The Insulin-like Growth Factor System and Colorectal Cancer

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Insulin-like growth factors (IGFs) are peptides which exert mitogenic, endocrine and cytokine activities. Together with their receptors, binding proteins and associated molecules, they participate in numerous pathophysiological processes, including cancer development. Colorectal cancer (CRC) is a disease with high incidence and mortality rates worldwide, whose etiology usually represents a combination of the environmental and genetic factors. IGFs are most often increased in CRC, enabling excessive autocrine/paracrine stimulation of the cell growth. Overexpression or increased activation/accessibility of IGF receptors is a coinciding step which transmits IGF-related signals. A number of molecules and biochemical mechanisms exert modulatory effects shaping the final outcome of the IGF-stimulated processes, frequently leading to neoplastic transformation in the case of irreparable disbalance.

colorectal cancer signaling therapy

1. Introduction

Insulin-like growth factors (IGFs), mitogenic and metabolic peptides, are involved in the etiology and progression of the colorectal cancer (CRC). The association was confirmed at the level of cell lines, animal models and patients with CRC. Initial studies on the role of IGFs, their receptors (IGFRs), high-affinity binding proteins (IGFBPs), IGFBP proteases, highly related insulin and its receptor (IR) expanded to investigate connections with an array of physiological molecules and systems which together build a very complex network not yet fully defined and characterized. Current research includes IGFBP-related proteins (IGFBP-RP, also known as low-affinity IGFBPs), messenger RNA (mRNA), responsible genes, circular-, micro- and long non-coding RNAs (circRNA, miRNA and lncRNA), RNA-binding proteins, other protein and nucleic acid binding partners inside specific compartments of cells and membrane-bound, present in the extracellular matrix and in the circulation. There are many pathways of interference, with the effects primarily based on the activation of the IGF system.

IGFs are known to exert endocrine, paracrine and autocrine effects. Many cell types synthesize IGFs, IGFRs and IGFBPs. The response of cells to IGFs depends on various factors, many of them being specific for the particular microenvironment at a specific pathophysiological moment. Modulatory effects of different agents have been detected, positive and negative, both at the expression level and on the activity of individual components of the IGF system. Tight control mechanisms are necessary to maintain the equilibrium in the normal physiological state since

overexpression or excessive activation/accessibility of some components, together with a reduced activity of suppressor molecules, can lead to disbalance and neoplastic transformation.

2. Epidemiology of Colorectal Cancer

The world's cancer burden represents one of the biggest hurdles for human life improvement [1]. According to estimates made by the World Health Organization (WHO) in 2019 [2], cancer is the primary or secondary cause of death of people below the age of 70 in 112 out of 183 countries, and the third or fourth cause in 23 additional countries [3].

Colorectal cancer is highly ranked for its incidence and mortality—it is the third most frequently occurring malignancy, responsible for 10.0% of all cancer cases for both sexes, and it was the second most fatal cancer in 2018, with 9.4% of reported deaths [3]. More than 1.9 million new CRC cases occurred in 2020, resulting in 935,000 new deaths globally [3]. Complications, mortality, treatment side effects, health care service utilization and medical costs associated with CRC present a considerable burden worldwide. There are, however, significant geographical differences in CRC incidence and mortality. The age-standardized rate (ASR) of CRC incidence was found to be six times higher in high human development index (HDI) countries compared to low HDI countries, with a similar ratio found for ASR of mortality [4][5][6].

Categorization of CRC cases can be performed by age—patients less than 50 years old belong to an early-onset CRC category, whereas older patients belong to a late-onset CRC category. In the late-onset CRC, HDI and EAPC (estimated annual percentage change) are negatively correlated for both sexes, implying that present lower incidence in low HDI countries might worsen in the next 30 to 50 years, posing a more serious health issue [5].

Men are more prone to developing CRC than women. Even though there is no discernable difference in the early onset of colon cancer between sexes (IRR = 0.98; 95% CI 0.94, 1.07), the incidence of early-onset rectal cancer (IRR = 1.08; 95% CI 1.04, 1.12), late-onset colon cancer (IRR = 1.50; 95% CI 1.37, 1.62) and late-onset rectal cancer (IRR = 2.03; 95% CI 1.84, 2.21) is considerably higher in males [5].

Smaller scale (i.e., continent- or region-specific) studies confirmed the correlation between an increased CRC incidence and high HDI. Chung et al. [7] reported such findings for Asia, while Sierra et al. [8] corroborated the impact of HDI on CRC in Central and South America.

Worldwide CRC incidence and mortality have generally increased in the 21st century and will continue to rise in the future, as estimated by numerous global [4][5][9][10], continental [7][8][11][12], regional [13][14][15][16][17] and country-specific [18][19][20][21] studies. Such trends warrant new and more effective screening and prevention strategies to be developed from evidence-based research.

3. Pathophysiology of the Colorectal Cancer

The etiology of CRC is multifactorial and usually represents a combination of the environmental and genetic factors. The process of neoplastic transformation consists of a series of (epi)genetic alterations that lead to changes in normal mucosa of the colon, resulting in cancer, which has the potential to culminate in metastasis in distant tissues [22]. Colon modifications can be divided into discrete stages which tissue passes, as proposed by Fearon and Vogelstein. Each stage is characterized by specific shifts in the genetic make-up of the cell [23].

There are several mechanisms that lead to neoplastic changes in colonocytes. The most common is the chromosomal instability (CIN) pathway, which is characterized by the loss of heterozygosity and various chromosomal abnormalities [24]. One of the first changes that occurs in this mechanism is dysregulation in the WNT/APC/β-cat pathway, responsible for the expression of *APC* gene, a tumor suppressor, leading to an increased presence of β-catenin, which induces proliferation, differentiation, migration and adhesion of colorectal cells [25][26]. Other changes follow, accompanied by new mutations and progression from benign to malignant state. The process includes mutations in *KRAS* and *p53* genes and their binding partners [27][28][29][30][31]. Another cause of CRC, which roughly accounts for 15% of cases, is a derangement in the DNA mismatch repair system (MMR), which is in charge of the production of proteins that recognize and repair single nucleotide mismatches arising in the replication process [32][33]. The third mechanism leading to CRC is based on hypermethylation of CpG islands in promoter regions of genes involved in cell cycle regulation, apoptosis, adhesion and invasion [34][35][36].

Chronic inflammation plays a pivotal role in disease etiology. Various inflammatory markers, such as tumor necrosis factor-α (TNF-α), signal transducer and activator of transcription 3 (STAT3), interleukin-6 (IL-6) and C-reactive protein (CRP), are associated with pathogenesis of CRC. TNF-α promotes tumor growth, proliferation and metastasis. IL-6 stimulates the expression of STAT3, which is a transcription factor that induces the expression of various genes that play active roles in cell proliferation, differentiation and apoptosis, such as *Bcl-2*, *CyclinD1*, *ICAM-1* and *MMP2-9* [37][38][39]. Cyclooxygenase-2 (COX-2) is an inducible cyclooxygenase that is up-regulated by cytokines, growth factors and tumor promoters. It is overexpressed in 40% of human colorectal adenomas, compared to normal epithelial tissue [40]. COX-2 regulates prostaglandin (PG) synthesis, apoptosis, angiogenesis and tumor invasiveness, being a mediator between the inflammation and neoplastic transformation in CRC.

4. Therapeutic Potential of the Insulin-like Growth Factor Signaling Pathways in Treating Colorectal Cancer

As already said, neoplastic cell growth and proliferation is driven via PI3K, Akt, mTOR and MAPK pathways after IGF-I binding to IGF1R [41]. The primary strategy in treating colon cancer includes the arrest of IGF1R overexpression by small inhibitors, antibodies or the inhibition of its ligands. A discovery of OSI-906, later termed linsitinib, a drug with a promising inhibitory effect on two receptor kinases, IR and IGF1R, was reported in 2009 [42]. This dual inhibitor intervenes in the process of autophosphorylation, demonstrating an antiproliferative effect on different tumor cell lines, including colorectal. One possibility to treat metastatic CRC is to use regorafenib (multi-kinase inhibitor) together with linsitinib and aspirin (both being IGF1R inhibitors) [43]. Linsitinib and aspirin reduce the resistance of CRC cells to regorafenib, enabling body weight gain and an increase in the survival rate of model animals (i.e., male mice). Leiphrakpam et al. reported on the down-regulation of X-linked inhibitor of apoptosis

(XIAP) in CRC xenografted male mice driven by MK-0646 (mAb that blocks IGF1R and IGF2R, also known as dalotuzumab) and linsitinib [44].

An interplay of various factors keeps cancer cells alive. Hyperactivation of IGF1R, for example, results in the resistance to epidermal growth factor receptor (EGFR) inhibition in RAS wild-type metastatic CRC via up-regulation of PI3K/AKT pathway, implying that targeting both receptors might be a promising therapy for metastatic CRC. Unfortunately, a combination of cetuximab (mAb targeting EGFR) and MK-0646 or IMC-A12 (mAb that blocks IGF1R, also known as cixutumumab) did not lead to the expected results, as suggested by two studies both involving male and female participants [45][46]. A phase I trial employing a combination of cixutumumab (anti-IGF1R antibody) and selumetinib (MEK ½ inhibitor) obtained promising results offering the evidence of the health benefit and target inhibition in a cohort of 30 patients, including those with CRC [47]. A combination of ganitumab (IGF1R mAb) and conatumumab (a pro-apoptotic death receptor 5 agonist) also exerted promising effects in the Colo-205 xenograft model, but caused no response in approximately 80 tested individuals (both male and female), some of whom were patients with CRC [48].

MEDI-573 (mAb to IGF-I and IGF-II) application inhibited tumor growth in a CRC female mouse model that over-expresses IGF-II, and this effect was enhanced if MEDI-573 was combined with other known therapeutics such as trastuzumab, AZD2014, AZD5363, selumetinib or cetuximab [49]. AvFc lectibody, a combination of the human immunoglobulin G1 Fc and Avaren (high mannose glycan-binding lectin), selectively recognizes a range of cancer cell lines including colon cells [50]. Although the observed cytotoxic effects were thoroughly investigated only in the lung cancer cell lines, it was confirmed that targets of this lectibody are EGFR and IGF1R. Since aberrant glycosylation is a hallmark of cancer, and altered glycosylation of IGFRs in the colon tissue of CRC patients was reported [51], the lectibody treatment may be considered as a novel approach in cancer therapy.

IGF1R depletion/inhibition sensitizes CRC cells to radiotherapy (converting them to radiosensitive), as shown in HT-29 and SW480 cell lines where IGF1R was inhibited by NVP-ADW742 [52] and in HT-29, SW480 and DLD-1 cells pretreated with BMS-754807 [53]. The inhibitory effect of BMS-754807 on colon cancer cell growth was stronger compared to the effect of linsitinib, and the anti-neoplastic effect was mostly independent of IGF1R [54]. A prolonged treatment of colon cancer cells with BMS-754807 and GSK1838705A (inhibitors of IGF1R and IR) leads to cell survival, due to the activation of ribosomal protein S6 kinase 1 [55]. In GEO tumors, BI885578 administration (inhibitor of both IGF1R and IR) induces apoptosis and inhibition of cell proliferation in female mice [56]. Zhu et al. reported on an anti-proliferative, anti-migration, anti-invasion and inhibitory effect of isovitexin on EMT in human colon cancer cell lines and xenograft tumor model on female mice [57]. The levels of signaling molecules involved in the IGF1R signaling pathway were decreased after this treatment, pointing to the mechanism of the isovitexin action. Simvastatin down-regulates IGF1R expression and pro-apoptotic ERK activation in human HT-29 cells [58]. Phloroglucinol treatment inhibits or decreases the expression of various IGF1R downstream signaling molecules, such as RAS, MAPK, ERK, PI3K, Akt and mTOR, in HT-29 cells [59].

In addition to synthetic molecules and antibodies, numerous plant metabolites were investigated as potential therapeutics in the treatment of cancer. Curcumol, isolated from *Rhizoma Curcumae*, inhibited proliferation and

induced apoptosis in LoVo cells, and inhibited CRC in xenograft models of nude mice, via inhibition of IGF1R and activation of p38 MAPKs [60]. Application of manuka honey (alone or in combination with 5-fluorouracil) on HCT-116 cell line decreased physical parameters of colonospheres and the survival ability of cancer cells, but also induced apoptosis via down-regulation of apoptosis inhibitors, including IGFs and IGF1R [61]. The expression levels of IGF-I and IGF1R were reduced, whereas the level of IGFBP-3 was normalized after *Bifidiobacterium longum* BAA-999 (with or without lycopene) was administrated to CD-A male mice in an azoxymethane-dextrane sulfate sodium-induced CRC model [62]. Polypeptides from *Arca subcrenata* Lischke inhibited growth of HT-29 cells and suppressed tumor growth in male mouse xenograft by reducing IGF1R phosphorylation and inhibiting IGF-I/IGF1R signaling activation [63]. Carnosic acid treatment also suppressed the growth of HT-29 cells; decreased the number of tumors and circulating concentrations of leptin, adiponectin, insulin and IGF-I; and reduced the expression of IR in a male mice model [64]. Fucoidan, sulfated polysaccharide from brown algae, inhibited IGF1R signaling through the IRS-1/PI3K/Akt pathway in HT-29 cells [65]. Laminarin, another polysaccharide from brown algae, decreased phosphorylation of ERK and MAPK and, consequently, IGF1R-dependent proliferation in the same cells [66]. Curcumin decreased the expression of IR and IGF1R in 5-fluorouracil-treated SW480 cells, and this down-regulation correlated with decreased proliferation and migration of cells [67]. Luteolin, a fruit and vegetable flavone, decreased IGF-II production in HT-29 cells and down-regulated the activation of PI3K/Akt and ERK1/2 pathways [68]. Cinnamaldehyde, isolated from stem bark of *Cinnamomum cassia*, inhibited PI3K/Akt signaling in SW480, HCT116 and LoVo cells [69]. Considering the incidence and mortality rates of CRC, together with limitations of the existing therapeutic procedures, the search for both natural and synthetic anti-CRC agents is expected to intensify.

It is sometimes necessary to apply multiple approaches, i.e., a combination of different therapeutics and therapies. A serious limitation in examining therapeutic potentials of various substances can be found in translation from cell line models to xenografts and further to humans as the results are unsatisfactory or the cancer cells are nonresponsive to just one therapeutic. It must also be noted that the gender equality was neglected in most of the mentioned studies, as some of the experiments were performed only on male or female animals (rarely both). Furthermore, the number of studies on humans is still low, which is understandable due to the limited number of potentially effective therapeutics, their toxicity and effective dose, as well as ethical principles related to studies on humans.

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