Journal of Cell Signaling
ISSN: 2576-1471

Zeng and Wu, J Cell Signal 2018, 3:1
DOI: 10.4172/2576-1471.1000176

Commentary Open Access

IGF-1/β-arrestin 2/ERK Signaling Contributes Intestinal Mucosal Repair in Colitis

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Received date: December 14, 2017; **Accepted date:** January 04, 2018; **Published date:** January 06, 2018

Commentary

Colitis is characterized by inflammation limited to the mucosal and sub-mucosal layers of the colon [1]. Ulcerative colitis (UC) is a disease of the mucosal layer, and activity of the disease is assumed to be related to mucosal appearance. Mucosal healing has emerged as a major therapeutic goal in UC. Although numerous theories have been proposed for the cause of UC, there has been less focus on the repair mechanism of colonic mucosa from UC. The physiological pathways involved in UC mucosal repair are poorly understood. A growing body of evidence has found that the attainment of mucosal repair led to improved clinical outcomes and the promotion of the recovery of UC [2]. Reports from us and others demonstrate that β-arrestin 2 play an important role in inflammation. β-arrestin 2 is a scaffolding protein that regulates G protein-coupled receptor (GPCR) desensitization and endocytosis [3]. Both β-arrestin 1 and β-arrestin 2 play an important role in ulcerative colitis [4-6]. Recently, mutiple studies have uncovered unexpected role of β-arrestin 2 as scaffold proteins for many signaling molecules in the cytoplasm and nucleus. This results regulation of gene expression and cellular responses, particularly those involve mitogen activated protein kinases (MAPKs), associated with cell growth, differentiation, proliferation, and apoptosis [7]. β-arrestin 2 can be involved in Insulin-like growth factor-1 (IGF-1) mediated signaling pathways, an important participant in mucosal repair during intestinal inflammation [8,9]. The interaction of IGF-1 and β-arrestin 2 in intestinal mucosal repair of colitis remains unexplored. However, Chen and our colleagues identified a mucosal repair-promoting role of β-arrestin 2 *via* IGF-1/β-arrestin 2/ERK signaling pathway. Present commentary aims to briefly discuss the significance of β-arrestin 2 mediated signaling in epithelial and goblet cell proliferation and regeneration in intestinal mucosal during inflammatory remission phase [10].

β-arrestin 2 is important in both colitis and colon cancer. In DSS-induced colitis, we have previously demonstrated that β-arrestin 2 is highly expression in acute phase of colitis in both UC patients and DSS-induced mouse colitis, contributing epithelial and goblet cells apoptosis *via* ER stress/PUMA signaling. β-arrestin 2 deficiency leads to a decrease in ER stress/PUMA expression, resulting in reduced epithelial apoptosis. TNF-α can induce β-arrestin 2 protein expression which promotes PUMA mitochondrial-dependent cell apoptosis and inflammation in ulcerative colitis [5,6]. Moreover, Mice with β-arrestin 2 depletion (knockout and siRNA) developed only 33% of the tumors detected in their β-arrestin 2-WT littermates. β-arrestin 2 dependent colon tumor is pre-dominantly involved in Wnt signaling, cell adhesion, migration, and extracellular matrix remodeling. β-arrestin 2 is essential for the initiation and growth of intestinal tumors displaying elevated Wnt pathway activity and identify molecular heterogeneity among tumors induced by truncating Apc mutations [11]. However, in our recent study, we found that β-arrestin 2 is sustains high expression in mucosal repair phase. During mucosal repair phase, expression of β-arrestin 2 is regulated by growth factors such as IGF-1 and TGF-β. Up-regulation of β-arrestin 2 during mucosal repair phase contributes to mucosal recovery by promoting cell proliferation and regeneration, especially epithelial and goblet cell. Consistent with that finding, cell proliferation and regeneration in mucosa delayed in β-arrestin 2 knockout mice. Thus, downregulation of β-arrestin 2 can disrupt cell proliferation, leading to delay intestinal mucosal repair, along that line, we found that overexpressing β-arrestin 2 in HCT116 cell line, PCNA expression by IGF-1 was enhanced significantly. Over expression of β-arrestin 2 is closely associated with cell proliferation, suggesting an important pathological role for β-arrestin 2 signaling in inflammatory remission phase.

Once damage occurs, the intestinal epithelium undergoes an injury-induced repair response to restore the structural and functional integrity rapidly [12]. The efficient repair is accomplished by a process that consists of epithelial restitution, proliferation, and differentiation [13,14]. After intestinal injury, progenitor cells proliferate and differentiate into mature epithelial cells to reestablish the epithelium. Studies have reported that IGF-1 is a well know important growth factor in intestinal remodeling and repairing. Biological activities of IGF-1 are mediated by IGF-1 receptor, leading to activation of extracellular signal-related kinase (ERK) signaling networks [15]. In intestinal remission phase DSS-induce colitis, IGF-1 is involved in the mucosal repair by regulating β-arrestin 2 mediated epithelial and goblet cell regeneration. β-arrestin 2 deficiency inhibites ERK1/2 activation during recovery phase. β-arrestin 2 could also enheance the phosphorylation of ERK1/2 leading to cell proliferation in response to IGF-1, both *in vivo* and *in vitro*. Thus, β-arrestin 2 acts as a downstream of the IGF-1 receptor pathway where increased ERK1/2 activation led to faster recovery. On the other hand, in β-arrestin2 deficiency mice, ERK1/2 activation was reduced, leading to decreased cell proliferation and reduced mucosal healing through regulation of its downstream proliferation signaling pathways Thus, IGF-1 contributes to the mucosal repair of experimental colitis mainly *via* β-arrestin2 mediated ERK activation.

In summary, our studies provide evidence for β-arrestin 2 a critical regulator of ERK activity (Figure 1). On one hand, IGF-1 mediates cell proliferation contributing to mucosal recovery and on the other hand, β-arrestin 2 directly activates ERK signaling in response IGF-1. Either way, β-arrestin 2 gains its function in epithelial and goblet cell results in proliferation and regeneration during mucosal repair under inflammatory conditions. Altogether, these results describe a role for β-arrestin 2 in promoting intestinal mucosal repair *via* IGF-1/β-

arrestin2/ERK signaling pathway and may provide a therapeutic node in colitis.

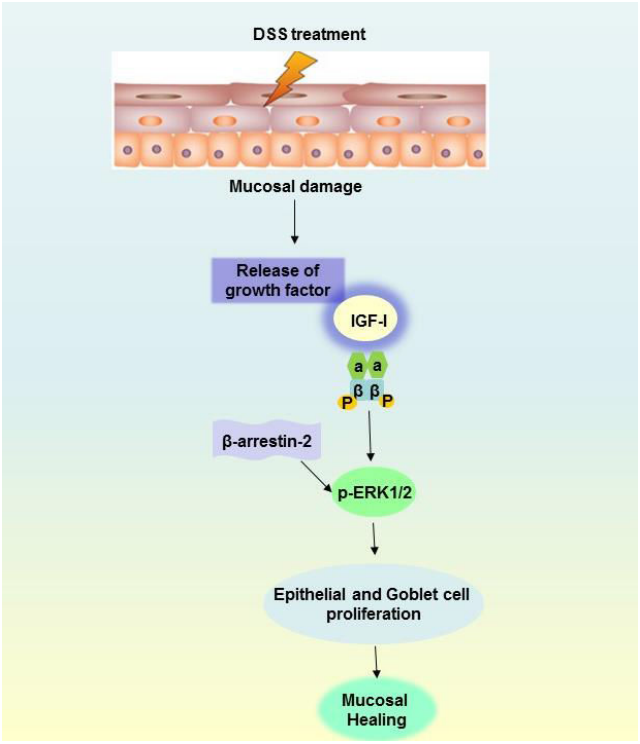

Figure 1: Schematic illustration of the IGF-1/β-arrestin2/ERK signalling pathways involved in regulating cellular proliferation and regeneration in intestinal mucosal repair.

Major finding

β-arrestin 2 contributes intestinal mucosal repair.

Mechanism

β-arrestin 2 activates IGF-1 involved ERK singling pathway.

Impact

β-arrestin 2 promotes intestinal epithelial and goblet cell regeneration and proliferation, and is a potential therapeutic target.

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