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Research Article

Progress of Research on the Function of Enteric Glial Cells in the Gastrointestinal Tract

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Abstract

In the enteric nervous system, there are a large number of Enteric Glial Cells (EGCs) around enteric neurons, and they interact with each other to regulate the function of the gastrointestinal tract. EGCs were only considered to have the function of nutrition and support of enteric neurons in the previous studies, but with the large number of researches in recent years, EGCs have an important regulatory role in the enteric nervous system, enteric mucosal barrier, and enteric neuroimmune system both in the physiological and pathological states. EGCs can affect the axonal maintenance of enteric neurons, enteric neuronal survival and genesis, and the regulation of intestinal motility; affect the integrity and permeability of the intestinal mucosal barrier; respond to intestinal inflammation; and influence the function of intestinal neuroimmunological regulation.

Keywords: Enteric glial cells; Enteric nervous system; Review

Enteric glial cells (EGCs) are distributed throughout the enteric nervous system and are closely associated with enteric neurons, which can nourish and support enteric neurons and play a homeostatic role in the enteric nervous system [1]. EGCs also have an important regulatory role in gastrointestinal motility, intestinal mucosal barrier function, intestinal immunity, etc., and are involved in a wide range of gastrointestinal disease development [1,2]. In recent years, the regulatory role of EGCs in the gastrointestinal tract has received more and more attention, and this paper will compile and review these research progresses.

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Overview of Enteric Glial Cells

The Enteric Nervous System (ENS) consists of enteric neurons and enteric glial cells, and is called the "second brain" because it can autonomously regulate gastrointestinal functions through the interaction between enteric neurons and EGCs [3]. The neural precursors of the ENS are mainly derived from the vagal and sacral neural crest cell fractions, and the number of EGCs is six times that of enteric neurons, and the interaction between the two has an important regulatory role in the maturation and normal function of the ENS [4,5]. The main markers expressed by the EGCs are Glial Fibrillary Acidic Protein (GFAP), central neural Specific protein β (S100β), Proteolipid Protein 1 (PLP1), and Sox10, but the markers expressed by the EGCs are not as important as the markers expressed by the EGCs [6]. Sox10, but there are EGCs subtype differences in marker expression [1,6]. Most EGCs are distributed in the plexus of the submucosal and myenteric plexus, where they associate with surrounding cells through protrusions. Studies have shown that EGCs not only can nutritionally protect enteric neurons and secrete a variety of neurotrophic factors, such as Glial Cell-Derived Neurotrophic Factor (GDNF) and Nerve Growth Factor (NGF), but moreover suggest that they have an important role in the maintenance of intestinal homeostasis, and have a modulatory effect on intestinal function in both physiological and pathological states [7].

Enteric Glial Cells and Enteric Neurons

EGCs are important components in the ENS, whose basic function is to maintain the dynamic balance of the nervous system, and whose protective effect on enteric neurons and their ability to regulate gastrointestinal motility have been demonstrated in a variety of in vivo and ex vivo research experiments in recent decades [8]. Abnormal development of colonic intermuscular EGCs was found in colonic specimens from children with congenital megacolon, which diminished the trophic protection of enteric neurons and affected the survival of intestinal neurons [9]. Several studies have used animal models of glial ablation or glial metabolic toxicity to validate the effects of EGCs on enteric neurons and gastrointestinal motility, but there are some discrepancies in the results of these studies. In an in vitro primary culture experiment of ENS, ablation of EGCs using viral gene targeting led to a reduction in the number of enteric neurons under both basal and oxidative stress conditions [10]. And further studies revealed that part of the mechanism of action of neuroprotection of EGCs under oxidative stress conditions was mediated by reduced glutathione rather than oxidised glutathione or S-nitrosoglutathione [10]. However, in vitro ablation of EGCs using Fluorocitric acid (FC) gliotoxin co-cultured with ileum and colon showed no inflammation or visible damage to the naked eye, but affected ileal contractility and gastrointestinal transit capacity without affecting colonic motility [11]. However, in pathological situations showing different experimental results, EGCs are over-activated by inflammation and release large amounts of inflammatory factors (e.g. : IL-6, IL-1β, prostaglandins), which promotes an increase in tachykinetic peptide-energy release from intestinal neurons, which in turn causes neuronal damage and

abnormalities in gastrointestinal motility. For example, a mouse model of high-fat diet-induced obesity exhibited low-grade inflammation in the gastrointestinal tract, hyperactivation of EGCs, increased release of substance P (SP), and significant enhancement of tachykinetic peptide-ergic contraction of colonic tissues mediated by the NK1 receptor. Whereas treatment with FC attenuated colonic contractility in high-fat diet mice, it had no effect on colonic motility in normal diet mice. Further co-culture of EGCs with lipopolysaccharide and palmitate to mimic the high-fat diet environment in vitro showed that, consistent with the in vivo experiments, there was an increase in the release of inflammatory factors and SP, leading to an increased loss of enteric neurons [12].

It has been further demonstrated that the loss of enteric neurons may be related to the purinergic receptor, Toll-like receptor-4 (TLR-4) (expressed in both enteric neurons and EGCs). EGCs express neurotransmitter receptors that receive purinergic, serotonin and cholinergic signals, triggering intracellular Ca2+ signalling pathways and feedback regulation of enteric neurons [13,14]. Stimulated by intestinal inflammatory mediators, inducible nitric oxide synthase (iNOS) in EGCs catalyses the generation of large amounts of NO to induce the opening of the gap junction protein Cx43 hemichannel, resulting in an increase in Adenosine Triphosphate (ATP) release from EGCs. ATP generated by activated EGCs in turn stimulates a signalling complex consisting of neuronal purinergic P2X7Rs, Pannexin-1 channels, adapter protein ASC and Caspases to mediate enteric neuron death, leading to gastrointestinal motility disorders [15-17]. The large amount of purinergic kinase generated during inflammation activates the purinergic receptors P2X7Rs on enteric neurons, promoting the death of enteric neurons mediated by them and facilitating the release of ATP through Panexin-1 channels on neurons. ATP is hydrolysed to Adenosine Diphosphate (ADP), which in turn further stimulates the purinergic receptors P2Y1Rs on EGCs, inducing an intracellular Ca2+ response in EGCs which in turn prompts the opening of Cx43 hemichannels, promoting ATP and Cx43-dependent ATP release, feedback regulating enteric neurons, and driving enteric neuron death. In the absence of TLR-4 leads to reactive gliosis, EGC in a hyperactivated state, and high levels of NO catalytically generated by iNOS, resulting in altered neuroplasticity and reduced numbers of HUC/D+ neurons. Fluoroacetate gliotoxin (FA) partially reduces glial reactive hyperplasia in TLR-4-deficient mice and partially eliminates NO- and ADP-mediated gastrointestinal smooth muscle relaxation [18]. However, the current study did not distinguish between different glial ablation models and subtypes of EGCs, which may account for the discrepancy in experimental results.

EGCs can also protect enteric neurons by secreting glial cell line-derived neurotrophic factor (GDNF), which is considered one of the most important neurotrophic substances in the ENS [19], and whose classical conduction pathway involves the phosphorylation of GDNF by GDNF and the GDNF family receptor α1 (GFR-α1), which phosphorylates the tyrosine kinase receptor (RET) and activates downstream pathways that affect neuronal migration, development and maturation, but its protective effects on enteric neurons after birth have been less studied [20]. GDNF was found to promote ganglion development and maturation and ameliorate colonic dyskinesia in a mouse model of intestinal neuronal dysplasia [21]. GDNF supports neuronal survival through activation of Src tyrosine kinases and multiple downstream pathways, of which the activation of c-JunN-terminal kinase (JNK) and phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt) is important for the neuronal axon extension and maintenance, neuronal survival and neuronal regeneration is critical [22,23]. In inflammatory environments, enteric neurons undergo programmed death due to ischemia and hypoxia (increased expression of hypoxia-inducible factor HIF-1α), metabolic disorders, and the protective effect of GDNF may be caused by the increased expression of HIF-1α. The HIF-1α signalling pathway is an important one for neuroprotection in vitro, and hypoxic preconditioning activates HIF-1α to protect neurons. Under inflammatory conditions, increased HIF-1α expression induces increased GDNF secretion, which further activates downstream pathways such as RET and HIF-1α to limit enteric neuronal death [24].

The development of intestinal diseases is usually associated with a decrease in enteric neurons, and it has been shown that regeneration of enteric neurons still occurs after birth and in adulthood, but the mechanism is not clear [5,25]. One study found neurogenesis in colitis mice, where enterocytes expressing Sox2+ and PLP1 (these labelling EGCs in the adult gastrointestinal tract) are converted into enteric neurons under inflammatory conditions and show 5-hydroxytryptamine 4 receptor (5-HT4R) signalling pathway dependence [26]. There were early studies suggesting that enteric neurogenesis does not exist in the healthy enteric nervous system, yet there were follow-up studies that found that there is still a continuous loss and genesis of enteric neurons in the small intestine in a healthy intestinal environment, where they maintain a dynamic equilibrium [27]. Certain types of EGCs maintain their progenitor cell potential and can transform into enteric neurons even in adulthood [28]. However, it is unclear whether all EGCs can be transformed into enteric neurons. Under certain conditions, EGCs can be directly converted to enteric neurons and have been shown to be associated with the transforming growth factor β receptor 1 (TGFβR1)/Activin Receptor-Like Kinase (ALK5) signalling pathway [25,26]. Repsox, a TGFβR1/ALK5 inhibitor, promotes the conversion of interosseous plexus ganglionic EGCs to enteric neurons; whereas longitudinal muscle EGCs could not be converted to enteric neurons [25]. The results of this experiment suggest that different types of EGCs may play different roles in maintaining intestinal homeostasis with different plasticity and functions. Moreover, this study was conducted in normal mice, and it is not clear whether this signalling pathway is feasible in the intestine under pathological conditions.

Enteric Glial Cells and the Intestinal Mucosal Barrier

Hundreds of species of bacteria, fungi, etc. are present in the intestinal tract, and the intestinal mucosal barrier is the front line of defense that separates these potentially pathogenic factors from the organism, allowing the organism to defend itself against invasion of pathogenic factors by ingesting the water, electrolytes, nutrients, etc. that the organism needs under normal conditions [29]. EGCs are known to come into direct contact with intestinal epithelial cells, extending their protrusions into the mucosal crypts and the tips of villi, and have been suggested to be an intestinal mucosal barrier regulator [30,31]. The absence of EGCs expressing Glial Fibrillary Acidic Protein (GFAP) was found to lead to the development of intestinal inflammation, increased intestinal epithelial permeability and damage to the intestinal mucosal barrier in a mouse model of ablation of EGCs [32,33]. However, the majority of mucosal and submucosal EGCs in ileal and colonic segments do not express GFAP, whereas almost all EGCs express proteolipid protein 1 (PLP1), S100B and SOX10 [34,35]. Selective ablation of PLP1-expressing cells in the

small and large intestine caused widespread loss of EGCs, but did not result in intestinal inflammation, epithelial cell proliferation, or impairment of barrier integrity [36]. The results of in vitro cell culture experiments have all demonstrated the modulatory effect of EGCs on intestinal epithelial barrier function, but it is controversial whether there is an equivalent effect under conditions of intestinal homeostasis in vivo [36-38]. These studies suggest that there may be subtype specificity in the effect of EGCs on intestinal mucosal barrier function and that it should be considered whether inflammation has an impact on experimental results, whether the absence of EGCs leads to intestinal inflammation that affects intestinal mucosal barrier function or whether intestinal inflammation and intestinal mucosal barrier damage is due to modelling methodology. EGCs are predominantly involved in the regulation of intestinal epithelial barrier function through the release of GDNF, 15-deoxy-(12, 14) prostaglandin J2 (15d PGJ2), transforming growth factor-β1 (TGF-β1), S-nitrosoglutathione, and 15-hydroxytetracosatetraenoic acid (15-HETE) to protect the intestinal mucosal barrier in inflammatory states [39-42]. Among them, the relationship between GDNF and intestinal epithelial cells has been more studied, and GDNF has been found to be an important signal for the intercommunication between EGCs and intestinal epithelial cells. Both in vivo and ex vivo studies have shown that GDNF has an important role in the maturation of the intestinal epithelial mucosal barrier, and its mechanism of action may involve binding to the RET receptor and inhibiting the p38MAPK phosphorylation signalling pathway [43-46]. However, it is important to note that the source of GDNF can be intestinal smooth muscle, enterocytes, etc., in addition to EGCs, which may be one of the reasons why the intestinal mucosal barrier function is not much affected in the ablation model of EGCs [47-50].

Enteric Glial Cells and Intestinal Immunity

The ability of enteric neurons to regulate the intestinal immune system has been extensively studied, but research on EGCs and the intestinal immune system is limited [51,52]. EGCs can express cytokine receptors, TLRs (Toll-like receptors), and related signaling substances to sense signals such as microorganisms and immune cell sources, and participate in regulating the intestinal immune system [53]. EGCs can participate in intestinal inflammation regulation by secreting cytokines and other substances involved in the regulation of intestinal inflammation, producing anti-inflammatory or pro-inflammatory effects [53-56]. EGCs are the main source of Macrophage Colony-Stimulating Factor (M-CSF) in the intestinal muscularis propria. In myenteric injury EGCs can release M-CSF to stimulate monocyte differentiation towards pro-catabolic macrophages, but in a mouse model of colonic inflammation it was found that EGCs activate pro-inflammatory macrophages by producing M-CSF, leading to visceral hypersensitivity [57,58]. EGCs have an antigen-presenting role, and can be used to stimulate the differentiation of monocytes towards pro-catabolic macrophages by releasing type II Major Histocompatibility Complex (MHC II) molecules Participating in intestinal immunomodulation, they contribute to B- and T-lymphocyte activation in inflammatory bowel disease; EGCs have also been found to inhibit T-lymphocyte proliferation in in vitro cell culture experiments [59-61].

Summary

EGCs have received increasing attention as one of the major components of the enteric nervous system. A large number of studies have gradually revealed their protective support and repair-regenerative effects on enteric neurons, protective effects on the intestinal mucosal barrier, and regulatory effects on the enteric nervous immune system. However, whether its mechanism of action is different in physiological and pathological states remains controversial, and there are still many unknowns about the molecular and functional characteristics among different glial isoforms and their regulatory mechanisms on gastrointestinal functions. In-depth studies on EGCs and gastrointestinal function are expected to provide new therapeutic ideas and methods for more related diseases.

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