

## Enteric glial cells and their role in the intestinal epithelial barrier

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### Abstract

The intestinal epithelium constitutes a physical and functional barrier between the external environment and the host organism. It is formed by a continuous monolayer of intestinal epithelial cells maintained together by intercellular junctional complex, limiting access of pathogens, toxins and xenobiotics to host tissues. Once this barrier integrity is disrupted, inflammatory disorders and tissue injury are initiated and perpetuated. Beneath the intestinal epithelial cells lies a population of astrocyte-like cells that are known as enteric glia. The morphological characteristics and expression markers of these enteric glia cells were identical to the astrocytes of the central nervous system. In the past few years, enteric glia have been demonstrated to have a trophic and supporting relationship with intestinal epithelial cells. Enteric glia lesions and/or functional defects can be involved in the barrier dysfunction. Besides, factors secreted by enteric glia are important for the regulation of gut barrier function. Moreover, enteric glia have an important impact on epithelial cell transcriptome and induce a shift in epithelial cell phenotype towards increased cell adhesion and cell differentiation.

Enteric glia can also preserve epithelial barrier against intestinal bacteria insult. In this review, we will describe the current body of evidence supporting functional roles of enteric glia on intestinal barrier.

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**Key words:** Enteric glia cells; Intestinal epithelial cells; Intestinal barrier function; Tight junctions

**Core tip:** This review offers a state-of-the-art discussion on the role of enteric glial cells (EGCs), an intriguing population of astrocyte-like cells within the gastrointestinal tract, on the regulation of intestinal epithelial barrier. The discussion will shed light on the novel mechanisms of EGC-intestinal epithelial cells interactions, which is invaluable in ultimately developing new therapeutic tools for the restoration of the intestinal barrier functions.

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### INTRODUCTION

The intestinal epithelial barrier (IEB) serves as the first boundary of defense between the organism and the luminal environment. It consists of a continuous monolayer of proliferating and differentiating intestinal epithelial cells (IECs) maintained together by intercellular junctional complex which establishes the cellular polarity and reduces the space between adjacent cells. Therefore, the IEB provides a highly selective permeability that prevents the passage of pathogens<sup>[1,2]</sup>. Loss of this barrier integrity would allow the translocation of the normally excluded

luminal contents (microbes, food antigens, *etc.*) into the mucosa, where inflammatory disorders and tissue injury are initiated and perpetuated<sup>[3-5]</sup>. Considerable evidence indicates that intestinal barrier dysfunction plays a pathogenic role in diseases such as inflammatory bowel disease, celiac disease and irritable bowel syndrome<sup>[6-8]</sup>. Therefore, mediators associated with reinforcing or re-establishing IEB functions could be of great interest in the intervention of these barrier dysfunction diseases.

Beneath the intestinal epithelial cells lies a population of astrocyte-like cells that are known as enteric glia cells (EGCs). The morphological characteristics and expression markers [glial fibrillary acidic protein (GFAP), S-100 $\beta$ ] of these enteric glia cells were identical to the astrocytes of the central nervous system<sup>[9,10]</sup>. Within the central nervous system, the blood-brain barrier, which shelters the nervous system from circulating blood, is maintained *via* interactions between astrocytes and cerebral endothelia<sup>[11]</sup>. Whether similar interactions between enteric glia and epithelia regulate intestinal barrier function has moved into the spotlight in recent years. In this review, we will summarize the current evidence supporting functional roles of enteric glia in the control of IEB functions and gut homeostasis.

## INTESTINAL EPITHELIAL BARRIER STRUCTURE

The important component of the intestinal barrier is the intercellular junctional complex, which consists of the tight junctions (TJs), gap junctions, adherens junctions and desmosomes<sup>[12-14]</sup>. TJs seal the space between adjacent epithelial cells near the apical surface. Structurally, the TJs are composed of membrane-spanning proteins, including claudins, occludin, and zona occludens<sup>[15,16]</sup>. Claudins, in particular, play a critical role in barrier function. Claudin-1, claudin-4 and claudin-5 reduce paracellular diffusion by sealing neighbor epithelial cells. Conversely, claudin-2 forms channels or pores contributing to epithelial leakiness<sup>[17,18]</sup>. Occludin, and the zona occludens could link the cytoplasmic component of the TJs to the actin-myosin cytoskeleton<sup>[19,20]</sup>. Adherens junctions are located beneath the TJs and are involved in cell-cell adhesion and intracellular communication<sup>[21]</sup>. As for gap junctions and desmosomes, they are reported to be involved in cell-cell adhesion and intracellular communication, respectively<sup>[22,23]</sup>. The intercellular junctional complex forms a selective barrier which allows nutrient absorption and defends against entry of infectious agents and foreign antigens into the body. Candidate mediators are reported to affect the intercellular junctional complex in two ways, first by expression regulation<sup>[24]</sup> and second, perhaps more importantly, by affecting the redistribution processes<sup>[25]</sup>. Further, the balance between apoptosis and regeneration of epithelial cells is also crucial for the maintenance of the intact mucosal barrier function<sup>[26]</sup>. Both disruption of the intercellular junctional complex and abnormal epithelial cell apoptosis have been reported to be involved in the

development of a “leaky” gut, which may promote the translocation of luminal antigens into the colonic mucosa and subsequently destroy gut mucosal homeostasis.

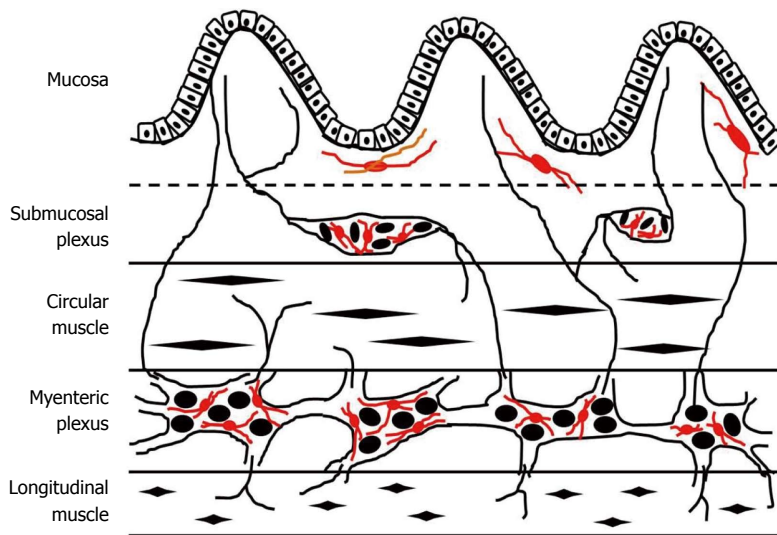
## ENTERIC GLIA IN THE INTESTINAL TRACT

The first description of EGCs within the gut was made in 1899<sup>[27]</sup>. However, for decades, the role of EGCs in gut was largely ignored, and was considered merely as foster cells accompanying and supporting enteric neurons. Interestingly, the current body of evidence expands the functional role of these cells within the gut.

In the intestine, the EGCs are the major constituent of the enteric nervous system and outnumber enteric neurons by a factor of 4 to 10<sup>[28]</sup>. They possess a densely integrated array of intermediate filaments rich in GFAP<sup>[29]</sup> and express the calcium-binding protein S-100 $\beta$ <sup>[30]</sup>. The mucosal EGC population are in close proximity (< 1  $\mu$ m) to the epithelial cells of the colonic crypts and their terminal end-feet processes often extend to the epithelial basement membrane and blood capillaries in the intestinal mucosa<sup>[10,28]</sup>. Meanwhile, major populations of enteric glia are found in enteric ganglia in the submucosal and myenteric plexuses of the enteric nervous system. These EGCs can ensheath the neuronal cell bodies within the enteric ganglia, as well as the connecting enteric neuronal interganglionic processes and the processes extending from the enteric plexi to the muscularis mucosae and externae, blood vessels, and mucosal glands<sup>[10,31]</sup>. The EGCs are typically described as highly irregular, stellate-shaped, small cells which provide regulatory signals for the development and function of neurons and ganglions in the gastrointestinal tract<sup>[32,33]</sup>. As is known, enteric glia share many structural and functional similarities to astrocytes in central nervous system. Amounts of evidence indicate the critical role of astrocytes in the maintenance of the blood-brain barrier. As for EGCs, it has been demonstrated that EGCs actively receive and propagate signals, both to and from nearby enteric neurons and the intestinal epithelium<sup>[27,34]</sup>. Thus, EGCs may be an ideal candidate cell type to maintain proper intestinal epithelial barrier integrity (Figure 1).

## ENTERIC GLIA AND BARRIER FUNCTION

Several lines of evidence implicate an essential role of mucosal EGCs for the integrity of the gut epithelium. Examination of noninvolved intestinal tissue from patients with Crohn’s disease demonstrated that the EGC network was significantly disrupted, and the diminished EGC network appeared to respond poorly to inflammatory signals in these patients<sup>[7,35]</sup>. Animal studies demonstrated that the conditional genetic ablation of EGC in mice could induce the disruption of the intestinal integrity and vascular disturbances, and ultimately lead to fatal hemorrhagic jejuno-ileitis<sup>[6,36,37]</sup>. Further observations showed that the destruction of the EGC network by chemical or autoim-



**Figure 1** General distribution of enteric glia in the gut wall. The glia cells are represented in red. Mucosal glia lie in the mucosa directly beneath the intestinal epithelial cells. Major populations of enteric glia are found in enteric ganglia in the submucosal and myenteric plexuses of the enteric nervous system.

immune T-cell-targeted methods resulted in a collapse of the epithelial lining, and the mucosa healing was obviously delayed<sup>[7,38,39]</sup>. In a mice model of intestinal injury caused by severe burns, stimulation of the vagus nerve could activate the EGCs, and the activated EGCs subsequently prevented burn-induced intestinal permeability and attenuated histological gut injury<sup>[40]</sup>. Hence, it is imaginable that EGCs are a major constituent of the IEB microenvironment favoring barrier protection.

## EGCS MEDIATORS AND MUCOSAL BARRIER FUNCTION

Mucosal EGCs lie in the mucosa directly beneath the epithelial cells, suggesting that regulation of IEB functions by EGC might be *via* paracrine pathways<sup>[41]</sup>. As is known, mucosal EGCs are producers of several mediators implicated in mucosal barrier function<sup>[42]</sup>, such as glial-derived neurotrophic factor (GDNF), transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1), 15-deoxy- $\Delta^{12,14}$ -prostaglandin J2 (15dPGJ2), glial-derived s-nitrosoglutathione (GSNO) and neurotrophins.

### GDNF

GDNF potently promotes the survival and differentiation of many types of neurons<sup>[43,44]</sup>, and is able to prevent apoptosis of neurons induced by axotomy<sup>[45]</sup>. In the intestine, the main source of GDNF could be identified as the EGCs of the mucosal plexus. It is reported that GDNF immunoreactivity was strongly up-regulated in the colonic epithelium during rat experimental colitis and GDNF had strong anti-apoptotic effects on the colonic epithelial cells<sup>[46,47]</sup>. Mechanism studies revealed that the GDNF-mediated antiapoptotic properties required the activation of both the MAPK and the PI3K/Akt signaling pathways<sup>[46,47]</sup>. Recent evidence further supports the anti-apoptotic role of GDNF on mucosal EGCs.

It showed that GDNF could feed back in an autocrine manner to protect EGCs from apoptosis in Crohn's disease patients<sup>[48]</sup>. Disruption of this protective network could contribute to a higher susceptibility towards EGC apoptosis, and subsequently induce alteration of the mucosal integrity. Abnormal mucosal immune responses are considered as a contributing event in the mucosal barrier dysfunction. At this point, role of GDNF in the mucosal inflammatory responses was also investigated. Interestingly, GDNF could inhibit the expression of pro-inflammatory cytokines [interleukin (IL)- $1\beta$ , tumor necrosis factor (TNF)- $\alpha$ ] and myeloperoxidase activity in the rat colon<sup>[47,49]</sup>. In addition, administration of the recombinant adenoviral vectors encoding GDNF (Ad-GDNF) *via* the rectum could significantly ameliorate the severity of dextran sodium sulfate-induced rat colitis<sup>[47]</sup>.

### TGF- $\beta$ 1

TGF- $\beta$ 1 has been reported to be secreted by astrocytes and plays a key role in neuronal homeostasis<sup>[50]</sup>. Interestingly, phenotypic studies of EGCs revealed that TGF- $\beta$ 1 could also be synthesized and released by EGCs<sup>[28,51]</sup>. Moreover, TGF- $\beta$ 1 was reported to account for approximately 12%-30% of the effects of EGCs on intestinal epithelial cell proliferation<sup>[52,53]</sup>. Growing evidence demonstrates that TGF- $\beta$ 1 inhibits epithelial cell proliferation while stimulates epithelial cell migration in a dose-dependent manner<sup>[54,55]</sup>. TGF- $\beta$ 1 mediates the anti-proliferative effects through either a down-regulation of cyclin-dependent kinases or an up-regulation of cyclin-dependent kinase inhibitors, and consequently induces a cell cycle blockade in the G<sub>1</sub>/S phase<sup>[56,57]</sup>. Interestingly, the effect assessment of cultured EGCs on cultured epithelial cell lines supports the concept that EGCs could significantly inhibit intestinal epithelial cell proliferation and concomitantly increase the cell surface of epithelial cells partly through a TGF- $\beta$ 1-dependent pathway<sup>[28]</sup>.

**15dPGJ2**

15dPGJ2, a cellular source of the natural peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) ligand, could also be provided by EGCs<sup>[58]</sup>. Through activation of PPAR $\gamma$ , 15dPGJ2 mediated the inhibitory effects of EGC on epithelial cells proliferation and the positive effects of EGCs on epithelial differentiation, which promises the continuous renewal process of the intestinal epithelium<sup>[59]</sup>. As is known, the renewal process of IECs involves the epithelial cell emergence from the mucosal crypts and subsequent cell migration along the crypt-villus axis, during which the IECs cease to proliferate and acquire differentiated function. However, it should be noteworthy that EGC-derived 15dPGJ2 had no effect on the colonic paracellular permeability<sup>[60]</sup>. Further evidence showed that the anti-proliferative effects of EGCs might be attributed to its induction of a cell cycle blockade at G0/G1 phase in epithelial cells<sup>[61,62]</sup>. Besides, Krüppel-like factor 4, which is expressed in IECs and plays major roles in IEC differentiation and maturation, was supposed to be the candidate cellular target of PPAR $\gamma$  following activation by EGCs<sup>[63]</sup>.

**GSNO**

GSNO is another potent barrier-inducing factor present in enteric glial cell-conditioned media. Interestingly, GSNO is the nitrosylated form of reduced glutathione (GSH), and nitrosylation of GSH is responsible for an antioxidant cytoprotective action<sup>[64]</sup>. It has been demonstrated that intraperitoneal administration of GSNO obviously inhibited the increased intestinal permeability induced by enteric glial cell ablation in transgenic mice. This barrier-inducing effect of GSNO might be associated with the up-regulated expression of peri-junctional F-actin and TJ-associated proteins such as zonula occludens-1 (ZO-1) and occludin<sup>[65]</sup>. GSNO may also maintain the epithelial barrier function by improving the localization of the intestinal tight junction proteins, such as ZO-1, occludin and phosphorylated MLC<sup>[66]</sup>. In addition, GSNO may inhibit the gut inflammatory response through redox-sensitive S-nitrosylation of nuclear factor  $\kappa$ B (NF- $\kappa$ B) inflammatory signaling, suppressing the transcription of pro-inflammatory mediators such as TNF- $\alpha$ <sup>[67]</sup>. Altering NF- $\kappa$ B inflammatory signaling also has important effects on the down-regulation of endothelial cell adhesion molecules that promote leukocyte infiltration<sup>[68]</sup>. However, it should be noteworthy that GSNO did not regulate the epithelial barrier in a dose-dependent manner. It was reported that disruptive effect of GSNO on the epithelial integrity was obtained at relatively higher concentrations<sup>[69]</sup>. The molecular mechanism remains unclear, but may be attributed to altered NO production. As is known, GSNO is a potent nitric oxide donor, which can function to S-nitrosylate proteins and play an important role in proper epithelial ion transport<sup>[70,71]</sup>.

**ROLE OF EGC ON IEC FUNCTIONS**

In concert with the barrier-inducing effects of EGCs,

microarray analysis was carried out to further identify the EGC influence on the intestinal epithelial cells transcriptome. The study was performed to identify statistically significant differences in gene expression profiling in Caco-2 cells cultured alone or in presence of EGCs. The results showed that EGCs could regulate the expression of various genes involved in the control of IEC adhesion, differentiation, motility, cell cycle and proliferation. These collective gene-related data reinforces the concept that EGCs play a major protective role upon IEB homeostasis<sup>[72]</sup>. Besides the protective role, a repair process-inducing role of EGCs has recently been put forward. The study showed that EGCs could promote mucosa healing by increasing epithelial restitution and cell spreading after mechanical injury to IEC monolayers. Epidermal growth factor precursor (proEGF), as a novel glial mediator, was confirmed to be involved in the EGC-mediated epithelial restitution<sup>[73]</sup>. Indeed, proEGF exhibits a lower wound healing ability compared with EGF. However, subsequent studies showed that EGC-derived proEGF could be activated by concomitant release of MMPs or proteases during inflammatory or infectious insults of IEB, which would process proEGF into mature EGF and therefore enhance mucosa repairing<sup>[73,74]</sup>.

**EGC PRESERVE IEB FROM BACTERIAL INSULT**

Recently, a protective role of EGCs on the mucosal barrier during enteric bacterial insult has drawn increasing interest, which may also provide new therapeutic tools in the protection and regeneration of intestinal barrier<sup>[75]</sup>. As is known, *Shigella flexneri* (*S. flexneri*) is one of the major enteroinvasive pathogens which are responsible for the destruction of the intestinal epithelium<sup>[76]</sup>. Flamant demonstrated for the first time that the protective effects of EGCs on the IEB could be due in part to its ability to inhibit *S. flexneri* invasion. Further, cdc42, a key molecular factor for *S. flexneri* invasion, was significantly down-regulated by performing co-culture experiments between IECs and EGCs. In addition, EGCs prevents tight-junction disruption during *S. flexneri* infection, and diminishes mucosal secretion of the pro-inflammatory cytokine IL-8<sup>[77]</sup>. Indeed, these EGC-mediated effects could also be reproduced by GSNO<sup>[78]</sup>. Under the stimulation of lipopolysaccharide (LPS), EGCs could play the protective effect on IEB functions by inhibiting the increase of inducible nitric oxide synthase activity induced by LPS<sup>[79]</sup>. A recent study has shown that Toll-like receptor 2 (TLR2), which plays key roles in sensing microbial structures, is expressed on glial cells. In the intestine, TLR2 exerts cytoprotective effects in intestinal epithelial cells and regulates epithelial barrier function. Besides, TLR2 could stimulate the intestinal expression of GDNF through NF- $\kappa$ B and p38 mitogen-activated protein kinase signaling pathway. In this context, the TLR2-GDNF axis might represent an attractive regulator for gut homeostasis<sup>[80]</sup>.

## EGCS AND INTESTINAL MUCOSAL INFLAMMATION

Because gut inflammation accompanies changes in intestinal permeability, roles of EGCs in mucosal inflammation have also been investigated. Similar to CNS astrocytes, EGCs are recognized as immunocompetent cells that have the ability to express major histocompatibility complex class I and class II molecules, and to produce and respond to a variety of chemokines and cytokines<sup>[10]</sup>. Co-cultured with interferon-gamma and TNF- $\alpha$ , EGCs acquire the ability to process and present antigens efficiently to specific T-cells, indicating that EGCs can act as antigen-presenting cells<sup>[7]</sup>. EGCs express substance P, which can induce the activation of mast cells and macrophages and promote lymphocyte proliferation<sup>[81]</sup>. S100B protein, specifically expressed by EGCs, can orchestrate a wide range of signal activation pathways which are directly correlated with the severity of gut inflammatory processes<sup>[82,83]</sup>. Palmitoylethanolamide can exert anti-inflammatory effects through the selective targeting of the S100B/TLR4 axis on EGCs, causing a downstream inhibition of nuclear factor kappa B-dependent colonic inflammation<sup>[84]</sup>. Further, EGCs have the ability to respond to inflammatory stimuli through the production of pro-inflammatory cytokines, such as IL-6<sup>[85]</sup>, TGF- $\beta$ <sup>[28]</sup> *etc.* EGCs could also inhibit inflammation in animal models of colitis as they produce mediators such as nerve growth factor and neurotrophin-3 which have anti-inflammatory properties<sup>[86,87]</sup>. In Cytomix-stimulated intestinal epithelial cells while EGCs were removed from the culture, the anti-inflammatory effects of nicotine were lost and consequently resulted in increased *in vitro* epithelial permeability<sup>[88]</sup>. These data support the hypothesis that EGCs are likely immune mediators in the gastrointestinal tract. However, so far, limited information is available to indicate the exact mechanisms of EGCs in the regulation of mucosal inflammation-induced permeability alterations.

Collectively, EGCs, intriguing cellular populations within the gastrointestinal tract, might be of interest as a source of novel molecules aiming at preventing relapse or increasing IEB repair. However, the precise mechanism of EGCs on the regulation of intestinal barrier is still partly unclear. Future research identifying precisely how EGCs participate in intestinal epithelium physiology and pathophysiology will be beneficial for our understanding of EGC-IEC interactions, which is also invaluable in ultimately developing new therapeutic tools for the restoration of the barrier functions.

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