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Glucagon-like peptide 2 in colon carcinogenesis: Possible target for anti-cancer therapy?

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ABSTRACT

The role of glucagon-like peptide 2 (GLP2) in colon tissue has been studied extensively, from the time it was discovered that GLP2 promotes intestinal growth. A large number of studies have shown potential applications for GLP2 in human therapy. However, recent data have suggested the notion that GLP2 plays a key role in colon carcinogenesis. Questions have been arisen regarding the pro-proliferative effects of GLP2 and whether they might promote intestinal healing or advance colon tumor growth. Here, we provide striking evidence to show that the physiological activities of GLP2 are closely related to cancer-related molecular pathways that have been shown to circumvent drug desensitization. We further explore the different pathways of GLP2-signaling to suggest suitable GLP2-based therapeutic strategies in colon cancer.

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1. Introduction

Over the last few decades, the American Cancer Society has estimated the numbers of new cancer cases and expected cancer-related deaths. In 2010 over 1.5 million new cases and 569,490 deaths from cancer were estimated (Jemal et al., 2010). Moreover, colon tumors have been highlighted as one of the major human malignancies worldwide (Konishi et al., 2010; Kannen et al., 2011b). A prospective study showed a 36% of mortality among men and women diagnosed with non-metastatic colorectal tumors during fifteen years of progression (Dehal et al., 2012).

Colon tumors develop through a progressive multi-stepped process that involves the accumulation of genetic and epigenetic mutations in tumor suppressor genes and oncogenes (Khare & Verma, 2012; Migheli & Migliore, 2012). Accordingly, proliferation has been shown to play a key role, either in maintaining colon tissue homeostasis (Burgess, 1998; Wong et al., 2002) or in driving tumor development (Burgess, 1998; Sasaki et al., 2000; Bossenmeyer-Pourie et al., 2002; Wong et al., 2002; Bartkova et al., 2005; Firestein et al., 2008, 2009);

Abbreviations: (5-FU), 5-Fluorouracil; Akt, protein kinase B; APC, adenomatous polyposis coli; CAFs, carcinoma-associated fibroblasts; CDK, cyclin-dependent kinase; DPP-IV, dipeptidyl peptidase IV; GLP1, glucagon-like peptides 1; GLP2, glucagon-like peptide 2; GLP2r, glucagon-like peptides 2 receptor; GSK-3, glycogen synthase kinase 3; IGF-1, insulin-like growth factor 1; IGF-1r, insulin-like growth factor 1 receptor; ISEMFs, intestinal subepithelial fibroblasts; GSK-3β, glycogen synthase kinase 3 β; PC 1/3, prohormone convertase 1/3; PI3K, phosphatidylinositol 3 kinase; TCF–LEF, transcription factor–lymphoid enhancer factor-1; TGF-β, transforming growth factor β.

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in addition, proliferation can drive the effects of chemotherapy in colon cancer patients (Kannen et al., 2011a, 2011b; Chibaudel et al., 2012). Indeed, stimulating tumoral proliferation with growth factors has been proposed to re-sensitize tumors to chemotherapy effects (Chibaudel et al., 2012; Hurwitz et al., 2012; Kyle et al., 2012). Alternative therapies have shown promising effects against advanced colorectal cancer. In particular, therapies that are targeting critical molecular pathways in tumor growth have been shown to delay tumor progression with fewer side effects than chemotherapy (Ko et al., 2007; Chibaudel et al., 2012).

Glucagon-like peptide 2 (GLP2) is a nutrient-responsive neuropeptide and intestinal hormone that promotes growth, which enhances cell survival and proliferation (Rowland et al., 2011; Shi et al., 2011). This intestinal hormone has great therapeutic potential in conditions of compromised intestinal capacity, like surgical resections and ulcerative colitis (L'Heureux & Brubaker, 2003; Rowland & Brubaker, 2011). However, GLP2 has also been shown to stimulate the development of colon tumors (Thulesen et al., 2004).

This review will focus on understanding the role of GLP-2 in colon cancer, and examine the evidence on whether GLP-2 activity might be a suitable target in colon cancer therapy.

2. Colon cancer

2.1. Multistep sequence

Foulds first proposed that tumors arise from a multi-stepped sequence of changes (Foulds, 1958). In 1990, Fearon and Volgestein suggested that colon tumors develop through a sequence of mutations, known as the adenoma–carcinoma model. It is thus thought that tumors develop in three different stages: initiation, promotion and progression (Fearon & Vogelstein, 1990). Initiation is a rapid stage in carcinogenesis, because mutations in one or two gatekeeper genes are sufficient to abrogate tissue homeostasis and disrupt regular cell turnover (Luebeck & Hazelton, 2002; Meza et al., 2008). During the promotion and progression stages, mutations in molecular signaling cascades are enhanced; this condition allows the expansion of malignant cell clones, tumor growth, invasion, and metastasis (Waldner & Neurath, 2010). One of the most well known and understood mutations is related to the adenomatous polyposis coli (APC) gene, which is a key point in colon carcinogenesis. APC mutations increase proliferation by causing hyperactivation of β-catenin transcriptional activity and blocking p53 activity (Burgess, 1998; Wong et al., 1999, 2002; Hinoi et al., 2007). Initiated cells automatically undergo clonal outgrowth after stimulation with growth factors (Luebeck & Hazelton, 2002); thus, high proliferation was also observed in hyperplastic polyps and colorectal adenomas (Wong et al., 2002). This suggested that hyper-proliferation is a unifying mechanism that drives and fixes mutations in colon epithelia (Wong et al., 2002; Waldner et al., 2010).

2.2. Growth factors in colon cancer

The pivotal role of proliferation in colon carcinogenesis (Burgess, 1998; Sasaki et al., 2000; Bossenmeyer-Pourie et al., 2002; Wong et al., 2002; Bartkova et al., 2005; Firestein et al., 2008, 2009) suggests that growth factors are responsible for survival-related proliferation in tumors. Survival-related proliferation assures the conveyance, establishment, and spread of mutations and epigenetic changes in the initiated tissue (Wong et al., 1999, 2002; Massague, 2004; Humphries & Wright, 2008; Timp et al., 2009; Waldner et al., 2010). Although growth factors are not mutagenic alone, they are able to support genetic mutations in DNA-sequences, and thus, promote tumor development (Slaga, 1983; Timp et al., 2009; Migheli & Migliore, 2012). Indeed growth factors can provide mutated cells with self-sufficient growth signaling, insensitivity to anti-growth signals, apoptosis evasion, and infinite replicative potential (Timp et al., 2009; Graham et al., 2010; Khare & Verma, 2012; Migheli & Migliore, 2012).

3. Glucagon-like peptide 2

3.1. Glucagon superfamily and glucagon-like peptide 2

The glucagon superfamily of peptide hormones includes a wide range of peptide hormones from proglucagon (a glicentin-specific peptide of 160 amino acids) to GLP2 (33 amino acids). These peptide hormones are expressed in the central and peripheral nervous system, pancreas, and intestines (Drucker et al., 1996; Kieffer & Habener, 1999; Dube & Brubaker, 2007; Dube et al., 2008; Drozdowski & Thomson, 2009; Velazquez et al., 2009). Although they exhibit 21 to 48% homology in amino acid sequences, none of the proglucagon-derived peptide hormones have the same biological activity. Briefly, glucagon increases glucose serum levels during fasting; glucagon-like peptide 1 (GLP1) stimulates insulin release which decreases glucose serum levels during feeding and re-feeding; and, GLP-2 enhances cellular proliferation (Kieffer & Habener, 1999; Rowland & Brubaker, 2008; Velazquez et al., 2009).

3.2. Cells that express glucagon-like peptide 2 and factors that regulate its expression

To understand GLP2 synthesis and expression, it must be recognized that in different cell types proglucagon undergoes alternative posttranslational processing, by tissue-specific processing enzymes (Kieffer & Habener, 1999). This clarifies how pancreatic α-cells are able to express GLP2, but predominantly produce glucagon, due to the expression of the prohormone convertase 2 (PC2). Moreover, prohormone convertase 1 and 3 (PC 1/3), which cleaves proglucagon to produce GLP2, is expressed mainly in intestinal L cells (Kieffer & Habener, 1999), although brainstem and hypothalamus produce GLPs that closely resemble those produced by L cells (Kieffer & Habener, 1999; Dube et al., 2008; Rowland & Brubaker, 2008).

3.3. Glucagon-like peptide 2 receptor and downstream signaling cascades

The GLP2 receptor (GLP2r) is a G-protein coupled receptor with 7 transmembrane domains. GLP2r is widely expressed in the hypothalamus, brainstem, lung, stomach, duodenum, jejunum, ileum, and colon (Munroe et al., 1999; Yusta et al., 2000). GLP2r has a single encoding gene at chromosome 17p13.3, and it is the main target of GLP2 in the gastrointestinal tract (Munroe et al., 1999).

Ørskov et al. proposed that GLP2 might stimulate GLP2r in intestinal subepithelial fibroblasts (ISEMFs); this stimulation causes the release of growth factors that enhance colonic epithelial proliferation (Orskov et al., 2005). Dubé et al. reported that GLP2r specifically stimulated the insulin-like growth factor 1 (IGF-1) expression through a β-catenin dependent signaling mechanism in ISEMFs (Dube et al., 2006; Dube & Brubaker, 2007). It was further shown that GLP2r recruited the phosphatidylinositol 3 kinase (PI3K)/protein kinase B (Akt)-related signaling pathway to increase IGF-1 release from ISEMFs (Leen et al., 2011).

4. Physiological activity of glucagon-like peptide 2 in colon tissue

4.1. Glucagon-like peptide 2: from synthesis to degradation

GLP2 is released from intestinal L cells. Tissue-specific posttranslational processing causes the cleavage of GLP1 and GLP2 from the 160 amino acid peptide proglucagon (Fig. 1). GLP2 is cleaved by PC 1/3 at Arg77, a single basic residue on the C-terminus of glucagon (Holst et al., 1987; Holst, 1997; Kieffer & Habener, 1999; Hartmann et al., 2000; Ellingsgaard et al., 2011). It was further shown that after release,