Review article

The role of activation of insulin-like growth factors in colorectal cancer

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ABSTRACT

Co-occurrence of metabolic disorders is a recognized risk factor for the development of colorectal cancer which is currently the leading cause of morbidity due to malignant neoplasms in the world. The pathogenesis of colorectal cancer is not well understood yet. Among the postulated neoplastic mechanisms is the activation of insulin-like growth factors, with both epidemiological and clinical observations of their role. In this paper, the authors synthesize the current knowledge about the importance of activation of insulin-like growth factors in the development of colorectal cancer.

Key words: colorectal cancer, insulin-like growth factors, IGF-receptors, metabolic disorders

INTRODUCTION

Epidemiological data suggest that incidence of malignant neoplasms is growing steadily [1]. The incidence rate in Poland has doubled over the last three decades and currently 140,000 new cases are reported each year. At present, the most common types of neoplasms among males are lung, prostate and colorectal cancer while breast, colorectal and lung cancer prevail among female patients. Epidemiological data relating to colorectal cancer indicate that incidence of this neoplasm increases with age. Nicotine addiction, alcohol abuse and lifestyle habits leading to obesity and metabolic disorders are risk factors for colorectal cancer. These factors may be modified which results in a significant mitigation of colorectal cancer risk. A fibre-rich diet with a reduction in red meat consumption decreases the risk by 19% while regular physical activity reduces the risk by 24% [2].

A correlation between metabolic disorders and neoplasia was first observed at the beginning of the 20th century. Rohdenburg noted that impaired "sugar" tolerance may lead to development of malignancy [3]. After nearly a century the study was extended in connection with the so-called insulin hypothesis. When exploring this theory, the researchers noticed the insulin's mitogenic potential which significantly increased the incidence of malignant tumours (including colorectal, liver, gallbladder, pancreatic, breast and endometrial cancers) in type 2 diabetes patients. Due to insulin resistance and exogenous insulin administration, those patients showed a relatively higher tissue exposure to insulin which, through activation of signalling pathways governing proliferation, could promote neoplasia [4–6]. Apart from the adverse effects of hyperinsulinemia, excess adipose tissue with metabolic and endocrine activity is also postulated to play a significant role. A metabolic syndrome is associated with, among other things, a dysregulation of adipokine levels whereby the level of adiponectin which has an anti-inflammatory effect and prevents insulin resistance decreases and the levels of resistin and leptin grow. Moreover, the homeostasis of gonadal steroids is disturbed while the serum levels of proinflammatory cytokines IL-6, TNF-α and CRP grow significantly [7–9].

At present, obesity and the resulting metabolic disorders are believed to account for approx. 20% of all neoplasms; in case of hormone-sensitive cancers this link is present in up to 33% cases [10]. Moreover, type 2 diabetes increases the risk of malignancy even regardless of BMI values [11].

INSULIN-LIKE GROWTH FACTOR SYSTEM

The insulin-like growth factor (IGF) system comprises three ligands: IGF1, IGF2 and insulin (INS); three cellular membrane receptors: type 1 and type 2 IGF receptors (IGF1R and IGF2R) as well as an insulin receptor (IR). In addition, the complex includes specific insulin-like growth factor-binding proteins (IGFBP 1–6), cysteine-rich proteins that resemble IGFBP as well as a number of regulatory proteins controlling the system activity, including: IRS, SHC, ADAM 12, ADAM 28 and matrix metalloproteinases [12–16].

When the IGF ligand is bound to IGF1R, a cascade of events is triggered that results in cell proliferation and differentiation as well as other anabolic effects, including creation of extracellular matrix.

IGF1 is the strongest among ligands and is dedicated for IGF1R. Once the ligand is bound to IGF1R, tyrosine kinase is activated by phosphorylation as a result of which a signal transduction cascade is initiated in two pathways. The first pathway leads through activation of Ras and Raf proteins while the other – through activation of phosphoinositide 3-kinase (PI3K). This triggers, among other things, an increased DNA synthesis and stimulates cyclin D expression that accelerates progression of cell cycle and transition from G1 to S phase. Moreover, IGF1R activation increases Bcl protein expression at the expense of a decreasing Bax protein expression, which leads to inhibited apoptosis.

IGF2 shows a regulatory effect on the process of proliferation and apoptosis primarily in the prenatal period. Once the embryonic development is completed, the role of IGF2 in mitogenesis decreases in favour of IGF1 whose maximum levels are reached in adolescence.

Insulin releases its metabolic effect by binding with an insulin receptor that exists in two isoforms (IRA and IRB). IRA insulin receptor recognises insulin, IGF1 and IGF2 as ligands, showing the highest affinity to IGF2. The effect of IRA stimulation is cell-type specific, e.g. IRA found on endothelial cells, when bound to the ligand, is responsible for inhibiting apoptosis and stimulating cellular proliferation [17]. A bond between insulin and insulin receptor B is closely related to intracellular metabolism of glucose while it shows less significance for the neoplasia mechanisms discussed in this paper.

The complexity of activation of IGF-related pathways is also attributable to the ability of individual receptor subunits for IGF1 and INS to form hybrid receptors which are sensitive to stimulation of all three ligands in the system: INS, IGF1 and IGF2 [18].

The number of hybrid receptors varies depending on tissue type. Their function has not been fully explored yet; however, overexpression of hybrid receptors in hyperinsulinemia and insulin-resistance has been demonstrated to potentially increase the risk of neoplastic transformation [18, 19].

Both IGFRs are glycoproteins but differ significantly in terms of structure. IGF1R has the form of a tetramer with two pairs of alpha and beta subunits. IGF2R has a monomeric structure. It also differs from IGF1R in that it does not have a tyrosine kinase activity. In its extracellular domain, IGF2R has three binding sites of which one is dedicated to IGF2 and two are intended for mannose-6-phosphate-tagged proteins, including renin, prolipherin, thyroglobulin and TGF-β. IGF1R also shows a high affinity to insulin receptor which is the reason for the cross-binding of ligands; however, the mutual affinity between these two factors is weaker [20].

Production of IGF and IGFBP depends on multiple factors, including age, gender, diurnal rhythm and genetics. The highest IGF1 levels are observed in adolescence, with girls showing a significantly higher concentration of IGF1 relative to boys. Once adulthood is reached, the levels start dropping only to stabilise around the age of 40. The IGF1 level is affected by protein-rich and fat-rich diet with concomitant carbohydrate restriction. Moreover, IGF1 is subject to regulation in endocrine axes. Its level depends mostly on the level of somatotropin which directly affects IGF production from hepatocytes, with TSH, pituitary gonadotropins and oestradiol also showing certain significance [20, 21]. In case of pathologies such as acute or chronic liver damage and kidney failure, IGF1 level and bioavailability diminish. In obese individuals, total IGF1 concentration is depressed despite high levels of the free fraction which is associated with hyperinsulinism.

IGFBP proteins display a much higher affinity to IGF relative to that of their receptors. They have been found to not only act as carriers and extend half-life period which for free IGF is below 10 minutes but also to modulate IGF biological availability and activity. It has also been observed that IGFBP may regulate cell growth independently of IGF by affecting the paracrine pathway. Following the foetal period, IGFBP-3 is the key binding protein for IGF and circulates in blood serum in ternary complexes with IGF and stabilizing glycoprotein called acid-labile subunit – ALS [20].

IGFBPs activity is regulated on multiple levels. Their expression depends, among other things, on the level of hormones (glucocorticosteroids, oestrogens, TSH and FSH), the active form of vitamin D, growth factors (EGF, FGF and IGF) and cytokines [22, 23]. IGFBPs may form a non-specific binding to membrane receptors for IGF while affecting their availability to growth factors. Moreover, these proteins are also subject to posttranslational modifications, including primarily proteolysis that leads to a release of free IGF which is aided by the presence of adamalysins, cathepsin D and intracellular matrix metalloproteinase [22].

ACTIVATION OF IGFR PATHWAY IN COLORECTAL CANCER PATHOGENESIS

Epidemiological and experimental data suggest that the IGF receptor plays a significant role in colorectal cancer pathogenesis. This mechanism is still being researched but the findings obtained so far corroborate the observations made over the years which suggest that unhealthy lifestyle habits leading to metabolic disorders including type 2 diabetes are a risk factor for colorectal cancer. The relationship between metabolic disorders and colorectal cancer incidence has been evidenced by a large meta-analysis conducted by Bardou who reviewed publications from the years 1980–2012. The analysis proves that excessive body weight is a risk factor for colorectal cancer (with a stronger correlation exhibited by the male population) and that a body weight loss reduces that risk [24].

Patients with type 2 diabetes and advanced symptoms of peripheral insulin resistance are exposed to higher serum levels of insulin (including due to exogenic administration) and free insulin-like growth factors with a substantial mitogenic potential. In case of hyperinsulinemia, an increased number of growth hormone (GH) receptors appears on hepatocytes which, when stimulated, are the key driver for the liver to generate insulin-like growth factors [25]. Moreover, a mechanism has been described in which high insulin levels reduce synthesis of IGF-binding proteins (IGFBP-1 and IGFBP-2) by liver cells [26]. Such observations were confirmed by Renehan who noted that IGFBP-1 and IGFBP-2 protein levels in obese individuals were significantly lower than in people with normal body weight; in addition, the levels were found to conversely correlate with serum insulin levels for those two groups of patients [27]. Said researchers also observed that once the insulin stimulus ceased, mRNA expression for IGFBP-1 returned to physiological levels faster than in the case of mRNA expression for IGFBP-2 [27].

The release of insulin-like growth factors from their bonds to binding proteins is also stimulated by paracrine signals by way of a positive feedback. A bond between ligand, IGF1 and IGF1R leads to, among other things, a higher synthesis of cellular matrix

metalloproteinases which are later secreted to the extracellular domain where they trigger a number of effects; in addition to lysis of matrix components and tumour growth promotion some metalloproteinases (MMP-7, MMP-9 and adamalysins) take part in degradation of the IGF/IGFBP-3 complex [28]. It has also been noted that obese individuals exhibit an excessive production of matrix metalloproteinases, particularly in subcutaneous and peritoneal tissue. Their activity through PPARγ signalling pathways may lead to progression of insulin resistance [29].

A higher level of free insulin-like growth factors circulating in blood serum and their correlation to colorectal cancer have been also demonstrated in prospective clinical studies in which a higher level of free IGF (concomitant with a low level of circulating IGFBP-3) was found in individuals in whom a subsequent colonoscopy revealed adenomas at a high risk of progressing to carcinoma [30]. The significance of IGF1 being bound by IGFBP-3 was also noted in an experiment in which a recombinant IGFBP-3 was added to a culture of colorectal and breast cancer cell lines leading to inhibition of cell growth [31, 32]. A particularly interesting observation was made in a study which found that in individuals with abnormal body weight, the IGF/ IGFBP-3 complex degrades intensively not only in colorectal cancer cells but also in the surrounding tissue which is believed to be a safe margin for a surgical resection; this dependency was not observed in individuals with normal body weight [33]. Moreover, high blood serum levels of free IGF1 have been found to be correlated with the presence of multiple distant metastases of colorectal cancer [30].

The Suh study demonstrated that colorectal cancer cells were characterised by a higher density of insulin receptors (particularly isoform A), IGF1R, IGF2R and hybrid receptors relative to cells of the normal colonic mucosa [26]. Slightly different findings were obtained by Liu who identified an increased expression of IGF1R in a colorectal cancer tissue but no difference in IR expression. However, as part of the same study Liu observed that insulin receptor expression was higher in the vascular endothelium located in the direct vicinity of the tumour which, in her opinion, was significant for neoangiogenesis and continued neoplasm growth [34].

It was also found that blocking IGF1R in colorectal cancer cells inhibits further growth of these cells and makes them sensitive to chemotherapy administered [24]. The Hakam study which analysed tissue samples of adenoma, adenocarcinoma and corresponding adenocarcinoma metastases found that the density of receptors on the cell membrane grows as malignancy increases, with the highest levels found in adenocarcinoma metastases [35]. These observations correspond with physiological information which indicates that activation of IGF1R stimulates, among other things, the pathway associated with Rec protein, thus promoting cell migration processes.

Given that the IGF pathway has been postulated to have a significant role in colorectal cancer, more and more attempts are being made to use the findings when planning anti-tumour therapies. Currently, three treatment strategies are adopted: receptor blocking with the use of monoclonal antibodies, inhibition of tyrosine kinase activated due to ligand bonding to the receptor, and ligand blocking with the use of antibodies or specific binding proteins [36].

To date, satisfactory outcomes have not been achieved which may be attributable largely to a tendency of tumour cells to generate receptors in hybrid combinations and various isoforms [36].

CONCLUSIONS

The significant role of the pathway associated with insulin-like growth factors in colorectal cancer pathogenesis is undisputable. Numerous studies have confirmed this dependency for other cancer types, like breast cancer, non-small cell lung cancer, gastrointestinal stromal tumour and pancreatic cancer [21, 22, 37–39]. These observations are highly relevant, particularly given that excess body weight and metabolic disorders leading to insulin resistance are among the risk factors for neoplasms which are modifiable. Moreover, learning the significance of IGF-related signalling pathways and the mechanisms of carcinogenesis may be, at a later stage, used to treat colorectal cancer and other malignant neoplasms with therapies individually tailored to specific metabolic disorders.

References

1. Krajowy Rejestr Nowotworów (KRN, National Cancer Registry) [online: http://onkologiaorgpl/]. (access: December 2016).
2. Baena R, Salinas P. Diet and colorectal cancer. Maturitas. European Menopause Journal 2015; 80(3): 258-264.
3. Rohdenburg GL, Bernhard A, Krehbiel O. Sugar tolerance in cancer. J Am Med Assoc 1919; 72: 1528-1530.
4. Czyżyk A, Szczepanik Z. Diabetes mellitus and cancer. Eur J Intern Med 2000; 11: 245-252.
5. Giovanucci E. Insulin and colon cancer. Cancer Causes & Control 1995; 6(2): 164-179.
6. Gallagher EJ, LeRoith D. Epidemiology and molecular mechanisms tying obesity, diabetes, and the metabolic syndrome with cancer. Diabetes Care 2013; 36 (suppl 2): 233-239.

7. Godsland IF. Insulin resistance and hyperinsulinaemia in the development and progression of cancer. Clin Sci 2010; 118: 315-332.
8. Muc-Wierzgoń M, Nowakowska-Zajdel E, Dzięgielewska-Gęsiak S et al. Specific metabolic biomarkers as risk and prognostic factors in colorectal cancer. World J Gastroenterol 2014; 20(29): 9759-9774.
9. Hopkins BD, Goncalves MD, Cantley LC. Obesity and cancer mechanisms: cancer metabolism. J Clin Oncol 2016; 34(35): 4277-4283.
10. Wolin KY, Carson K, Colditz GA. Obesity and cancer. Oncologist 2010; 15: 556-565.
11. Campbell PT, Newton CC, Patel AV et al. Diabetes and cause-specific mortality in a prospective cohort of one million US adults. Diabetes Care 2012; 35: 1835-1844.
12. Wang L, Ma W, Markovich R et al. Insulin-like growth factor I modulates induction of apoptotic signalling in H9C2 cardiac muscle cells. Endocrinology 1998; 139: 1354-1360.
13. Hwa V, Oh Y, Rosenfeld RG. The insulin-like growth factor-binding protein (IGFBP) superfamily. Endocr Rev 1999; 20(6): 761-787.
14. Rajah R, Katz L, Nunn S et al. Insulin-like growth factor binding protein (IGFBP) proteases: functional regulators of cell growth. Prog Growth Factor Res 1995; 6(2-4): 273-284.
15. Kreitschmann-Andermahr I, Suarez P, Jennings R et al. GH/IGF-1 regulation in obesity-mechanisms and practical consequences in children and adults. Horm Res Paediatr 2010; 73: 153-160.
16. Juul A. Serum levels of insulin-like growth factor-I and its binding proteins in health and disease. Growth Horm IGF Res 2003; 13: 113-170.
17. LeRoith D. Insulin-like growth factor I receptor signalling – overlapping or redundant pathways? Endocrinology 2000; 141: 1287-1288.
18. Jones JI, Clemmons DR. Insulin-like growth factors and their binding proteins: biological actions. Endocr Rev 1995; 16: 3-34.
19. Suwała A, Ziora K, Landowska D. Budowa i funkcja insulinopodobnych czynników wzrostowych oraz objawy kliniczne niedoboru IGF-1. Endokrynol Ped 2010; 3: 47-62.
20. Filus A, Zdrojewicz Z. Insulinopodobny czynnik wzrostu-1 (IGF-1) – budowa i rola w organizmie człowieka. Pediatr Endocrinol Diabetes Metab 2014; 22(4): 161-169.
21. Belfiore A. The role of insulin receptor isoforms and hybrid insulin/IGF-I receptors in human cancer. Curr Pharm Des 2007; 13(7): 671-686.
22. Baxter RC. IGFBP Special Issue. J Cell Commun Signal 2015; 9(2): DOI: 101007/s12079-015-0295-5.
23. Józefiak A, Pacholska J, Kędzia W. Rola IGF-1 i IGFBP w procesie neogenezy. Perinatologia, Neonatologia i Ginekologia 2008; 1: 175-183.
24. Bardou M, Barkun AN, Martel M. Obesity and colorectal cancer. Gut 2013; 62: 933-947.
25. Cohen DH, LeRoith D. Obesity, type 2 diabetes and cancer: the insulin and IGF connection. Endocr Relat Cancer 2012; 19: 27-45.
26. Suh S, Kim KW. Diabetes and cancer: is diabetes casually related to cancer? Diabetes Metab J 2011; 35: 193-198.
27. Renehan AG, Frystyk J, Flyvbjerg A. Obesity and cancer risk: the role of insulin-IGF axis. Trends Endocrinol Metab 2006; 17(8): 328-336.
28. Walkiewicz K, Gętek M, Muc-Wierzgoń M et al. The importance of ADAM family proteins in malignant tumours. Post Hig Med Dośw 2016; 70: 67-73.
29. Tinahones FJ, Coin-Araguez L, Mayas MD et al. Obesity-associated insulin resistance is correlated to adipose tissue vascular endothelial growth factors and metalloproteinase levels. BMC Physiology 2012; 12(4): DOI: 101186/1472-6793-12-4.
30. Sax AT, Jenkins DG, Devin JL et al. The insulin-like growth factor axis: a biological mechanism linking physical activity to colorectal cancer survival. Cancer Epidemiol 2014; 38: 455-459.
31. Parrizas M, LeRoith D. Insulin-like growth factor-1 inhibition of apoptosis is associated with increased expression of the bcl-xL gene product. Endocrinology 1997; 138: 1355-1358.
32. Singh P, Alex JM, Bast F. Insulin receptor, and insulin-like growth factor receptor signalling systems novel treatment strategies of cancer. Med Oncol 2014; 31(805): DOI: 101007/s12032-013-0805-3.
33. Nowakowska-Zajdel E, Mazurek U, Wierzgoń J et al. Expression of ADAM 28 and IGFBP-3 genes in patients with colorectal cancer – a preliminary report. Int J Immunopathol Pharmacol 2013; 26: 223-228.
34. Liu JJ, Druta M, Shibata D et al. Metabolic syndrome and colorectal cancer: is hyperinsulineamia/insulin receptor-mediated angiogenesis a critical process? J Geriatr Oncol 2014; 5: 40-48.
35. Hakam A, Yeatman TJ, Lu L et al. Expression of insulin-like growth factor receptor in human colorectal cancer. Hum Pathol 1999; 30(10): 1128-1133.
36. Sandhu MS, Dunger DB, Giovanucci EL. Insulin, insulin-like growth factor-1, IGF bindings proteins, their biologic interactions, and colorectal cancer. J Natl Cancer Inst 2002; 94(13): 972-980.
37. Durai R, Yang W, Gupta S et al. The role of insulin-like growth factor system in colorectal cancer: a review of current knowledge. Int J Colorectal Dis 2005; 20: 203-220.
38. LeRoith D, Werner H, Beitner-Johnson D, Roberts CT Jr. Molecular and cellular aspects of the insulin-like growth factor I receptor. Endocr Rev 1995; 16: 143-163.
39. Furlanetto RW, Harwell SE, Frick KK. Insulin-like growth factor-I induces cyclin-D1 expression in MG63 human osteosarcoma cells in vitro. Mol Endocrinol 1994; 8: 510-517.

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Katarzyna Walkiewicz: development of the concept and assumptions, elaboration of the paper; Ewa Nowakowska-Zajdel: development of methodology, elaboration of the paper; Joanna Strzelczyk: development of the concept and assumptions; Michał Walczak: elaboration of the paper; Angelika Copija: review and analysis of literature; Karolina Janion: development of methodology; Małgorzata Muc-Wierzgoń: development of the concept and assumptions.
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