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The role of some ADAM-proteins and activation of the insulin growth factor-related pathway in colorectal cancer

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Abstract

Colorectal cancer (CRC) is the third most common malignant neoplasm worldwide. In Poland, colorectal cancer ranks second in tumor incidence regardless of sex; moreover, there has been a steady increase in the incidence of CRC. CRC results from complex interactions between inherited susceptibility, clinical conditions and environmental/lifestyle-related risk factors such as physical inactivity, smoking, alcohol consumption, high-fat/low-fiber diet, and obesity/overweight. The activation of pathways associated with insulin resistance and insulin-like growth factors (IGF) appears to be the epidemiological link between the metabolic syndrome and the development of CRC, which is of particular importance. What is significantly associated with the pathway of IGF is ADAM12 and 28-protein, which belong to a broad family of the adamalysines. These proteins, by adjusting the bioavailability of growth factors, influence the process of carcinogenesis. The aim of this article is to analyze the role of selected adamalysines and activation of the IGF system associated with the formation of colon cancer.

Key words: *obesity, colorectal cancer, diabetes mellitus.*

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Introduction

Colorectal cancer (CRC) is the third most common malignant neoplasm worldwide. The global incidence of this cancer is estimated at 1 million people per year. According to the National Cancer Society, in 2013, 143,460 new cases and 51,690 deaths because of colorectal cancer were noted worldwide [1, 2]. In Poland, colorectal cancer ranks second in tumor incidence regardless of sex; moreover, there has been a steady increase in the incidence of CRC [3].

Experimental, molecular, and socio-epidemiologic studies [4, 5] have suggested that CRC results from complex interactions between inherited susceptibility (Lynch syndrome I and II, familial polyposis), clinical conditions and environmental/lifestyle-related risk factors, such as physical inactivity, smoking, alcohol consumption, high-fat/low-fiber diet, and obesity/overweight. The hypothesis that diet and, in consequence, related metabolic markers play a role in cancer etiology was initially supported by a series of early case-control studies, epidemiological correlation studies and pioneering work on rodents in experimental laboratory studies carried out in the 1940s [6]. Previous studies emphasize the role of activating multiple signaling pathways, including those related to the system of the IGF, EGF/HER, VEGF, TNF, TGF-β. In the context of the epidemiological link between the interaction of the components of the metabolic syndrome and the development of CRC, what it appears to be of particular importance is the activation of pathways associated with insulin resistance and insulin-like growth factors [3, 5, 7-10].

A high risk of colorectal cancer in obese patients is associated, inter alia, with metabolic activity of white adipose tissues. Fat tissue treated like glandular tissue, performing many endocrine, paracrine and autocrine functions, regulating, inter alia, triglyceride metabolism, influencing the coagulation system and inhibiting the anti-lipolytic effect of insulin. The most important colorectal cancer risk factors among metabolic disorders are insulin resistance, hyperinsulinemia, and hyperglycemia. Moreover, the prevalence of diabetes mellitus (DM) is growing exponentially, having increased over 50% throughout the past ten years and currently affecting more than 347 million people worldwide [11].

The relationship between type 2 DM and the risk of CRC was investigated in a multicenter case-control study [12].

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It concluded that an important role in CRC development is played by ADAM12 and 28 proteins which belong to the family of adamalysines [13]. These proteins, by adjusting the bioavailability of growth factors, significantly influence the process of carcinogenesis, which has been confirmed, inter alia, by Kuroda and Mochizuki [14].

The aim of this article is to analyze the role of selected adamalysines and activation of the IGF system associated with the formation of colon cancer.

IGF system

Insulin (INS), with elevated levels marking the initial stage of impaired glucose metabolism, has been suggested to be involved in carcinogenesis through its growth-promoting effects on cells. Similar mutagenic effects have been suggested for a closely linked marker, insulin-like growth factor 1 (IGF1). Numerous studies have demonstrated that the insulin/insulin-like growth factor system plays a key role in the development and progression of colorectal cancer [15].

The insulin-like growth factor system is composed of three ligands, IGF1, IGF2, and INS; three cell membrane receptors – type 1 and 2 IGF receptors (IGF1R and IGF2R) and the insulin receptor (IR); as well as specific binding proteins (IGFBP 1-7); and several associated proteins, such as IRS and shc [6, 15-19].

IGF signaling through the IGF1R is involved in cell proliferation, differentiation, apoptosis and general anabolic cell processes (including the production of the extra cellular matrix). These processes occur through the activation of the phosphoinositide 3-kinase (PI3K), protein kinase B (Akt), mTOR, PI3K/Akt/forkhead box O (FoxO), and Ras/MAPK/ERK1/2 pathways [21]. INS signal transduction occurs through its receptor, which has two isoforms (IRA and IRB). IRA recognizes INS, IGF1 and IGF2 but has the highest affinity for IGF2. The INS signal is transduced through the IRB isoform associated with glucose homeostasis.

Moreover, IGF1 and INS receptors can form hybrid receptors sensitive to stimulation of all three ligands of the system: INS, IGF1, and IGF2 [22].

Some research has indicated that high circulating levels of IGF 1 and an increased IGF1/IGFBP3 ratio disturb GH/IGF1 homeostasis, which could be an indicator of a risk of cancer development. For our analysis, it is particularly important that the disintegration of the IGF/IGFBP3-complex is mediated by ADAM12 and ADAM28. The only disintegration of the IGF with its binding protein released biologically active IGFs. Thus, ADAM12 and ADAM28 proteins take an important part in regulating the bioavailability of IGFs.

Our study of the expression profile of gene encoding proteins of signal cascades activated by IGFs in colorectal cancer indicated that GRB10, PIK3R3, PIK3R1, and IRS1 were qualified as differentiating transcripts [23]. They were classified among the transcripts related to the signal pathway activated by IGF by a parameter signal log ratio and the statistical analysis conducted in the Significance of Analysis of Microarrays (SAM) Program.

Adamalysines

Adamalysines (ADAM proteins) belong to a large family of zinc-dependent proteins. They are a group of more than 30 type I transmembrane glycoproteins, containing a metalloproteinase and disintegrin domain that combines both protease and adhesive functions [24]. This multidomain structure enables diverse roles in a wide range of cellular processes, ranging from proteolytic "shedding" of surface-bound signaling molecules and degradation of the extracellular matrix, to adhesion, cell migration, and the transduction of specific intracellular signals. The active form of the ADAM proteins is formed with the participation of matrix metalloproteinases 2 and 7 (MMP2, MMP7). In turn, the natural inhibitors of their activity are, among other proteins, tissue inhibitors of metalloproteinases (TIMPs).

These interactions are important for both physiological (embryogenesis, angiogenesis) and pathological processes (e.g. carcinogenesis, metastases, Alzheimer's disease and AIDS). Probably due to numerous features of the ADAMs, there is a growing number of reports on their role in the process of carcinogenesis. There are many reports showing that members of the ADAMs family are overexpressed in human cancer (Table 1).

The above-mentioned IGF system correlates with the biological activity of some ADAMs and depends on concomitant metabolic disorders, which has a considerable influence on the development and progression of, inter alia, colorectal cancer [25]. IGF1 and IGF2 are released from IGF/IGFBP-3 complex by ADAM12 or/and ADAM28

Table 1. Overexpression of ADAMs in human cancers

ADAM protein	Overexpression in malignant tumors	References
ADAM 10	Mouth, stomach, ovary, uterus, colon, prostate	[Chen, 2013, Jones, 2013, Mochizuki, 2007]
ADAM 12	Brain, breast, stomach, colon	[Chen, 2013, Mochizuki, 2007]
ADAM 17	Breast, ovary, kidney, colon, brain, stomach, prostate	[Chen, 2013, Mochizuki, 2007, Gao, 2013, Ni, 2013, Richards, 2013]
ADAM 28	Lung, colon, kidney, bladder	[Chen, 2013, Mochizuki, 2007, Kuroda, 2010, Yang, 2011]

in selective digestion of IGFBP-3 into two fragments. ADAM12 and ADAM28 metalloproteinases may selectively target IGFBPs for degradation, potentially giving fine control over the total IGF concentration in the tissue/serum and the ratio of IGF1/IGF2. This process can be represented by biomolecular reaction where k is the dissociation rate constant:

$$\text{IGFs/IGFBP-3} \xrightarrow[\textit{ADAM12, 28}]{k} \text{IGFBP-3} + \begin{matrix}\text{free IGF-1}\\ \text{free IGF-2}\end{matrix}$$

That dynamic, nonlinear equation changes in time according to the concentrations of the pri mary variables (IGFBP-3/IGFs, ADAM12, ADAM28). New therapeutic interventions for these conditions are actively being developed through the investigation of this system.

ADAM12-S (secreted form) primarily degrades IGFBP3 and IGFBP5 [26] while ADAM28 cleaves insulin-like growth factor binding protein-3 only.

Free IGF1 (half-life < 10 min) induces phosphorylation of IGF-1R and promotes cell proliferation through the ERK pathway [27]. In light of this fact, the study on dependence between obesity and development of CRC is very interesting. In this study CRC-patients were divided by BMI and said previous occurrence of the molecular changes in the tissue of patients with aberrant body weight. The initial study revealed that changes of ADAM28 and IGFBP-3 gene expression, perhaps overexpression or silencing, were observed in the normal tissue in overweight/obese patients with colorectal cancer. It can lead to increase IGF1 activity and thus to promote cell growth, and carcinogenesis. Moreover, this study showed that the surgical "clear" margin in the group of obese patients was not equal to the molecular margin, because in the surgical margin, in these patients, changes in gene expression were also observed [25]. This observation is very important to the reflection about the range of the surgical treatment, and effectiveness of current treatment, especially in obese patients. Moreover, IGFBP-3 cleavage can be inhibited by treatment with anti-ADAM28 antibody or an ADAM28 inhibitor, KB-R7785 [28].

However, ADAMs are involved in the development of CRC, not only through the IGF pathway; another signaling pathway is activation of the epidermal growth factor receptor (EGFR), and initiation of EGFR tyrosine kinase activity. The ligand for EGFR is e.g. transforming growth factor-alfa (TGFα), which is formed with the participation of ADAM17 and ADAM10 [29]. They work together as "sheddases" to cleave hundreds of diverse transmembrane substrates including growth factor ligands, receptor tyrosine kinases (RTKs) and adhesion molecules. Merchant conducted a study with human colorectal cancer cell line, and a tissue array of normal colonic mucosa and primary and metastatic colorectal cancer, to localize ADAM17 on the cell surface, and to investigate effects of EGFR axis inhibition in colorectal cancer. In this study, they showed that ADAM17 is overexpressed in primary and metastatic CRC tumors compared with normal colonic mucosa, and also that the intensity of their immunoreactivity inversely correlated with that of TGFα [30]. Merchant also expanded his observations on the issues of possible therapies: the pharmacologic blockade with an EGFR monoclonal antibody, a selective EGFR tyrosine kinase inhibitor, or a selective ADAM17 inhibitor, results in decreases in cell proliferation [30]. Moreover, ADAM17 is important in the development of drug resistance in patients during therapy with 5-fluorouracil (5-FU). Kyula proved, in his in-vivo and in-vitro study on CRC models, that chemotherapy (with 5-FU) correlates with increased ADAM17 activity. This significantly decreases chemotherapy effects on tumor growth and apoptosis [31]. Kyula also suggests that the solution may be pharmacologic inhibition of ADAM17, together with 5-FU chemotherapy. ADAM10 proteins, together with ADAM17, are also involved in cleavage of transmembrane protein Klotho (KL). This process is, moreover, stimulated by insulin.

The loss of cellular adhesion is a key element in the cascade of metastasis. ADAMs, by participating in the processes of degradation of extracellular matrix, play an important role also at this stage. The study on colorectal cancer cell line (HT 29) showed the influence of ADAM9 on the decreased cell adhesion via E-cadherin degradation [32]. Similar overexpression on the CRC cell surface, of ADAM10 was demonstrated [33]. Lowering of the intracellular integrity, through digestion of extracellular matrix by metalloproteases, is the major cause of CRC metastasis [34].

Discussion

The above analysis is a part of a series of ongoing studies on the pathogenesis of colon cancer. These analyses are important due to the unfavorable epidemiological data of this cancer. Referring once again to the worldwide data, we note that CRC is one of the leading causes of cancer mortality. Chronic hyperinsulinemia accompanying obesity, especially visceral obesity, causes activation of the IGF-axis and importantly increases the risk of neoplasia, as shown previously [35, 36].

Obesity increases serum-concentrations of the ADAM17 and 28 proteins, as well as some pro-inflammatory cytokines, TNFα for example, which together are responsible for the induction of inflammation and tumorigenesis [37, 38]. The relationship between obesity and the levels of ADAM17 and TNFα are especially complex because ADAM17 is responsible for the release of biologically active TNFα. Moreover, in white fat tissue ADAM17 activation leads to the expression of inflammatory molecules: suppressor of cytokine signaling 3 (SOCS3), interleukin 6 (IL-6) and monocyte chemotactic protein 1 (MCP-1) [38].

In turn, studies on animal models have shown that some of the adamalysines may be responsible for stimulating the development of white fat tissue. Thus they can contribute to exacerbating insulin resistance and inflammation processes [39].

The above reports indicate the significance of recommendations for weight reduction and "healthy-lifestyle" to reduce the risk of colorectal cancer. But still, the question is about the difference in gene expression of the IGF system and ADAMs in the neoplastic and normal tissues of patients with colorectal carcinoma and concomitant type 2 diabetes and obesity ("the epidemics of the 21st century"). The interpretation of their role in pathophysiological processes is not obvious [40]. The role of ADAMs is also complex. ADAMs are involved in the activation of multiple signaling pathways, often staying with other substrates in feedback relations.

Current trends in oncology clinical trials lead to the optimization, personalization, and increasing the effectiveness of new therapeutic strategies [41]. The IGF system and adamalysines are a target for some drugs currently in development [42].

Conclusions

1. Activation of the IGF system associated with insulin resistance is an important component of the pathogenesis of colorectal cancer.
2. ADAM family proteins are involved in multiple stages of tumorigenesis activation of the IGF system and other cytokines.
3. The role of ADAM proteins and activation of the IGF pathway in tumorigenesis is not fully understood and requires further studies.
4. The future research should be focused on molecular personalization of the CRC treatment. The target for the therapy could be the IGF system and ADAM proteins.

The authors declare no conflict of interests.

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