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Insulin-like growth factor (IGF) axis in cancerogenesis

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ABSTRACT

Determination of the role of insulin-like growth factor (IGF) family components in carcinogenesis of several human tumors is based on numerous epidemiological and pre-clinical studies, experiments in vivo and in vitro and on attempts at application of drugs affecting the IGF axis. Investigative hypotheses in original studies were based on biological functions manifested by the entire family of IGF (ligands, receptors, linking proteins, adaptor molecules).

In the context of carcinogenesis the most important functions of IGF family involve intensification of proliferation and inhibition of cell apoptosis and effect on cell transformation through synthesis of several regulatory proteins. IGF axis controls survival and influences on metastases of cells. Interactions of IGF axis components may be of a direct or indirect nature. The direct effects are linked to activation of PI3K/Akt signaling pathway, in which the initiating role is first of all played by IGF-1 and IGF-1R. Activity of this signaling pathway leads to an increased mitogenesis, cell cycle progression, and protection against different apoptotic stresses. Indirect effects of the axis depend on interactions between IGF and other molecules important for cancer etiology (e.g. sex hormones, products of suppressor genes, viruses, and other GFs) and the style of life (nutrition, physical activity). From the clinical point of view, components of IGF system are first of all considered as diagnostic serous and/or tissue biomarkers of a given cancer, prognostic factors and attractive target of modern anti-tumor therapies. Several mechanisms in which

Abbrevistions: ACTH, Adrenocorticotropic hormone; ADC, adenocarcinoma; AHR, adjusted hazard ratio; AFP, alpha-fetoprotein; AI, androgen-independent; Akt (or AKT) (protein kinase B), serine/threonine protein kinase; ALS, acid-labile protein subunit; AR, androgen receptor; BECs, bronchial epithelial cells; BCC, basal cell carcinoma; BMI, body mass index; BPH, benign prostatic hyperplasia; BR, breast cancer; CA, cytosine-adenine; CA 19-9, cancer antigen 19-9; CC, cervical cancer; CI, confidence interval; CIN, Cervical Intraepithelial Neoplasia; c-MET (MET), proto-oncogene, receptor tyrosine kinase; CpG (CG), cytosine nucleotide is followed by a guanine nucleotide; COX-2, cyclooxygenase-2; CRC, colorectal carcinoma; CRNDE, colorectal neoplasia differentially expressed (non-protein coding); CRPCa, castrate-resistant PCa; CSCs, cancer stem cells; CSCC, cutaneous squamous cell carcinoma; DM, diabetes mellitus; EBV, Epstein-Barr virus; EC, endometrial cancer; ECM, extracellular matrix; EGF/R, epidermal growth factor/receptor; mEGFR, mutated form of EGFR; EMT, epithelial-to-mesenchymal transition; ER, estrogen receptor; ERE, Estrogen Response Element; Erk, extracellular signal-regulated kinase; FA, follicular adenoma; FGF, fibroblast growth factor; FoxO1, forkhead box protein O1; FSH, follicle-stimulating hormone; GC, gastric cancer; GFs, growth factors; GH, growth hormone; GPR30/GPER, G protein-coupled receptor 30/G protein-coupled estrogen receptor 1; GRE, Glucocorticoid Response Element; GSK-3β, Glycogen synthase kinase 3 beta; HBV/HCV, hepatitis B/C virus; HCC, hepatocellular carcinoma; HER-2, human epidermal growth factor receptor 2; HDACs, histone deacetylases; HGF, hepatocyte growth factor; Hh, Hedgehog; HIF-1, hypoxia-inducible factor 1; HNPCC, hereditary nonpolyposis colorectal cancer; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; HR, hazard (risk) ratio; IGF, insulin-like growth factor; IGF-R, IGF receptor; IGFBPs, IGF binding proteins; IHC, immunohistochemistry; IL, interleukin; ILK, integrin-linked kinase; IR, insulin receptor; IRS-1/2, insulin receptor substrate 1/2; kbs, kilobases; KGF (or FGF-7), keratinocyte growth factor; LC, lung cancer; LCR, long control region; LH, luteinizing hormone; MAPK, mitogen-activated protein kinase (originally called ERK); MEK, mitogen-activated protein kinase (also known as MAP2K, MEK, MAPKK); MGF, mechano growth factor; MM, melanoma malignum; MMPs, metalloproteinases; mTOR, mammalian target of rapamycin; NSCLC, non small cell lung cancer; OC, ovarian cancer; OR, odds ratio; PC, pancreatic cancer; PCa, prostatic cancer; PCOS, polycystic ovary syndrome; PDAC, pancreatic duct adenocarcinoma; PDGF, Platelet-derived growth factor; PIN, prostate intraepithelial neoplasia; PI3K, phosphatidylinositol 3-kinase; PR, progesterone receptor; pRB, retinoblastoma protein; PRE, Progesterone Response Element; PrSC, prostate stromal cells; PSA, prostate-specific antigen; PTC, Papillary Thyroid Carcinoma; Ptch1, Patched 1, protein patched homolog 1; PTEN, phosphatase and tensin homolog; Raf, proto-oncogene serine/threonine-protein kinase; RR, relative risk (risk ratio); SCC, squamous cell carcinoma; SCLC, small cell lung cancer; SD, standard deviation; SIL (H-SIL, L-SIL), Squamous Intraepithelial Lesion (H–high gradeL–low grade); SMT, somatic mutation theory; SNP, single-nucleotide polymorphism; Src (c-Src), proto-oncogene tyrosine-protein kinase; TCGA, The Cancer Genome Atlas; TDLU, terminal duct lobular unit; TGF, transforming growth factor; TNBC, triple-negative BC; TOFT, Tissue Organization Field Theory; TRH, Thyrotropin-releasing hormone; uPA/uPAR, urokinase plasminogen/urokinase plasminogen receptor; UTR, untranslated region; VEGF, vascular endothelial growth factor; wt, wild-type; VPF, vascular permeability factor.

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IGF system components act in the process of carcinogenesis need to be clarified, mainly due to multifactorial etiology of the neoplasms. Pin-pointing of the role played in carcinogenesis by any single signaling pathway remains particularly difficult.

The aim of this review is to summarize the current data of several epidemiological studies, experiments in vitro and on animal models, to increase our understanding of the complex role of IGF family components in the most common human cancers.

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1. Introduction

For at least 30 years the dominant theory of carcinogenesis has been the somatic mutation theory (SMT), which postulates that the formation of a cancer is a multistep process characterized by accumulation of molecular alternations in cell DNA that involves genetic and epigenetic mechanisms [1,2]. The SMT theory of cancer proposes that cancer is a clonal, cell-based disorder. However, most of the cancers are histopathologically diverse, and possess cytologically different clones that arise from one transformed cell through genetic alterations. Generally, agents causing cancers can be classified as genotoxic or non-genotoxic (epigenetic). The biological activity of many genotoxic agents is manifested by changing information encoded in cell DNA. The main cause of cancer is accumulation of multiple DNA mutations in oncogenes, tumor suppressor genes, microRNA genes, DNA-mismatch repair genes or genes involved in the control of cell proliferation, cell cycle and apoptosis. Massive chromosomal rearrangements, gene amplification, or gene deletion are also observed in many tumor cells [3].

The non-genotoxic agents can change the degree of methylation of the DNA, and/or chromatin conformation what is manifested through changes of the genes activity without causing mutations. The cancer can be caused by a number of internal factors such as hereditary, immunological and hormonal ones as well as external factors (including genotoxic agents) such as chemicals, life style factors (e.g. diet, cigarette smoking, physical activity, sun exposure), radiations or viral infections (e.g. HBV, HCV, EBV, HPV and other ones) [1,2].

Tomasetti and Vogelstein [4] have recently shown that spontaneous mutations occurring during stem cells division can also cause cancer in some tissues, and lifetime risk of cancers is strongly correlated with the total number of divisions of the normal self-renewing cells maintaining tissues homeostasis. Such mutations arise during DNA replication of non-cancerous stem cells [4]. The origin of cancer stem cells (CSCs) within a tumor has not been clarified.

The SMT theory is now supplemented by a theory called the Tissue Organization Field Theory (TOFT), which suggests that the origin and subsequent behavior of cancer results from disorders of the microenviromental tissue of the cell in which tumor arises, lives and grows. In molecular dialog in this zone and cells communication participate a variety of host cells (e.g. endothelial cells, pericytes, fibroblasts, inflammatory cells), soluble factors and structural components, such as ECM proteins (e.g. integrins, metalloproteinases), various GFs and their receptors, as well as

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