

The Importance of the Enteric Glia and its Related Product S100b Protein in Gut Inflammation

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ABSTRACT

The urgent need of new pharmacological approaches that may enlarge the tools against inflammatory bowel diseases, lowering side effects and costs of the actually-used drugs is a very important challenge for gastroenterologists and pharmacologists. This short communication is aimed to highlight the importance of enteric glia and its derived signaling molecule S100B in the pathogenesis of chronic inflammation occurring in the gut. Once hyper-secreted, S100B, a small signaling diffusible Ca^{2+}/Zn^{2+} -binding protein, orchestrates a massive pro-inflammatory reaction in the gut, through the paracrine induction of nitric oxide and the recruitment of immune cells in the mucosa. A better understanding of the mechanisms by which enteric glia may trigger and perpetuate gut inflammation may address scientists to selectively target this cell population and decrease S100B overproduction may thus represent a significant innovation in this sense and open the field to novel therapies for inflammatory bowel diseases.

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Key words: Enteric glial cells; S100B protein; Inflammatory bowel disease

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INTRODUCTION

Traditional therapies for inflammatory bowel diseases (IBD) include administration of glucocorticosteroids and sulfasalazine^[1]. These drugs often exert only limited beneficial action. Steroids are effective in the short-term treatment of acute flares of either form of IBD (ulcerative colitis and Crohn's disease) but they are not suitable for maintenance therapies due to a variety of systemic adverse reactions. Sulfasalazine and its derivative 5-aminosalicylic acid (5-ASA) are effective only in mild-to-moderate phases of the disease and in preventing relapse^[1,2]. Biological drugs such as monoclonal anti-TNF α (tumor necrosis alpha) antibody (Infliximab) had a revolutionary impact on the management of steroid-resistant forms of IBD^[3]. However, the long term safety of this drug, the possibility to induce severe side effects^[4] together with the high costs of the therapy, forces gastroenterologists to accurately evaluate their introduction in the therapy. For these reasons, there is an urgent need for the identification of drugs that may efficiently contain IBD, with manageable side toxicity and low costs for patients. To this aim, the identification and the characterization of new molecular targets for new anti-IBD drugs is crucial.

IBD etiology is still not completely understood. For many years, Crohn's disease and ulcerative colitis have been identified univocally as autoimmune pathologies and the gut mucosal macrophage and lymphocytes infiltration has been considered as the main responsible for chronic inflammation occurring in the bowel. In the last years there is increasing evidence highlighting the crucial role played by Enteric Nervous System (ENS) in intestinal inflammation^[5]. Although morpho-functional abnormalities of the ENS in patients with IBD have been consistently reported, additional studies are necessary to better understand the changes in the enteric cells, including neurons (of both submucosal and myenteric layers) and glial cells, in the inflamed gut. Targeting ENS will pave the way to the development of new drugs for future options for IBD that may enlarge the actual therapeutic tools for these disabling diseases^[6].

In this short communication we highlight the importance of enteric glial cells and their signaling molecule S100B as one of the

most intriguing molecules involved in reactive gliosis in the attempt to better understand their role in IBD as possible new target for future anti-IBD drugs.

Enteric Glial cells (EGCs) and gut pathophysiology

EGCs are small cells with a “star-like” appearance containing intracellular arrays of glial fibrillary acidic protein (GFAP)^[7,8] (Figure 1). Despite the ancient assumption that EGCs may serve as mechanical support for enteric neurons, nowadays the knowledge on these cells is consistently expanded. EGCs assure the correct function of vicinal neurons and actively participate in the course of intestinal inflammation acting as first defensive line against pathogens^[9,10]. Thus, EGCs play important functions in the maintenance of ENS homeostasis, but they may also proliferate and be activated in response to injury and inflammation undergoing reactive gliosis (entero-gliosis)^[9,12]. In fact, EGCs release neurotrophins, growth factors and cytokines cross-talking with other infiltrating immune cells such as macrophages, neutrophils and mast cells in the intestinal milieu^[13,14].

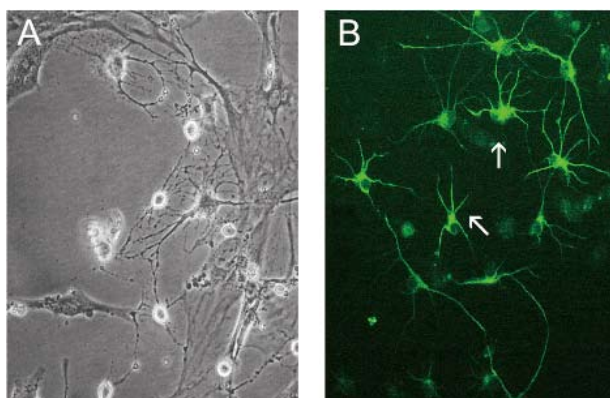


Figure 1 Enteric glia (A); Star shape morphology and GFAP immunofluorescence positivity of enteric glial cells (B).

Very interestingly, different evidences let hypothesize that EGCs act as ‘primum movens’ that may trigger and amplify the inflammatory cascade during chronic inflammatory conditions of the gut^[9,12,15]. An intriguing correlation between the degree of enteric gliosis and severity of gut inflammation has been also reported. The pathophysiological activation of EGCs is not merely restricted to typical inflammatory conditions of the gut. This has brilliantly demonstrated by different studies showing that in patients with irritable bowel syndrome (IBS) mild/moderate inflammatory infiltrates are closely associated to enteric nerves and mucosal activation of the immune system^[14,16]. De Giorgio *et al.*^[17] also demonstrated that patients with severe intestinal dysmotility and megacolon may present myenteric ganglionitis.

S100B protein: a key signaling molecule released by EGCs

EGCs are of neuroectodermal origin^[18] and so they are not morphologically and functionally related to microglia in the central nervous system, which has a monocyte-macrophage lineage^[19]. For this reason EGCs are mainly linked to astrocytes in the central nervous system, which regulate synaptic transmission^[20] and the formation and function of the blood-neural barrier^[21]. EGCs physiologically express vimentin, GFAP, and S100B protein, the latest considered not only a typical glial marker but also a crucial signaling molecule^[9]. In fact, S100B protein participates to the onset and the progression of the inflammatory status in the gut. This protein orchestrates a wide range of pro-inflammatory pathways that are

directly involved in intestinal degenerative processes^[9].

S100B is the homodimer of β subunit and it belongs to the S100 protein family that includes more than 20 EF-hand Ca^{2+} - Zn^{2+} binding proteins^[22].

In the brain, S100B in nanomolar concentrations regulates physiological processes such as neuronal survival, neurite outgrowth and it stimulates astrocytic proliferation by increasing the intracellular free Ca^{2+} levels^[23,24]. On the other hand, micromolar amounts of S100B protein are responsible for deleterious events within the cell and they have been observed in patients with neuropathologies such as Alzheimer’s disease and Down’s syndrome^[25].

In the gut S100B protein is physiologically expressed by EGCs^[9] while other members of S100 family, such as S100A8, S100A9 and S100A12 are found in phagocytes and in intestinal epithelial cells in the inflamed gut^[9,26]. The role exerted by this protein in gut inflammation has been only recently discovered. Since that moment, many studies have been addressed to better understand the intimate connection between EGCs-derived S100B release and the instauration of acute/chronic scenario in the gut and now it appears clear that EGCs and S100B participate to the chronic mucosal inflammation in the gut^[9,12,13,15].

More in detail, researches performed by comparing patients with ulcerative colitis and healthy subjects demonstrated that in the rectal mucosa of diseased patients there is a significant increase in S100B mRNA, protein expression and secretion^[15]. This up-regulation cannot be considered a mere epiphenomenon because it is associated with enhanced NO production through the specific induction of inducible Nitric Oxide synthase (iNOS) protein. Thus, S100B up-regulation has a prominent role during ulcerative colitis. The correlation between S100B up-regulation and NO production is very interesting since ulcerative colitis is characterized by abnormal mucosal NO production in response to iNOS induction by pro-inflammatory cytokines^[27].

The ability of EGCs to modulate NO production through S100B protein has been confirmed also in absence of a chronic inflammatory scenario. In fact, the application of micromolar concentrations of exogenous S100B induces a significant and concentration-dependent increase in NO production, through the induction of iNOS expression, in the human non-inflamed rectal mucosa of healthy subjects^[15]. This finding suggests that EGCs are able to mediate mucosal NO-dependent inflammatory responses by increasing S100B protein level within the intestinal milieu and let hypothesize that S100B release might be a first step in the onset of inflammation^[28]. Once released, S100B may accumulate at the RAGE (receptor for advanced glycation end products) site only in micromolar concentrations^[29,30]. Such interaction leads then to mitogen-activated protein kinase (MAPK) phosphorylation and consequent nuclear factor- κ B (NF- κ B) activation which, in turn, induces the transcription of different cytokines, such as iNOS protein^[31,32]. Thus, S100B can be considered a full-title pro-inflammatory cytokine.

CONCLUSIONS

Compelling evidence indicates that EGCs participate to the modulation of inflammatory responses in the human gut. Targeting glial alteration during inflammatory disorders might represent a novel approach to diminish tissue damage and to counteract the lack of long-term effectiveness of classical immunosuppressant agents used, for instance, to treat ulcerative colitis. EGCs trigger and promote chronic inflammation in the intestinal mucosa since these cells over-release S100B that in turn determinates NO production. Such detrimental loop is responsible for a substantial recruitment of other

target cells, including immune cells. In fact, EGCs-derived S100B is able to affect peripheral macrophages and intestinal mucosal immune cell. Additional studies investigating the relationship between EGCs and immune cells are warranted in order to carry out an in-depth assessment of these cell populations, and their derived factors, in the modulation of immune/inflammatory responses in the human gut. Such approach would be extremely important to establish new therapies towards the treatment of gut inflammatory diseases.

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