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REVIEW

Role of glucagon-like peptides in inflammatory bowel diseases—current knowledge and future perspectives

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Abstract

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic, relapsing, intestinal inflammatory disorders with complex and yet unrevealed pathogenesis in which genetic, immunological, and environmental factors play a role. Nowadays, a higher proportion of elderly IBD patients with coexisting conditions, such as cardiovascular disease and/or diabetes is recorded, who require more complex treatment and became a great challenge for gastroenterologists. Furthermore, some patients do not respond to anti-IBD therapy. These facts, together with increasing comorbidities in patients with IBD, imply that urgent, more complex, novel therapeutic strategies in the treatment are needed. Glucagon-like peptides (GLPs) possess numerous functions in the human body such as lowering blood glucose level, controlling body weight, inhibiting gastric emptying, reducing food ingestion, increasing crypt cell proliferation, and improving intestinal growth and nutrient absorption. Thus, GLPs and dipeptidyl peptidase IV (DPP-IV) inhibitors have recently gained attention in IBD research. Several animal models showed that treatment with GLPs may lead to improvement of colitis. This review presents data on the multitude effects of GLPs in the inflammatory intestinal diseases and summarizes the current knowledge on GLPs, which have the potential to become a novel therapeutic option in IBD therapy.

Keywords Crohn's disease · GLP-1 · GLP-2 · Incretins · Inflammatory bowel disease · Ulcerative colitis

Abbreviations

CD	Crohn's disease
DPP-IV	Dipeptidyl peptidase IV
DSS	Dextran sulfate sodium
EEC	Enteroendocrine cells
GI	Gastrointestinal tract
GIP	Gastro-insulinotropic peptide
GLP	Glucagon-like peptide
GM-CSF	Granulocyte-macrophage colony-stimulating factor
IBD	Inflammatory bowel diseases
IFN-γ	Interferon γ
IGF-1	Insulin-like growth factor 1
IL	Interleukin
LPS	Lipopolysaccharide
PC 1/3	Prohormone convertase 1/3
PEG	Polyethylene glycosyl
SCFA	Short-chain fatty acids
TNBS	2,4,6-trinitrobenzenesulfonic acid
TNF-α	Tumor necrosis factor α
UC	Ulcerative colitis

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Introduction

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic, relapsing, intestinal inflammatory conditions with complex and yet unrevealed pathogenesis in which genetic, immunological, and environmental factors play a role (Sobczak et al. 2014). Inflammation in CD involves the entire gut wall and may occur in any part of gastrointestinal (GI) tract, whereas in UC, only colonic mucosa is affected (Zatorski et al. 2015). Both diseases are associated with alterations of the innate and adaptive immune system, microbiota, and epithelial function (Zietek et al. 2017; Siczek et al. 2017). Thus, inappropriate response to different pathogens in epithelial surface may cause release of inflammatory cytokines and induce inflammation.

The incidence and prevalence of IBD are the highest in westernized countries, suggesting the increasing role of environmental factors (Molodecky et al. 2012). Importantly, while incidence of IBD is still rising, the mortality is low and thus the prevalence of IBD escalates globally (Molodecky et al. 2012). Nowadays, a higher proportion of elderly IBD patients with coexisting diseases, such as cardiovascular disease and/or diabetes (Román and Muñoz 2011), is recorded; these patients require more complex treatment and became a great challenge for gastroenterologists. Moreover, recent studies showed that 15–40% of IBD patients suffer from obesity, which becomes an increasing problem in IBD treatment. It has also been evidenced that obese IBD patients have shorter time to first surgery as well as lower quality of life in comparison with non-obese IBD sufferers (Singh et al. 2017).

Currently, 5-aminosalicylates, immunosuppressive agents, corticosteroids, and biological therapeutics are widely used in IBD therapy. However, some patients do not respond to the treatment. Moreover, the side effects and economic costs of IBD patients' treatment cannot be ignored (Stallmach et al. 2010; van der Valk et al. 2016). These facts, together with increasing comorbidities in patients with IBD, imply that urgent, more complex, novel therapeutic strategies in the treatment are needed.

Enteroendocrine cells (EEC) comprise approximately 1% of the intestinal epithelium, but secrete more than 30 different peptide hormones, which makes them the largest endocrine system in the whole body (Worthington 2015). Most important bioactive compounds secreted by enteroendocrine L cells in the gut due to nutrient uptake are glucagon-like peptides (GLPs) including GLP-1 and GLP-2. GLP-1 plays a fundamental role in lowering blood glucose level and controlling body weight through stimulating the islet B cells to secrete insulin, inhibiting gastric emptying and reducing food ingestion (Zietek et al. 2017). Thus, GLP-1-based therapy is nowadays widely used in the treatment of type 2 diabetes, especially in obese subjects. On the other hand, GLP-2 analogs due to their effects on crypt cell proliferation, improving intestinal expansion and nutrient absorption, are used for intestinal injury and short bowel syndrome (Litvak et al. 1998; Yazbeck et al. 2010a). GLPs are rapidly degraded by dipeptidyl peptidase IV (DPP-IV), which results in their short half-lives in vivo. Thus, GLPs and DPP-IV inhibitors have recently gained attention in IBD research (Lund et al. 2011; Moran et al. 2013; Mimura et al. 2013; Duan et al. 2017; Salaga et al. 2018). Several investigations showed that treatment with GLPs may lead to improvement in dextran sulfate sodium (DSS)- and 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced colitis (Table 1).

This review presents data on the multitude effects of GLPs in the inflammatory intestinal diseases. It summarizes the current knowledge on GLPs, which have the potential to becoming a novel therapeutic option in IBD therapy.

Glucagon-like peptides

GLP-1 and GLP-2 derive from transcription product of the proglucagon gene *gcg* located on chromosome 2. Both GLP-1 and GLP-2 are simultaneously produced via posttranslational processing of proglucagon by prohormone convertase 1/3 (PC 1/3) (Fig. 1). GLP-1 is mainly produced in the ileum and the colon and it is known as the most potent incretin in the human body, which delays gastric emptying and lowers postprandial blood glucose level through augmentation of glucose-dependent insulin release (Lim et al. 2009). Moreover, GLP-1 is able to increase pancreatic B cell growth by promoting proliferation and reducing apoptosis (Ellingsgaard et al. 2011). The GLP-1 is released upon food consumption in a biphasic pattern with an early phase 10–15 min and a longer second phase 30–60 min after meal. Secreted form of GLP-1 is GLP-1 (1–37), which is susceptible to amidation and proteolytic cleavage resulting in two equipotent biologically active forms GLP-1 (7–36) and GLP-1 (7–37). Endogenous GLP-1 is rapidly degraded by DPP-IV to inactive form GLP-1 (9–36), with half-life of approximately 2 min (Baggio and Drucker 2007). Meal ingestion, especially one rich in fats and carbohydrates, is the primary physiologic stimulus for GLP-1 secretion (Brubaker 2006). GLP-1 acts through a specific G protein-coupled receptor, which is expressed in pancreatic islets, the central nervous system, lungs, kidneys, heart, intestine, and immune cells, explaining the numerous roles for GLP-1 signaling beyond blood glucose control (Zietek and Rath 2016).

GLP-1, when secreted by L cells, may act in the endocrine (being released into the bloodstream) or paracrine fashion, i.e., stimulating neurons. GLP-1 exerts anorexigenic effect mediating signals from the gut to the brain through vagal nerves (Gallwitz 2012). Moreover, GLP-1 has a protective effect on neuronal damage as shown by reducing ibotenic acid-induced depletion of choline acetyltransferase immunoreactivity (Perry 2002). In addition, mice lacking GLP-1 receptor exhibit impairment of cognitive function, synaptic plasticity, and memory formation (Duan et al. 2017). Presented data show that GLP-1 possesses pleiotropic functions in multitude of diseases. To date, exenatide, liraglutide, albiglutide, lixisenatide, and dulaglutide, which are structurally modified GLP-1 analogs with extended half-life in vivo, are used in a clinical setting (Gupta et al. 2017).

GLP-2 is a 33-amino-acid proglucagon-derived peptide, which is expressed in the small intestine, mainly in terminal ileum. Moreover, expression of GLP-2 may be observed in the colon, although to a lesser extent than in the terminal ileum (Yusta et al. 2017). In the colon, the density of the GLP-2-immunoreactive cells increases from proximal to distal part with maximal number of GLP-2-positive cells in the rectum (Litvak et al. 1998; Caddy et al. 2001; Schmidt et al. 2005). GLP-2 (1–33) is an active form of GLP-2 which is released in response to nutritional, hormonal, and neural stimulation. Recent data

Table 1 GLPs analogs and DPP-IV inhibitors under investigation in preclinical studies

Model	Treatment	Result	Reference
DSS-induced mouse model of colitis	GLP-1 coated with sterically stabilized phospholipid micelles (GLP-1 SSM) 15 nmol/day i.p.	Improvement of intestinal, epithelial architecture alleviation of diarrhea, increase in goblet cell number, reduction of IL-1β expression	Anbazhagan et al. 2017
DSS-induced mouse model of colitis Ischemia/reperfusion mouse model of colitis	–	Plasma GLP-1 levels were increased after LPS administration through TLR-4 dependent manner prior to measurable changes in inflammatory status and plasma cytokine.	Lebrun et al. 2017
DSS-induced mouse model of colitis in GLP-1R knockout mice	GLP-1 agonist – Exendin – 4 10 nmol/kg s.c.	GLP-1R knockout mice exhibited dysregulated intestinal gene expression, an abnormal representation of microbial species in feces and enhanced sensitivity to intestinal injury after DSS administration. Exendin-4 administration resulted in increased expression of genes encoding cytokines and chemokines in injured intestine	Yusta et al. 2015
DSS-induced mouse model of colitis	GLP-2② degradation-resistant GLP-2 analog dimer 200 μg/kg/day s.c.	Increase in total gut weight, length, villus height, crypt depth and crypt cell proliferation	Gu et al. 2018
Radiation-induced mouse model of intestinal injury	GLP-2② degradation-resistant GLP-2 analog dimer 200 μg/kg/day s.c.	Protection against radiation-induced gastrointestinal toxicity, down-regulation of inflammatory responses, decrease in structural damage of the intestine and apoptosis of intestinal cells	Gu et al. 2017
DSS-induced mouse model of colitis	Teduglutide [Gly^2] GLP-2 350 and 750 ng s.c.	Increase in total body weight, colon length, crypt depth and integrity of the colon, reduction in IL-1 β expression	Drucker et al. 1999
DSS-induced mouse model of colitis	Teduglutide [Gly^2] GLP-2 40 μg/kg s.c	Increase in overall survival, intestinal weight, number of proliferating cells in colonic crypts, decrease in body weight loss and colonic damage	L'Heureux 2003
HLA-B27 rat model of colitis	Teduglutide [Gly^2] GLP-2 50 μg/kg/day i.v	Decrease in histological lesions in small and large intestine, decrease in expression of IFN-γ and TNF-α	Alavi et al. 2000
HLA-B27 rat model of colitis	Teduglutide [Gly^2] GLP-2 50 μg/kg/day i.v or intraluminal pomp	Improvements of stool consistency and histological inflammation scores	Arthur et al. 2004
TNF- α/actinomycin D-induced mouse model of intestinal injury	Teduglutide [Gly^2] GLP-2 200 μg/kg s.c.	Induction of epithelial cell proliferation, inhibition of apoptosis, prevention of intestinal damage and oxidative stress	Arda-Pirincci and Bolkent 2011
TNBS- and DSS-induced mouse model of colitis	GLP-2 (1–33) 50 μg/kg/bid s.c	Increase in crypt depth, villus height, Significant reduction of proinflammatory markers such as IL-1β, INF-γ and TNF-α	Sigalet et al. 2007
IL-10 knockout (IL-$10^{-/-}$) mouse model of colitis	GLP-2 (1–33) 50 μg/kg twice daily s.c	Increase in IGF-1 production, Decrease in animal weight loss, MPO levels, crypt proliferation crypt cell apoptosis, proinflammatory cytokines, CD4 (+) T cell population	Ivory et al. 2008
Indomethacin-induced rat model of enteritis	GLP2-2G-XTEN 25 and 75 nmol/kg s.c.	Increase in small intestine weight and length, reduction in inflammatory scores and proinflammatory cytokines levels	Alters et al. 2012
DSS-induced mouse model of colitis	GLP-2 analog peptide 10 7.5 nmol/kg s.c. twice daily	Increase in small intestine weight and length, Reduction in inflammatory cytokine levels	Yang et al. 2018
DSS-induced rat model of colitis	PEGylated GLP-2 12.5, 25 and 100 nmol/kg i.p.	Reduction of colon damage scores, proinflammatory cytokine expression and increase in body weight	Qi et al. 2017
DSS-induced model of colitis in DPP-IV deficient mouse	–	Lack of DPP-IV resulted in increase of myeloperoxidase activity and expression of NF-κB p65 subunit	Detel et al. 2016
TNBS-induced mouse model of colitis DSS-induced mouse model of colitis	DPP-IV inhibitor - EMDB-1 1 mg/kg i.c.	Increase in total body weight, colon length and weight, Reduction of colon damage scores, myeloperoxidase activity, bowel thickness, IL-1β and TNF-α expression	Salaga et al. 2017
TNBS-induced mouse model of colitis DSS-induced mice model of colitis	DPP-IV inhibitor - Tyr-Pro-D-Ala-NH_2 1 and 3 mg/kg i.c.	Reduction of macroscopic and microscopic colon damage scores, inflammatory cytokines and myeloperoxidase activity	Salaga et al. 2018
DSS-induced mouse model of colitis	DPP-IV inhibitor - ER-319711 100 mg/kg p.o.	Amelioration of disease activity index and colon length and increase in crypt height	Ban et al. 2011

DPP-IV, dipeptidyl peptidase IV; *DSS*, dextran sulfate sodium; *GLP*, glucagone-like peptide; *i.c.*, intracolonic; *i.p.*, intraperitoneal; *IGF*, insulin growth factor; *INF-γ*, interferon γ; *LPS*, lipopolysaccharide; *MPO*, myeloperoxidase; *p.o.*, per os; *s.c.*, subcutaneous; *TNBS, 2,3,6*, -Trinitrobenzenesulfonic acid; *TNFα*, tumor necrosis factor α

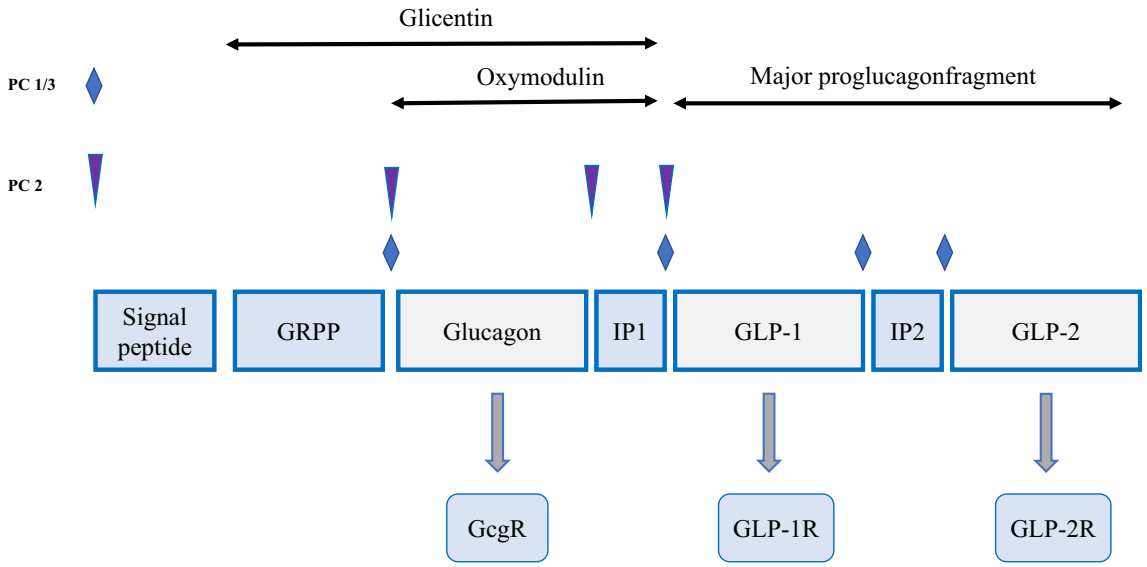

Fig. 1 Production of GLPs in humans from *gcg* gene. IP1, inverting peptide 1; IP2, inverting peptide 2; GcgR, glucagon receptor; GLP-1, glucagon-like peptide 1; GLP-2. glucagon-like peptide 2; GLP-1R. glucagon-like peptide 1 receptor; GLP-2R, glucagon-like peptide 2 receptor; GRPP. glicentin-related pancreatic polypeptide, PC 1/3, prohormone convertase 1/3

demonstrated that dietary fiber and short-chain fatty acids (SCFA), carbohydrates, and fats are potent stimulators of GLP-2 secretion. The GLP-2 (3–33), a biologically inactive form of GLP-2, which is a product of degradation of N-terminus of GLP-2 (1–33) by DPP-IV, may act as a weak partial agonist of the GLP-2 receptor in a negative feedback mechanism.

GLP-2 acts through a G protein-coupled receptor GLP-2R. Current research shows that stimulation through GLP-2/GLP-2R signaling involves activation of adenylyl cyclase, increased cAMP and PKA accumulation, and eventually ELK-1/c-fos/c-jun gene activation. Moreover, data show that MAP, EGFR/TyrK pathways are involved (Martin et al. 2006). It is also known as a GI growth factor: it increases intestinal blood flow (Mayo et al. 2017), increases absorption (Feng et al. 2017), proliferation, decreases apoptosis (Li et al. 2016) and reduces intestinal permeability (Zhang et al. 2018), and suppresses gastric secretion and motility. Recent data demonstrated that exogenous administration of GLP-2 correlates with increase in total gut weight, length, villus height, crypt depth, and crypt cell proliferation (Gu et al. 2018). GLP-2 and its analogs showed to be efficient in the treatment of short bowel syndrome in children and adults as demonstrated by increase in nutrient absorption, reduction in parenteral nutrition requirements, and improved Z scores in pediatric population (Sigalet 2018).

DPP-IV, a major enzyme responsible for GLPs degradation

DPP-IV is a type II integral transmembrane glycoprotein. In plasma, a soluble form of DPP-IV with preserved catalytic activity can be detected (Zhong et al. 2013, 2015). Although the exact mechanism of DPP-IV expression regulation remains poorly understood, TNF-α has been implicated as one of the regulators (Duan et al. 2017). As primary substrates for DPP-IV are GLP-1, GLP-2, and gastro-insulinotropic peptide (GIP), DPP-IV gene-deficient mice show improved postprandial glucose control and are resistant to progression of obesity and hyperinsulinemia (Drucker 2002; Gupta et al. 2017). Inhibition of DPP-IV activity in wild-type mice by pharmacological agents results in improvement in glucose tolerance, whereas this effect has not been observed in DPP-IV knockout mice (Marguet et al. 2000). Besides GLPs, DPP-IV is able to cleave some chemokines and cytokines such as IL-3, and granulocyte-macrophage colony-stimulating factor (GM-CSF), thereby regulating the immune responses (Kameoka et al. 1993; Broxmeyer et al. 2012). DPP-IV also exhibits non-catalytic actions through interaction with caveolin-1, fibronectin, and adenosine deaminase. Interaction of DPP-IV with the latter may result in the promotion of T cell activation (Kameoka et al. 1993; Broxmeyer et al. 2012). A recent study performed by Higashijima et al. demonstrated that DPP-IV inhibitors alter immune cell recruitment and reduce macrophage infiltration probably through GLP-1-dependent signaling in a rat model of nephritis (Higashijima et al. 2015).

DPP-IV is also responsible for the regulation of macrophage/dendric cell-mediated adipose tissue inflammation (Zhong et al. 2013). In addition, in non-obese diabetic mice, DPP-IV inhibitors significantly increase Treg expansion and TGF-β level. DPP-IV activity is significantly increased in obese subjects and in animal models of obesity (Yang et al. 2007; Lee et al. 2013).

Furthermore, DPP-IV inhibition prevented inflammation and mediated neuroprotective effect in two major complications of

diabetes mellitus, namely ischemic stroke and retina damage. This effect was attributed to antioxidant properties of DPP-IV, suppression of NF-κB, IL-6, TNF-α, and elevation of IL-10 (Gonçalves et al. 2014; El-Sahar et al. 2015).

Role of GLP-1 in inflammatory regulation in IBD

To date, researchers focused mainly on the anti-diabetic and anti-atherosclerotic effects of GLP-1 agonists, while the GI effects remained poorly understood. Nevertheless, a study by Jensen et al. (2018) showed that patients after colectomy exhibit increased risk of type 2 diabetes when compared with non-colectomy patients (HR 1.40; 95% confidence interval Cl 1.21 to 1.62). In another study, Palnaes et al. showed that release of GLP-1 in response to the intake of glucose is slower in UC patients who underwent colectomy (Palnaes Hansen et al. 1997). Moreover, postprandial GLP-1 response was also impaired in patients with ileostomy (Robertson et al. 1999). These data reveal the connection between GLP-1 and the colon; however, it is still not known whether inflammation also affects the GLP-1 release in IBD. Interestingly, subsequent studies showed that GLP-1R mRNA was reduced in samples obtained from inflamed area of the colon in IBD patients (Bang-Berthelsen et al. 2016). In contrast, GLP-1 was upregulated in IBD patients' serum, when compared with controls (Keller et al. 2009, 2015). These data clearly show that GLP-1 expression may be associated with inflammation in IBD.

To explore how GLP-1 is implicated in IBD studies were performed in experimental animal models of colitis. Yusta et al. demonstrated that GLP-1R knockout mice exhibited dysregulated intestinal gene expression such as IL-1β IL-6, IL-12 β, and trefoil factors 1 and 2. Moreover, GLP-1R knockout mice exhibited abnormal representation of microbial species in feces as well as enhanced sensitivity to intestinal injury after DSS administration in comparison to wild-type mice. Moreover, the authors showed that bone marrow transplant using wild-type mice donors normalized expression of multiple genes regulating immune function and epithelial integrity. Moreover, administration of Exendin-4, a GLP-1 agonist, resulted in induction of expression of genes encoding multiple cytokines and chemokines responsible for immune response (Yusta et al. 2015). In T cell adoptive transfer-induced colitis, the GLP-1 expression in colonic tissue was significantly lower in mice with colitis when compared with control mice (Schmidt et al. 2000). Moreover, increased level of GLP-1 was detected in mice with colitis after DPP-IV inhibitor treatment when compared with untreated mice (Yazbeck et al. 2010b). In a study performed by Bang-Berthelsen et al. (2016), treatment with GLP-1 analog liraglutide significantly improved histological scores, colon weight/length ratio, and reduced inflammatory cytokines and chemokines such as CCL20, IL-33, and IL-22. Treatment with GLP-1 coated with sterically stabilized phospholipid micelles (GLP-1-SSM) for 7 consecutive days in a dose 15 nmol/day markedly alleviated the development of DSS-induced colitis in mice by significantly improving epithelial architecture and reducing the expression of proinflammatory cytokines such as IL-1β (Anbazhagan et al. 2017). Lebrun et al. evaluated the role of GLP-1 in mucosal integrity and inflammation. They demonstrated that plasma GLP-1 level is increased by lipopolysaccharide (LPS) administration in mice, in DSS-induced and ischemia/reperfusion-induced colitis model, through toll-like receptor 4-dependent mechanism. Importantly, the authors showed that GLP-1 may be considered a sensor of local inflammation and barrier integrity (Lebrun et al. 2017).

Role of GLP-2 in inflammatory regulation in IBD

Administration of teduglutide, a GLP-2 analog to mice with DSS-induced colitis, resulted in a significantly greater small bowel and colon weight and length compared with untreated mice. Moreover, mice treated with teduglutide had improvements in histological morphology and crypt cell proliferation (Drucker et al. 1999). In addition, teduglutide was as effective as sulfasalazine and corticosteroids (L'Heureux 2003). In the HLA-B27 rat model of colitis, administration of teduglutide at the dose of 50 μg/kg/day decreased histological lesions in small and large intestine, decreased expression of the inflammatory cytokines, such as IFN-γ and TNF-α, and improved stool consistency in comparison with control group (Alavi et al. 2000; Arthur et al. 2004). In another study performed by Sigalet et al., therapeutic effect of GLP-2 administration in TNBS- and DSS-induced mouse model of colitis was investigated. GLP-2 injection resulted in increase in crypt depth and villus height as well as significant reduction of proinflammatory markers such as IL-1β, IFN-γ, and TNF-α (Sigalet et al. 2007). In the IL-10 knockout mouse model of colitis, administration of GLP-2 in dose 50 μg/kg s.c. for 5 consecutive days resulted in a significant amelioration of animal weight loss, reduction of histopathological inflammation score, and myeloperoxidase levels compared with control mice. In addition, GLP-2 treatment reduced crypt proliferation and apoptosis, decreased proinflammatory cytokines (IL-1β, IFN-γ, and TNF-α) levels, and increased the level of IL-4. Moreover, GLP-2 injection reduced CD4(+) T cell population. Researchers suggested that the anti-inflammatory effects of GLP-2 are IL-10-independent and that GLP-2 alters the mucosal response to inflammation through a decrease of lamina propria macrophage TNF-α as well as an increase in insulin-like growth factor 1 (IGF-1) production (Ivory et al. 2008). In another study, Arda-Pirincci et al. demonstrated that teduglutide has a protective, antiapoptotic, proliferative, and

antioxidant effects in TNF- α/actinomycin D-induced intestinal injury (Arda-Pirincci and Bolkent 2011).

Considering short half-life of native GLP-2 in human circulation and promising results of teduglutide, which half-life is modestly extended to 3–5 h, current research focuses on an increase of the time of GLP-2 action by developing new, more stable, GLP-2 analogs. Yang et al. (2018) investigated a GLP-2 analog, *peptide-10*, with 10 times longer life. *Peptide-10* exhibited improved efficiency and better intestinotrophic effects in comparison with teduglutide in DSS-induced mouse model of colitis (Yang et al. 2018). Alters et al. reported that GLP-2 analog GLP-2G genetically fused to protein polymers called XTEN has a greatly improved half-life (240 h) and lower dose requirements in a rat model of indomethacin-induced inflammation. According to presented data, one injection of GLP-2-2G-XTEN in a dose of 75 nmol/kg is as effective as 10 injections of GLP-2G in a dose of 12.5 nmol/kg. Administration of GLP-2-2G-XTEN resulted in a significant increase in small intestine weight and length as well as reduced inflammation scores and proinflammatory cytokines (Alters et al. 2012). In another study, Qi et al. investigated the effect of polyethylene glycosylated (PEGylted) porcine GLP-2, with a half-life 16-fold longer than native GLP-2, in the DSS-induced rat model of colitis. PEG-GLP-2 reduced colon damage scores, and increased body weight and proinflammatory cytokines expression (Qi et al. 2017). Gu et al. designed degradation-resistant GLP-2 analog dimer, GLP-2②, which increased total gut weight, length, and villus height as well as crypt depth and crypt cell proliferation in DSS-induced mouse model of colitis (Gu et al. 2018). Moreover, administration of GLP-2② in a radiation-induced mouse model of intestine injury protected against radiation-induced GI toxicity and resulted in down-regulation of inflammatory responses, decrease in structural damage of the intestine, and apoptosis of intestinal cells (Gu et al. 2017).

Xiao et al. reported that UC and CD patients with active disease have elevated levels of bioactive GLP-2 compared with healthy subjects (Xiao et al. 2000). In contrast, a study performed by Schmidt et al. demonstrated no difference in either plasma or tissue concentrations of meal stimulated GLP-2 between patients with IBD and non-IBD controls (Schmidt et al. 2005). Teduglutide in three different doses, 0.05, 0.1, and 0.2 mg/kg daily, has been investigated in a prospective placebo-controlled study in 100 human subjects for the treatment of moderate to severe CD in an 8-week trial. It was demonstrated that remission was induced in over 55% of study participants at the highest dose, compared with only 33% of those receiving placebo after 8 weeks, although study failed to reach statistical significance over placebo (Buchman et al. 2010). To our knowledge, no other clinical trials with IBD patients were performed.

Inhibition of DPP-IV as a potential therapeutic strategy in IBD

The involvement of DPP-IV in the pathogenesis of IBD might be dependent on two major pathways: the catalytic and non-catalytic (Duan et al. 2017). It has been proposed that the protective effect of DPP-IV inhibition may be a result of increased levels of GLP-1 and GLP-2 (Yazbeck et al. 2010b; Ban et al. 2011). Detel et al. investigated the role of DPP-IV in the pathogenesis of colitis (Detel et al. 2016). In DPP-IV-deficient mice induction of colitis by DSS resulted in a stronger increase of myeloperoxidase activity and expression of NF-B p65 subunit in the colonic tissue compared with wild-type mice (Detel et al. 2016). Furthermore, in DPP-IV deficient mice, increase in the percentage of splenic CD+ cells and NKT cells as well as increase in macrophages was observed (Detel et al. 2016). Salaga et al. (2017) demonstrated that EMDB-1, a new peptide analog of endomorphin-2, with a potential to inhibit DPP-IV ameliorated colonic inflammation in both DSS- and TNBS-induced mouse model of colitis. Moreover, treatment with EMDB-1 extended half-life of GLP-2 (Salaga et al. 2017). In another study, Salaga et al. (2018) evaluated the series of novel EMDB-1 analogs and evaluated their inhibitory potential. Authors demonstrated that the novel peptide inhibitor of DPP-IV (Tyr-Pro-D-Ala-NH_2) blocks DPP-IV activity and attenuates acute, semi-chronic, and relapsing TNBS- and DSS-induced colitis in mice after topical administration (Salaga et al. 2018).

On the other hand, DPP-IV is responsible for the degradation of numerous signaling molecules such as endogenous opioid peptides including endorphins, dynorphins, and enkephalins which play crucial role in basic functions of the GI tract (e.g., motility, pain signaling, and secretion) (Sałaga et al. 2013). Thus, it cannot be excluded that in some IBD patients' disruption of GI tract homeostasis may be observed leading to development or exacerbation of IBD. Thus, there is an unmet need for research on the mechanism of DPP-IV inhibitors actions in the GI tract as well as long-term post-marketing surveillance of these drugs to assess their safety.

Concurrently, the results of a meta-analysis performed by Radel et al. (2019) who investigated the risk of developing IBD in patients on DPP-IV inhibitor therapy point out the need for further research. In this meta-analysis, which included 16 studies and 198,404 patients, the authors demonstrated—using primary random-effects analysis—that the DPP-IV inhibitor exposure resulted in a non-significant increase of IBD risk (RR = 1.52, 95% CI = 0.72–3.23). However, based on conservative random-effect analysis, DPP-IV inhibitors did not appear to increase the risk of developing IBD. This means that there is an urgent need to develop prospective studies unraveling the exact impact of DPP-IV administration on IBD. The main disadvantage of the cited meta-analysis is that all findings were driven by the inclusion of 1 large study

evaluating the effect of DPP-IV inhibitors on IBD risk in 141,170 individuals whereas other 15 studies accounted for 57,234 individuals (Abrahami et al. 2018; Radel et al. 2019). Of note, the effect of DPP-IV in conditions such as IBD is not well understood. On the contrary, studies in animal models of IBD suggest that the use of DPP-IV inhibitors decreases disease activity. On the other hand, IBD patients have lower serum DPP-IV concentrations in comparison with healthy subjects; however, DPP-IV expression on T cells from IBD patients is elevated. Furthermore, lower concentrations of DPP-IV are inversely associated with increased disease activity, although is not clear whether this is the cause or consequence of disease.

Future perspectives

Currently, there is not enough data from randomized placebo-controlled trials in patients with IBD to determine the efficiency of GLPs in this disease. Considering promising preclinical data (Table 1) and clinical pilot study results in the GLP-2 analog, teduglutide may have potential to become a new therapeutic option in IBD treatment, showing higher response and remission rates in comparison to placebo (Buchman et al. 2010). On the other hand, it is worrisome that up to 42% of patients who were treated with GLP-2 analog in induction phase discontinued the study (Buchman et al. 2010). Nevertheless, further studies are needed to determine the safety, tolerability, and clinical effectiveness of GLPs analogs in therapy. Moreover, new studies should be developed to assess the effect of GLP-2, as well as GLP-1 analogs and DPP-IV inhibitors on intestinal mucosal healing. Considering the fact that teduglutide targets barrier function of the gut and available IBD therapies target mainly immune and inflammatory pathways, new studies should focus on determination whether administration of teduglutide would allow to decrease a dose of corticosteroids or biologics in IBD patients (Blonski et al. 2013). Of note, development of new compounds with longer half-life and higher stability will decrease the number of injections and certainly improve patients' acceptance of treatment.

Conclusions

Apart from typical symptoms due to extensive intestinal inflammation, patients with IBD also suffer from malnutrition and metabolic disorders. Both GLP-1 and GLP-2 exert potential anti-inflammatory properties as well as improve glycemic control, nutrient absorption, and stimulate intestinal proliferation. Taking into consideration all currently available data, GLP-2 might be much more promising than GLP-1. Nevertheless, more studies emerge on the role of GLP-1 in

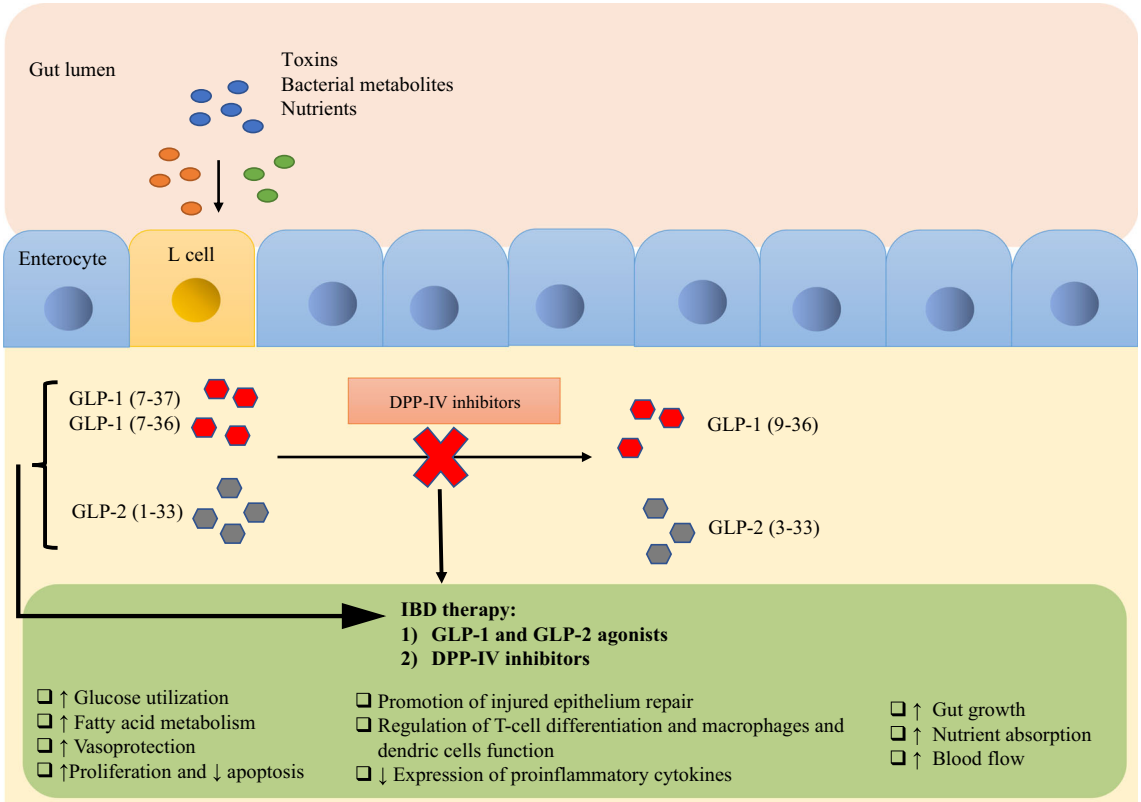

Fig. 2 GLPs as novel therapeutic options in IBD—potential mechanisms of action

mucosal integrity and modulation of inflammatory response and suggest that it may become an equally important tool in the IBD therapy. It may thus be suggested that targeting both GLPs will be the most beneficial treatment for IBD sufferers, especially in obese patients not only decreasing inflammation but also helping maintain proper weight. The potential mechanism of GLPs action in IBD may include promotion of tissue repair of injured epithelium, regulation of T cell differentiation and functions, regulation of innate immune cells such as macrophages and dendric cells, and reduction of proinflammatory cytokines (Fig. 2). Whereas corticosteroids and biologics affect immune system and may expose patients to adverse effects such as infections, GLPs do not act directly as immunosuppressants and may become first-line therapy in the treatment of IBD. Nevertheless, future clinical randomized trial is warranted to determine the effectiveness of currently used therapies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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