The Association between Polymorphismsin Insulin and Obesity Related Genesand Risk of Colorectal Cancer

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Abstract

Colon cancer is the cancer of the large intestine (colon), which is located in the lower part of digestive system. Colon cancer is the third most common cancer in men and the second in women worldwide. Genetic background is thought to play a role in modulating individual risks of this cancer. Many studies support an association between insulin pathway gene polymorphisms and regulation of tumor cell biology in colorectal cancer. This review examines the role of polymorphisms of insulin and obesity pathway genes (IGFs, INS, INSR, ADIPOQ, ADIPOQR, LEP and LEPR) in development of colorectal cancer.

Keywords: Insulin; Obesity; Colorectal cancer

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Introduction

More than one million individuals develop Colorectal Cancer (CRC) each year worldwide, and the disease-specific mortality rate is nearly 33% in the developed countries [1]. CRC can be separated into two sites: colon cancer (72%), and rectum cancer (28%), although incidence of CRC is generally reported together. Classification of CRC is referred to their pathological stage, which can be observed after surgery. Because the clinical and pathological stages may be different, imaging tests of the observed stage is suggested after surgery [1]. About 95% of CRCs are sporadic (with no background of a family history of the disease); in such cases, mutated genes occur by chance. Familiar CRCs are less common (about 5%) and occur when gene mutations are passed within a family from one generation to the next. In these cases, mutated genes (germline mutation) are inherited. Inherited CRCs include: Hereditary Nonpolyposis Colorectal Cancer (HNPCC) or Lynch syndromes I and II, Familiar Adenomatous Polyposis (FAP), MYH Associated Polyposis (MAP), Peutz-Jeghers Syndrome (PJS), and Juvenile Polyposis Syndrome (JPS) [1, 2].

Factors that regulate and control cell growth are key points to the development of the cancer [1]. Proteins in insulin pathway play a significant role in the initiation of cell growth and proliferation of colorectal cancers [1]. Diet, lifestyle, physical activity, body size, and sex steroids, and genetic factors affect the regulation of insulin [1].

Inflammation, hormones and energy-related factors are critical elements associated with colon cancer [1]. A Single Nucleotide Polymorphism (SNP) is a source variance in a genome. A SNP ["snip"] is a single base variation in DNA. SNPs are the most common source of genetic polymorphism in the human genome [2].

SNP related functional proteomics involve the identification of functional SNPs that modify structure and function of protein active sites. SNP helps to discover new therapeutic targets [3]. Developing a source of the modifications generated by functional (coding) SNPs in disease related proteins will direct the mutations in the population for proper treatment [4]. Accumulation of genetic mutations can cause colorectal carcinogenesis. These mutations occur spontaneously throughout life [5]. Insulin has metabolic effect and promitotic and antiapoptotic activity that may be tumorigenic. Polymorphisms in genes which are involved in insulin pathway cause hyperinsulinemia; insulin resistance and hyperinsulinemia are prevalent in obese patients. Hyperinsulinemia has been hypothesized to play a role in the obesity-colorectal cancer relationship [6].Epidemiological studies have demonstrated that interactions between genetic and environmental factors may play important roles in the pathogenesis of cancer [7]. Individual genetic susceptibility [8] suggests that genetic background is one of the critical CRC risk factors [9, 10].

In this review, we integrate and assess studies from the literature relating to polymorphisms of

insulin pathway protein genes in the context of colorectal carcinoma.

Insulin like Growth Factors (IGFs)

Insulin, insulin-like growth factors, insulin-like growth factor receptors (IGF R of type 1 and type 2) and Insulin-like Growth Factor Binding Proteins (IGF-BP 1-6), play an important role in the normal control of growth related processes. They have mitogenic and distinct apoptotic effects. Also, they can act in endocrine (like a hormone), and in an autocrine/paracrine manner. IGF can act as mitogen, and may induce tumor growth [11]. Indeed, tumor cells could induce their own proliferation by the synthesis of endogenous IGF molecules. This process of autocrine stimulation causes faster tumor growth [12].Hormone induction and polymorphism in IGFs gene influence the expression level of IGFs [13]. Some studies have demonstrated a relationship between higher IGF1 levels, lower IGFBP3 levels, and an increased risk of colorectal cancer [14-16]. In addition to serum IGF and IGFBP levels, it is important to understand the frequency of a genetic polymorphism in a given population to assess its role in potential risk of a disorder. Data suggests high heterogeneous relationship between colorectal cancer and insulin like growth factor polymorphisms [17-20].In 2013, a meta-analysis suggested that IGFBP3 A-202C and Gly32Ala polymorphisms may not be associated with colorectal cancer development [21]. IGF family is involved in the regulation of somatic growth, cell proliferation, transformation, and apoptosis [22]. IGF-I, by binding to the IGF-I receptor, stimulates growth and metabolism and activates a protein tyrosine phosphorylation signal transduction cascade that is similar to the one involved in insulin action [23].

Growth Hormone (GH) binds to GH Receptor (GH-R) which leads to IGF-1 production. IGF-1 binds to IGF-R1, and causes enhanced growth cell proliferation, and also anti-apoptotic effects. Interactions of IGF-BPs with IGF-1 reduce the affinity of IGF-1 for IGF-R1 [24]. Connection of IGF-BPs with ECM decreases the affinity of IGFBPs for IGFs, and therefore increases the level of free IGFs [25]. IGFBPs control the level of IGF and its function which lead to change in IGF signaling [26]. IGFBPs by binding to IGF-I, generally inhibit its action and thereby reduce its bioavailability [27, 28].

Insulin and Insulin Receptor

In rats, insulin enhances the growth of aberrant crypt foci, CRC precursor lesions, and increases the number and size of the tumors [29]. Some studies have confirmed that insulin increases the neoplastic proliferation of cell lines and that the insulin receptor is commonly expressed in human neoplasms [30]. Several common genetic variants within the insulin signaling pathway that are associated with hyperinsulinemia and insulin resistance have been identified [31]. The relation between genetic variants that cause insulin resistance and colorectal cancer can predispose insulin resistance and also increase susceptibility to colorectal neoplasia [32, 33]. Population based studies have provided evidences that polymorphic variation of relevant genes can cause colorectal cancer risk by changing the circulating level of insulin and insulin like growth factors [28].

Observations are consistent with vivo experimental studies [29, 34] that demonstrate growth-promoting effects of exogenous insulin, and dietary-induced hyperinsulinemia [35]; they have shown that insulin increases the growth of colon epithelial and carcinoma cells in vitro [36].

It has been suggested that insulin may promote colorectal carcinogenesis directly by activating its own receptor, the receptors for IGF-I, or hybrid insulin/IGF-I receptors. These results indicate that insulin may play an important role in colorectal carcinogenesis [37]. The role of insulin in colorectal carcinogenesis is supported by recent experimental and observational studies [15, 38]. Elevated circulating levels of insulin may lead to changes in IGFBP concentrations through increasing IGF-I bioavailability; and this insulin mediation [39], via inducing pathophysiologic changes in concentrations of circulating IGF-I and IGFBPs, promotes colorectal carcinogenesis [40].

When insulin binds to its receptor, PI3K pathways can be activated and cause cell proliferation and survival. Polymorphism of insulin gene and its association with colorectal cancer were demonstrated by some studies [41].

Overexpression of the Insulin Receptor (IR) can induce cell transformation in vitro and human colorectal adenocarcinomas. The insulin receptor indicates sensitivity to the growth effects of insulin at high levels [42].

Adiponectin and Adiponectin Receptor

Studies show a relationship between adiponectin [ADIPOQ] and its receptors [ADIPORs] with obesity and insulin resistance. The association

of ADIPOQ and its receptor genes in the development of obesity and insulin resistance confirms the role of ADIPOQ and its receptor genes in colorectal carcinogenesis [43, 44]. Several studies have demonstrated the inverse association between serum ADIPOQ and colorectal cancer risk [45-47].

It was demonstrated that in vitro, ADIPOQ presented growth inhibition and apoptosis induction in colorectal cancer cell lines [48]. In vivo, mice with lack of ADIPOQ in serum showed more intestinal tumors [49]. Circulating ADIPOQ level showed a significant negative association with metabolic syndrome traits, whereas ADIPORs level had a positive association with metabolic syndrome traits [49]. Adiponectin can suppress the cell proliferation of colon cancer via AdipoR- and -R2-mediated AMPK activation [50]. ADIPOQ has the anticancer role through connection to its receptors, which have been demonstrated to repress colon cancer cell lines [51]. ADIPOQ plays a suppressing role by activating Peroxisome Proliferator-Activated Receptor-a (PPAR-a) which causes inhibition of FAS activity [52, 53]. Some studies have demonstrated the elevated expression of ADIPORs in colorectal carcinomas than in normal gastrointestinal tissue [54].

It was shown that the inverse relation of adiponectin with risk of endometrial cancer is not always depend on IGF-I, IGF-II, IGFBP-3, leptin, BMI, but the combination of high BMI and low adiponectin levels lead to a more than six-fold excess risk of endometrial cancer [55, 56].In obesity, reduced adiponectin levels lead to the development of insulin resistance and compensatory and chronic hyperinsulinemia [57, 58]. Adiponectin has a proapoptotic activity because of inhibition of TNF-a production and angiogenesis [59]. Therefore, altered effects of TNF-a on tumor cell due to low adiponectin levels can potentially lead to carcinogenesis through proliferation. The association between genes of the adiponectin pathway and risk of colorectal cancer has been reported in case–control studies [56, 60].

LEP and LEP Receptor:

Leptin is a 16 kDa glycolprotein product of the leptin gene (LEP), which is expressed almost exclusively (>95%) by adipocytes [61]. Plasma leptin levels are elevated in obesity and are raised with an increase of fat mass [62]. Leptin exerts its physiological action through the leptin receptor, which is expressed in colon cancer cell lines, human normal colonic, and adenomatous polyps [63, 64]. It is evident that leptin physiological properties are associated with energy homeostasis function and obesity. In addition, leptin is associated with inflammatory response, insulin signaling, bone remodeling and neuroendocrine function [65]. Leptin can act as a mitogen, transforming or migration factor for many different cell types [66, 67]. Some studies have shown an association between high leptin levels with increased CRC risk [68, 69].

The leptin receptor plays a key role in how leptin functions. Leptin and its receptor are associated with energy balance, adiposity, insulin, inflammation and vitamin D; and these mentioned factors are associated with colon cancer [70-72].

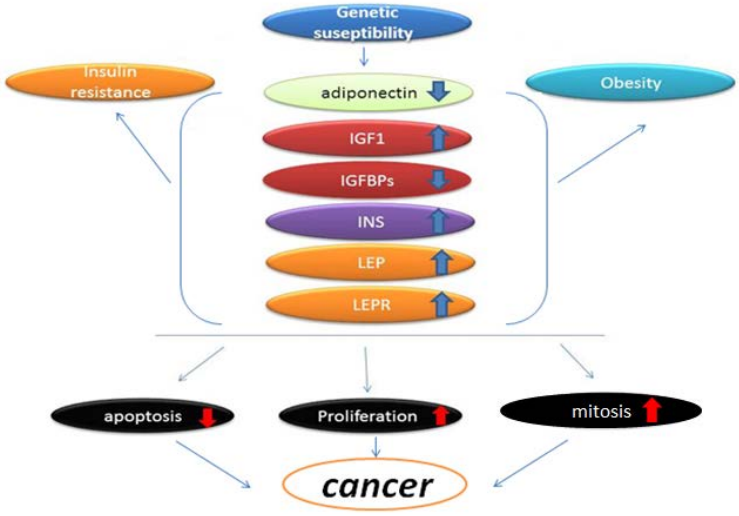

Figure 1. It shows a multidimensional model of cancer development, which suggests insulin resistance and obesity as driving forces behind cancer.

Table 1. Pathways and its genes that involved in colorectal cancer

Pathway	gene symbols	Function	Disorders	Ref.
Insulin pathway	IGFs	Growth hormone/mitotic effect	Diabetes and cancer	[73]
	IGFBPs	Carrier protein for IGF1	Diabetes and cancer	[74]
	INS	Glucose homeostasis /mitotic effect	Diabetes, cancer,polycystic ovary syndrome, metabolomics syndrome	[75]
	INSR	Regulation of glucose homeostasis	Diabetes and metabolomics syndrome	[76]
Obesity pathway	ADIPOQ	Glucose regulation and fatty acidoxidation	Type 2 diabetes, obesity, atherosclerosis, Non-alcoholic Fatty Liver Disease [NAFLD]	[77] [78]
	ADIPOQR	Increased AMPK and PPAR-α ligand activities	Diabetic, obesity and metabolomics syndrome	[79]
	LEP	Apoptotic suppressor/ mitotic effect	Obesity, overeating, and inflammation-related diseases, hypertension, metabolic syndrome, and cardiovascular disease	[80] [81]
	LEPR	By interaction to leptin hormone regulates adipose-tissue mass	Obesity, overeating, and inflammation-related diseases,	[82]

IGFs: insulin growth factors; IGFBPs: insulin growth factors binding proteins; INS: insulin; INSR: insulin receptor; ADIPOQ:adiponectin; ADIPOQR:adiponectin receptor; LEP:leptin; LEPR:leptin receptor

Conclusion

Colon cancer is the third most common cancer in men and the second in women worldwide. Therefore, understanding the role of genetic alteration in colorectal neoplasia will provide improved interventions for this malignancy. Polymorphisms in insulin *[IGFs, IGFBPs, INS,and INSR]* and obesity *[ADIPO, ADIPOR, LEP, LEPR]* genes promote cancer development and progression at various stages of the carcinogenic process. Since genetic mutations are involved in the initiation and progression of colorectal cancer, information on these changes may provide a clue for better diagnostic, prognostic, and appropriate treatment.

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Conflict of Interest

The authors have no conflict of interest in this article.

Authors' Contribution

The subject selection and article structure were made andwritten by MostafaRezaei-Tavirani and AkramSafaei.Mohamad Reza zali providedmany useful consultations. Finally, all authorscommented on the manuscript and approved it as well.

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