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Review

New advances on the functional cross-talk between insulin-like growth factor-I and estrogen signaling in cancer

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ABSTRACT

There is increasing awareness that estrogens may affect cell functions through the integration with a network of signaling pathways. The IGF system is a phylogenetically highly conserved axis that includes the insulin receptor (IR) and the insulin-like growth factor I receptor (IGF-IR) pathways, which are of crucial importance in the regulation of metabolism and cell growth in relationship to nutrient availability. Numerous studies nowadays document that estrogens cooperate with IGF system at multiple levels both in physiology and in disease. Several studies have focused on this bidirectional cross-talk in central nervous system, in mammary gland development and in cancer. Notably, cancer cells show frequent deregulation of the IGF system with overexpression of IR and/or IGF-IR and their ligands as well as frequent upregulation of the classical estrogen receptor (ER)α and the novel ER named GPER. Recent studies have, therefore, unraveled further mechanisms of cross-talk involving membrane initiated estrogen actions and the IGF system in cancer, that converge in the stimulation of pro-tumoral effects. These studies offer hope for new strategies aimed at the treatment of estrogen related cancers in order to prevent an estrogen-independent and more aggressive tumor progression.

Contents

1. The IGF-I system

In mammals the IGF system includes at least three ligands, insulin and the insulin-like growth factors I and II (IGF-I and IGF-II), six high-affinity binding proteins (IGFBP-1 to 6) and four cell surface receptors (*i.e.* the IGF-I receptor (IGF-IR), the insulin receptor (IR), the insulin receptor-related receptor (IRR) and the Mannose-6-phosphate/IGF-II receptor (M6P/ IGF-IIR). So far, the latter two receptors are the less studied. IRR is a poorly characterized orphan receptor, whose function is still unknown. The M6P/IGF-IIR is a structurally distinct, multifunctional transmembrane glycoprotein, with no enzymatic activity. Its main function is to target IGF-II to endocytosis and to lysosomal degradation, thus reducing IGF-II signaling [1].

Insulin and IGFs are phylogenetically related peptides that play a major role as regulators of energy metabolism as well as development, growth and reproduction in response to nutrient availability [2,3].

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Insulin is mainly produced by pancreatic β cells and it reaches target tissues (for instance liver, muscle and adipose tissue) through the circulation to promote proper metabolism, energy balance and maintenance of normal body weight. By contrast, IGF-s are largely secreted from the liver, but also by extrahepatic tissues. IGF-I is mainly under the control of the pituitary growth hormone (GH) [4–7], while the regulation of IGF-II is less well understood [8]. The expression of IGFs is also influenced by several hormones including estrogens, thyrotropin, adrenocorticotropic hormone, as well as other growth factors such as EGF (Epidermal Growth Factor), FGF (Fibroblast Growth Factor), PDGF (Platelet-Derived Growth Factor). Noteworthy, while insulin largely circulates in free form, more than 90% of IGFs circulates bound to IGFBPs, which regulate both the half-life and the biological effects of IGFs [9]. IGFBP-1 and IGFBP-3 are the best characterized of the six circulating IGFBPs [9]. IGFBP-3 binds with the same affinity both IGFs and, by increasing their half-life, it provides an IGFs reservoir [9]. In physiological conditions, insulin and IGF-I are regulated by the endocrine system and act as hormones, and specifically bind to their cognate receptor (IR and IGF-IR respectively). However, in cancer tissues both IGF-I and IGF-II are often locally produced in a deregulated manner and act through autocrine and paracrine mechanisms [10].

IR and IGF-IR, are tetrameric glycoproteins composed of two extracellular α- and two transmembrane β-subunits linked by disulfide bonds and belong to the tyrosine-kinase growth factor receptors superfamily [11,12]. The α-subunits contain the ligand-binding site while the β-subunits contain the tyrosine kinase domains. These two receptors share more than 50% overall amino acid sequence homology and 84% homology in the tyrosine kinase domains. The transmembrane domain has a crucial role in recruiting intracellular mediators [13] through two conserved tyrosine residues.

The IR exists in two isoforms that differ for the inclusion (isoform B or IR-B) or the exclusion (isoform A or IR-A) of 12 aminoacid residues encoded by exon 11 [14,15]. These two IR isoforms appear to have different ligand specificity and tissue distribution [16].

Because of the high sequence similarity between the IR and the IGF-IR [11,12], IGFs and insulin are able to cross-bind to each other's receptor, albeit with much weaker binding affinity than that for the cognate ligand. With regard to IR, although both isoforms bind insulin with high affinity, they differ for the affinity for IGFs. IR-B has low affinity for both IGFs, while IR-A binds to IGF-II with relatively high affinity and IGF-I with lower affinity. IGF-IR exhibits high binding affinity for IGF-I, relatively high affinity for IGF-II and poor affinity for insulin [17]. Moreover, because of the high sequence homology, IR hemireceptors may assemble with IGF-IR hemireceptors forming hybrid IR/IGF-IR receptors (HRs), which have similar affinity for IGFs than IGF-IR [18–20]. HRs containing the IR-A isoform may also be activated by insulin, although with low affinity [21]. Although the biological functions of HRs remain largely unknown, these receptors may have a significant role in cancer where they are often expressed at high levels [22].

Activation of IR and IGF-IR is initiated when ligands bind to the extracellular α-subunit, which undergoes to a conformational change that activates the tyrosine kinase activity and trans-phosphorylation of the β-subunits. Intra-chain phosphorylation allows the recruitment and activation of numerous docking proteins, including the IRS family members (IRS-1, IRS-2) and adaptors molecules, among which Shc and Grb2 [23,24]. These substrates, in turn, are involved in the activation of transduction pathways that transmit the receptor signals to intracellular signaling cascades like mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K) and the Janus kinase/signal transducer and activator of transcription pathway (JAK/STAT), which mediate important biological responses as glucose metabolism regulation, cell proliferation, inhibition of apoptosis, cell size, cell survival [10,25–27]. Classically, IR and the activation of the downstream PI3K signaling pathway have been considered as the metabolic branch of the IGF system while IGF-IR and the MAPK dependent signals as mediators of mitogenic effects. However, insulin by binding to IR, may also mediate mitogenic effects linked to the activation of both MAPK and PI3K. These two pathways are interconnected and may converge on the common mTOR/p70S6k axis that is involved in cell growth, survival and metabolism. The preferential activation of specific signals depends on many variables that may affect the predominant metabolic or mitogenic effect of the IGFs components. Thus, on the basis of these variables, IR and IGF-IR and their specific ligands may induce similar or different effects. The mechanisms of signaling overlaps and diversification of the IGF system components have been the subject of numerous studies but remain still not fully clarified. For instance, the crosstalk of the IGF axis with other systems (oncogenes, tumor suppressors, tyrosine kinase receptors, steroid hormones) represents not only one of these mechanisms of diversification between the IGF-IR and IR signaling but also a key point to understand the role of each IGF system components in several physiological and pathological processes, including cancer. For instance, by inducing membrane-initiated effects, sex steroids may elicit IGF-IR, but not IR, upregulation (see below).

The evidence for the involvement of the IGF system in the development and progression not only of prostate cancer but also of several other malignancies arises from a large body of recent *in vitro* and *in vivo* studies [10,28]. The activation and expression of components of the IGF signaling trigger proliferation, angiogenesis, metastasis, and resistance to apoptosis in different types of tumors [29–32]. Further corroborating these findings, epidemiological studies have shown that elevated IGF-I plasma concentrations are associated with a higher risk of developing different malignancies, like breast, colon, prostate, and lung carcinomas [33–36] and that diseases characterized by hyperinsulinemia (type 2 diabetes and obesity), are associated with an increased risk for cancer [37]. Furthermore, recent studies have partially elucidated the molecular bases of IR involvement in cancer. These include the aberrant expression of IR in malignant cells, namely of IR isoform A, which is a second receptor for IGF-II [38], and the formation of IR/IGF-IR hybrids [22]. To increase the complexity of the mechanisms responsible for the involvement of the IGF system in cancer, is the observation that IGF-IR overexpression and autocrine and/or paracrine production of IGF-IR ligands, like IGF-I and IGF-II, induce tumor initiation and progression [28,39]. Indeed, *in vivo* studies have shown that an abnormal expression of the IGF-IR or its ligands IGF-I and IGF-II is linked with cancer initiation in various organs and with accelerating tumor metastasis [40–46]. Because of its permissive role in cell transformation and its deregulated expression in a variety of malignancies, the IGF system has been considered an excellent target for anti-cancer therapies [47–49].

2. Estrogen signaling

Estrogens are key regulators of growth and differentiation in a broad range of target tissues, including the reproductive organs, mammary gland, the nervous, cardiovascular and skeletal systems [50,51]. Estrogens are also involved in many pathological processes, particularly breast and endometrial tumors [52]. The biological effects of estrogens are mainly mediated by the binding to and activation of the estrogen receptor(ER)α, ERβ and the G protein-coupled estrogen receptor (GPER) [53–56]. ERα and ERβ regulate transcription by interacting with the estrogen response elements (EREs) located within the promoter regions of target genes and forming a multiprotein complex which contains co-activators, co-repressors, histone acetyltransferases and histone deacetylases involved in the specific ER action at the tissue levels [57]. In addition to these classical mechanisms, other transcription factors like Sp1, AP1, Runx1 and FOXA1 contribute to the multifaceted ER function [58–61]. In recent years, increasing evidence has also suggested that the biological responses to estrogens can be mediated by membrane-initiated signals, which trigger rapid intracellular transduction pathways like MAPK, PI3K, protein kinase A (PKA), PKC as well as the induction of calcium or nitric oxide levels [62,63]. Fig. 1 shows a