The role of Reg IV in colorectal cancer, as a potential therapeutic target

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Introduction

Colorectal cancer is the third most commonly diagnosed cancer in males and the second in females, with over 1.2 million new cancer cases and 608,700 deaths estimated to have occurred in 2008 [1]. Despite improvements in cancer diagnosis and therapy, many patients are still diagnosed at the late stages of the disease, and the disease often recurs even after curative surgery. Multiple genetic alterations lead to carcinogenesis. Research on the candidate differentially expressed genes may help us to find biological markers for the evaluation of cancer diagnosis and offer novel molecular targets for anticancer therapy.

Over the past three decades, considerable attention has focused on the Reg (regenerating) gene family, which belongs to the calcium-dependent lectin superfamily, encoding a group of small multifunctional secretory proteins [2]. Reg family proteins are primarily involved in cell proliferation and differentiation, inflammation, diabetes, and carcinogenesis [3]. Regenerating islet-derived family member 4 (Reg IV), the most recently discovered member of the Reg gene family, is thought to be a candidate gene for cancer-specific expression [4]. In this review, we summarize current understanding of Reg IV, and discuss the relevance of Reg IV as a potential therapeutic target in the treatment of colorectal cancer.

Expression and function of Reg IV in gastrointestinal tract tumors

Reg IV is expressed in a large variety of normal tissues in humans, such as stomach, small intestine, colon and pancreas [2, 5]. The expression of Reg IV is abundantly enhanced in colorectal adenocarcinoma and adenoma [6, 7], and gastric cancer [5, 8], whereas Reg IV expression is not detected in lung or breast cancers [5]. Therefore, Reg IV may be a good marker for gastrointestinal tumors. Previous studies have suggested that Reg IV may take part in early carcinogenesis in certain cancers. Many colorectal cancers develop through the ‘adenoma to carcinoma sequence’ model [9], in which adenomas are recognized as precursor lesions of the vast majority of colorectal cancers. Zhang et al. found that Reg IV was expressed in both colorectal adenoma and adenocarcinoma [7]. This result constituted further evidence that overexpression of Reg IV may be an early event in the colorectal adenoma-carcinoma sequence and carcinogenesis, and its detection may be useful in the early diagnosis of colorectal adenoma formation [10].

Whether Reg IV is associated with tumor clinicopathological features is unknown yet. Violette et al. reported that there was no significant relationship between Reg IV and the TNM state of the tumors or their localization [6]. But Yamagishi et al. suggested that Reg IV staining was observed more fre-
Reg IV as a therapeutic target in colorectal cancer

It is reported that advanced colorectal adenocarcinoma is generally poorly responsive to chemotherapy and radiation [26, 27], and patients with Reg IV positive gastric cancer tend to show a poor outcome [28]. As demonstrated in other systems [13, 29], there are diverse mechanisms of resistance to drug toxicity. 5-fluorouracil (5-FU) is one of the most widely used chemotherapeutic agents for breast cancer, colorectal cancer, and gastric cancer [30]. Unfortunately, some patients show a poor response. High Reg IV expression is thought to be associated with 5-FU resistance in colon cancer cell lines [6].

Possible mechanisms of Reg IV inhibition of apoptosis

It has been reported that recombinant Reg IV increases expression of Bcl-2 [14], B-cell lymphoma-2 is an antiapoptotic protein located on mitochondria and is expressed at high levels in some tumor cells and tissues [24, 31]. In the mitochondrial pathway, antiapoptotic Bcl-2 family proteins prevent mitochondrial membrane permeabilization and thereby inhibit changes in the mitochondrial membrane potential and cytochrome c release [31]. Mitani et al. suggested that overexpression of Reg IV may suppress 5-FU-induced apoptosis by inhibiting the mitochondrial apoptotic pathway [8].

It has been reported that AP-1 induces expression of dihydropyrimidine dehydrogenase (DPD) [32], which is an initial and rate-limiting enzyme in 5-FU catabolism, and has significance for the pharmacokinetics and toxicity of 5-FU. Overexpression of DPD in tumor cell lines is associated with resistance to 5-FU [33]. Degradation of 5-FU by induction of DPD expression may also inhibit 5-FU-induced apoptosis. Also, Mitani et al. confirmed that Reg IV inhibits apoptosis by activating the EGFR/Akt/AP-1/DPD signaling pathway, inhibiting 5-FU.

In conclusion, Reg IV can confer resistance to 5-FU-induced apoptosis in colorectal cancer and gastric cancer. At least two mechanisms are involved in inhibition of apoptosis by Reg IV, including Bcl-2 and DPD. Bishnupuri et al. reported that Reg IV is a potent activator of the EGFR/Akt/AP-1 signaling pathway in human colon cancer cell lines [14]. Interestingly, Nanakin et al. found that EGF and TGF-α enhanced Reg IV gene expression by the extracellular signal-regulated kinase (ERK) signaling pathway in the SW403 cells line [22], and high phospho-ERK expression is associated with a lower survival rate of colorectal cancer [34]. These studies suggest that a positive expression feedback loop between EGF and Reg IV exists in the signaling pathways. So disruption of Reg IV/EGFR signaling may have utility as a novel therapeutic intervention for human gastrointestinal cancer.

The proteoglycan ‘P1’ disrupts the Reg IV/EGFR/Akt/AP-1 signaling pathway

Li et al. suggested that a proteoglycan named ‘P1’ which is from Phellinus linteus (PL) could disrupt the Reg IV/EGFR/Akt/AP-1 signaling pathway [35]. They found that
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The treatment of colonic adenocarcinoma cells with P1 resulted in significant dose-dependent inhibition in cell numbers and cell mitosis. P1 had the capacity to downregulate the expression of Reg IV and EGFR. Therefore, the proteoglycan P1 was considered to block the EGFR signaling pathway and induce Reg IV downregulation. Also, a study in vivo confirmed this hypothesis. P1 has a direct antitumor effect through inducing apoptosis and inhibiting the karyokinesis of HT-29 cells. The results are consistent with the previous report by Li et al. [36]. Therefore we expect that it will be possible to use P1 as an adjuvant chemotherapeutic and chemopreventive agent. Numerous proteins in the Reg IV/EGFR/Akt/AP-1 signaling pathway are potential therapeutic targets for colorectal cancer treatment awaiting discovery.

Conclusions and future perspective

This review focuses on the expression and roles of Reg IV in gastrointestinal tract cancers. Reg IV is generally upregulated in gastrointestinal tract cancers. Available evidence suggests that Reg IV seems to have functions, including promoting tissue regeneration, proliferation, and resistance to apoptosis, resulting in relatively worse clinicopathological features, or worse survival in patients with high Reg IV expression than those without. Reg IV is expressed in colorectal adenoma and intestinal metaplasia of the stomach, and is considered to be a good potential marker for gastrointestinal tumors. Reg IV activates the EGFR/Akt/AP-1 signaling pathway in colon cancer cells, increases cell proliferation, angiogenesis, and metastasis, and reduces apoptosis. Reducing endogenous Reg IV expression or blocking downstream signaling may be a feasible therapeutic strategy. Further investigations are still needed to confirm these observations and find more anti-cancer agents targeting the Reg IV/EGFR/Akt/AP-1 signaling pathway.

The authors declare no conflict of interest.

References


Fig. 1. Reg IV activates the EGFR/Akt/AP-1 signaling pathway. Regenerating islet-derived type IV (Reg IV) could activate the epidermal growth factor receptor (EGFR) signaling pathway in colon cancer cells and increases expression of Bcl-xl and Bcl-2, resulting in cell proliferation and inhibition of apoptosis. B-cell lymphoma-2 prevents mitochondrial membrane permeabilization and leads to 5-FU resistance. Dihydropyrimidine dehydrogenase is an initial and rate-limiting enzyme in 5-FU catabolism, which can be induced by AP-1.


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