore, NLRP6 ablation has been shown to induce drastic changes to the microbiota composition which has been associated with dysregulated immune responses and induction of intestinal inflammation [62]. Another NLR molecule, NLRP12, functions independent of the inflammasome and inhibits NF-κB signaling, and played a protective role in mouse models of colitis [65]. Furthermore, the potent intracellular flagellin receptor, NLRC4, which is critical for host defense against pathogenic bacteria, protected against colitis models [66]. Together, these studies highlight the importance of NLR signaling molecules on regulating the host-microbiota relationship (Fig. 1A).

**Microbiota-derived metabolites**

In addition to interacting with host cells through PAMP–PRR engagement, the microbiota can influence host pathways through metabolites (Fig. 1B). Metabolites are small molecules that are produced as intermediates or end products of microbial metabolism. These metabolites can derive from bacterial breakdown of dietary components, modification of host molecules, such as bile acids, or directly from bacteria. Signals from microbial metabolites can calibrate immune cell activation, host energy metabolism, IEC barrier integrity, and overall intestinal homeostasis. The importance of bacterial-derived metabolites in mediating host physiology has been illustrated by GF mice, and rodents exposed to broad-spectrum antibiotics, which have both shown dramatic alterations in the systemic and tissue profiles of metabolites [67–70]. Mono-association studies where a single microbe was used to colonize GF mice have further demonstrated how specific microbes and their metabolites modulate intestinal homeostasis. For example, association of *Clostridium sporogenes* alone resulted in detectable levels of the metabolite, indole-3-propionic acid, which was absent in GF mice [67]. Further, deletion of the gene responsible for indole-3-propionic acid production in *C. sporogenes* led to increased barrier permeability and intestinal inflammation compared to the wild-type *C. sporogenes* strain [71], highlighting the influence of a single metabolite on host physiology. Reintroduction of a single metabolite can have profound effects on the epithelial barrier integrity. Moreover, changes in the diversity or functionality of the microbiota can influence the metabolite profile, or metabolome, which has been associated with development of inflammatory conditions. Indeed, specific classes of metabolites, including bile acids, short-chain fatty acids (SCFAs), and tryptophan metabolites, have been implicated in the pathogenesis of IBD [72]. Below we will discuss the role of bacterial-derived metabolites in mediating epithelial barrier integrity and intestinal homeostasis.
**Short-chain fatty acids**

SCFA, including acetate, propionate, and butyrate, are produced when dietary fiber is fermented by the microbiota and are among the most abundant microbial metabolite present within the intestine. SCFAs are a main energy source for colonocytes [73], and are crucial for intestinal epithelial homeostasis. In fact, dysbiosis observed in IBD patients was associated with the loss of SCFA-producing bacteria including *Faecalibacterium prausnitzii* [74] and *Roseburia hominiswith* [75]. This was consistent with an overall trend of reduced intestinal levels of SCFA in IBD patients [72, 76]. Moreover, although still under investigation, some evidence suggests that increased intake of dietary fibers, or SCFAs, could be clinically beneficial in the treatment of IBD [77–80]. In addition, supplementation of SCFAs improved chemically-induced intestinal inflammation in conventional as well as GF mice [81, 82]. SCFAs have been shown to have diverse effects on mucosal immune cell function and are essential for maintaining and fortifying epithelial barrier function. Stimulation with SCFAs enhanced expression of tight junction proteins and other claudin molecules [83–87], promoted AMP secretion in Paneth cells [88], and upregulated mucus production in goblet cells [89–91]. Furthermore, SCFAs play an important role in regulating IEC proliferation and turnover. GF or antibiotic-treated mice exhibited reduced IEC proliferation, however, upon colonization with SCFA-producing bacteria or supplementation with SCFAs, IEC turnover was restored [92]. Conversely, butyrate has also been shown to inhibit intestinal epithelial cell proliferation [73, 93], suggesting SCFAs, and butyrate in particular, may exert cell type-specific effects on IECs that may be linked to local SCFA concentrations [73].

SCFAs mediate cellular functions through activation of cell surface G-protein coupled receptors such as GPR43 and GPR109A, which are expressed on IECs as well as immune cells. Deletion of GPR43 and GPR109A, specifically in non-hematopoietic cells, enhanced host susceptibility to mouse models of colitis [81, 82], indicating an important role for GPR signaling in maintaining intestinal homeostasis. Furthermore, loss of GPR43 reduced Paneth cell production of AMPs including REG3γ and β-defensin [88], and GPR109A expression was required for butyrate to exert anti-inflammatory effects by suppressing LPS-induced NF-κB activation [94]. In addition to signaling through cell surface GPRs, SCFAs can freely diffuse into cells or can be taken up through specific transporters [95]. SCFAs, butyrate particularly, inhibit histone deacetylase (HDAC) enzymatic activity thereby promoting histone acetylation and regulating gene expression. SCFA inhibition of HDAC activity has been shown to influence immune cell function and promote anti-inflammatory or tolerogenic immune responses [95].

In addition, the use of HDAC inhibitors reduced disease severity in experimental mouse colitis models [96]. However, loss of HDAC activity in IECs resulted in dysregulated intestinal homeostasis. Specifically, mice with loss of IEC expression of the class I HDAC, HDAC3, exhibited reduced Paneth cells, impaired epithelial barrier function, and exacerbated intestinal inflammation [97], suggesting HDAC3 activity is essential for intestinal homeostasis. IEC expression of other HDACs, including HDAC1 and HDAC2, have also been found to be important for maintaining epithelial cell differentiation and intestinal barrier function [98–100]. Given the necessity for IEC-intrinsic HDAC activity in promoting intestinal homeostasis, SCFA inhibition of HDAC activity must be carefully calibrated. A recent study demonstrated that wild-type mice containing abundant SCFAs, actually displayed increased HDAC activity in IECs relative to GF mice, suggesting that other microbiota-derived metabolites may counter SCFA-mediated inhibition of HDAC activity [93]. Indeed, digestion of dietary phytate by the microbiota into inositol phosphate derivatives increased HDAC activity in IECs and promoted stem cell proliferation and epithelial repair [93]. Thus, SCFAs and inositol phosphates fine-tune HDAC activity in IECs.

**Secondary bile acids**

Bile acids are small molecules that are synthesized from cholesterol by liver hepatocytes. Primary bile acids are secreted into the small intestine after eating and are critical for lipid digestion and absorption. The vast majority of primary bile acids are reabsorbed by the time they reach the terminal ileum. In the colon, the remaining bile acids dynamically interact with commensal microbes where they exert mutual effects on each other. Bile acids can be toxic to some microbial species and therefore can directly influence microbiota composition and diversity [72]. Bile acid signaling through the bile-responsive receptor, farnesoid X receptor (FXR), can prevent bacterial overgrowth and microbial translocation [101, 102] as well as induce host production of AMPs [103–105]. Moreover, direct FXR stimulation induced anti-inflammatory effects and protected mice against models of colitis [105, 106], demonstrating the importance of bile acid signaling on regulating intestinal homeostasis. However, these results were obtained through the use of FXR-null mice, thus the specific contribution of bile acid sensing by IECs remains to be determined. Several commensal microbes have developed mechanisms to counteract bile toxicity [107], and can chemically modify bile acids into deconjugated secondary bile acids by expressing bacterial bile salt hydrolases [108, 109]. In fact, GF mice lack secondary bile acid production and mice mono-associated with a bile salt hydrolase-expressing...
*Escherichia coli* demonstrated improved host metabolism, increased production of AMPs, and altered epithelial barrier infection. Intestinal biopsy samples from patients with active IBD demonstrated reduced FXR expression and altered bile acid profiles characterized by increased fecal primary bile acids and reduced serum and fecal secondary bile acids [111].

**Tryptophan metabolites**

Tryptophan, an essential amino acid acquired through the diet, is a precursor for the synthesis of several important molecules including serotonin, melatonin, and vitamin B3 [72]. The intestine is the primary location for dietary tryptophan metabolism which can occur through one of three distinct pathways [72]. One pathway depends on the microbiota to metabolize tryptophan into a variety of indole metabolites that can signal through the aryl hydrocarbon receptor (AhR). AhR is a widely expressed transcription factor that is required for immune and epithelial cell development and homeostasis. AhR signaling in T cells and innate lymphoid cells promotes intestinal barrier integrity and AMP production via regulation of IL-22 production [112, 113]. In IECs, AhR is required for the proliferation of colonic stem cells as well as tight junction integrity and IL-10 receptor expression [114–116]. Indeed, IEC-specific loss of AhR rendered mice highly susceptible to mouse models of colitis [117], highlighting the importance of IEC-intrinsic AhR signaling. In addition, AhR expression was sensitive to the presence of microbiota in IECs [118]. AhR expression was also reduced in inflamed mucosal tissues from IBD patients [119] and IBD patients display reduced indole derivates, including indole-3-propionic acid serum levels [120], which have been shown to promote intestinal barrier integrity [71].

In addition to breakdown directly by the microbiota, tryptophan can be metabolized through the kynurenine pathway, which is mediated by the enzyme, indoleamine 2,3-dioxygenase-1 (IDO1), to produce kynurenine. Kynurenine concentrations are known to increase along the intestinal tract and play barrier protective and immunoregulatory roles [112]. IDO1 was upregulated by the presence of the microbiota and mice deficient for IDO1 expression were highly susceptible to colitis models [112], suggesting an important role for IDO1 in mediating intestinal inflammation. Lastly, tryptophan can be metabolized by tryptophan hydroxylase 1 to produce serotonin within specialized IECs called enterochromaffin cells. While serotonin can be produced within the brain, the majority of serotonin is actually generated in the intestine [112]. Serotonin is critical for neuron signaling in the central nervous system as well as in the enteric nervous system where it coordinates intestinal motility, secretion, and nutrient absorption. The microbiota regulates serotonin production as GF mice have reduced intestinal and systemic serotonin levels [112]; however, the mechanism of how the microbiota mediates serotonin production remains unknown. Together, these studies highlight the multifaceted effects of tryptophan metabolism by microbiota in the intestine.

**Succinate**

Succinate is an intermediate of the citric acid cycle and is produced by host cells as well as the microbiota. Many microbial commensals and pathogens have evolved metabolic pathways to thrive in the nutrient-rich, oxygen-deprived environment of the intestine; thus, production of succinate is a frequent by-product. Recent studies have demonstrated the necessity of succinate signaling by epithelial tuft cells for induction of type 2 immunity and protection against parasitic infections [121, 122]. Interestingly, succinate metabolism has recently been linked with IBD. IBD patients exhibited elevated fecal and serum levels of succinate and increased expression of the succinate receptor within the intestine [123]. Similarly, loss of succinate signaling in mice was protective against the development of colitis [123], suggesting succinate may promote pro-inflammatory immune responses. However, further research will be needed to unravel the role of succinate metabolism in intestinal homeostasis.

**Conclusion and future perspectives**

The microbiota plays a significant role in regulating health and disease. IECs are non-hematopoietic cells that are uniquely positioned to receive signals from the microbiota and direct intestinal homeostasis. Increasing evidence demonstrates that IECs are well equipped to detect and respond to microbial products, and defects in these sensing pathways are commonly associated with inflammatory conditions, stressing the importance of these mechanisms. This Review highlights pathways by which IECs sense microbial signals to enhance epithelial barrier integrity and promote intestinal homeostasis. Beyond sensing and fortifying barrier functions, IECs play critical roles in orchestrating downstream immune responses to the microbiota and evading pathogens. IECs can direct immune responses through the secretion of numerous cytokines and chemokines. However, the exact role IECs play in promoting immune education and tolerance to the microbiota remain under investigation. Several studies have focused on understanding microbiota-immune cell interaction in early life. However, few have investigated how IECs incorporate signals from the developing microbiota to educate immune cells. Further understanding of the contribution of IECs in
promoting intestinal tolerance to the microbiota may have profound consequences for intestinal homeostasis.

While numerous sensing pathways have been uncovered in IECs, the field of microbiota-derived metabolites and their role in intestinal health is still evolving. Studies have commonly focused on the contribution of a single metabolite, or a class of metabolites, on intestinal homeostasis. However, how different metabolites, or the whole metabolome, function in concert to mediate health and disease remain unknown. Future studies investigating how fluctuations in the microbiota diversity and overall metabolome affect IECs and intestinal integrity, and how these pathways can be therapeutically targeted will have wide-reaching implications for human health.

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Compliance with ethical standards

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