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Invited critical review

Insulin-like growth factor binding protein-related protein 1 and cancer

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ABSTRACT

Insulin-like growth factor binding protein-related protein 1 (IGFBP-rP1) belongs to the IGFBP family whose members have a conserved structural homology. It has a low affinity for IGFs and a high affinity for insulin, suggesting that IGFBP-rP1 may have a biological function distinct from other members of the family. IGFBP-rP1 is ubiquitously expressed in normal human tissues and has diverse biological functions, regulating cell proliferation, apoptosis and senescence; it may also have a key role in vascular biology. Increasing evidence suggests that IGFBP-rP1 acts as a tumor suppressor. It elicits its biological effects by both insulin/IGF-dependent and -independent mechanisms. This paper provides a brief overview of the structure and regulation of IGFBP-rP1 and its various biological functions in cancer, as well as the underlying molecular mechanisms.

Contents

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1. Introduction

The insulin-like growth factor (IGF) system plays a critical role in normal growth and development; it has also been implicated in a range of pathological conditions. In general, IGF-I and IGF-II bind to their specific cell surface receptors (IGF-IR and IGF-IIR) and carry out biological functions through regulating the activation of the phosphatidylinositol 3-kinase (PI-3K) and mitogen-activated protein kinase (MAPK) signaling pathways (Fig. 1). IGFBPs (insulin-like growth factor binding proteins) and IGFBP proteases are important components of the IGF system. Accumulating evidence demonstrates that IGFBPs, as the transporters of IGFs, can prolong their half-life and modulate their bioavailability and function. Additionally, they execute biological activities independently of IGF action [1,2].

Based on different affinities to IGFs, IGFBPs are divided into two groups — IGF high-affinity binding proteins (IGFBP1-6) and IGF low-affinity IGFBP-related proteins (IGFBP-rP1-10). The first IGFBP-related protein to be demonstrated is IGFBP-rP1, also referred to as IGFBP7. IGFBP-rP1 has been cloned in several cellular systems and given different names, such as mac25, angiomodulin, tumor-derived adhesion factor and prostacyclin-stimulating factor. Unlike the conventional IGFBP1-6, IGFBP-rP1 has a low affinity for IGFs and a high affinity for insulin [1]. IGFBP-rP1 exists in a wide range of normal tissues, as well as biological fluids [3,4]. Moreover, its biological functions have been studied in numerous cancers. Most research implicates IGFBP-rP1 as a tumor suppressor gene through the induction of apoptosis and senescence [5–11].

2. Structure and distribution of IGFBP-rP1

2.1. The structure of IGFBP-rP1

Based on sequence homology, members of the IGFBP superfamily comprise three distinct domains — conserved N- and C-terminal domains, and a linker domain. The N-terminal domain contains an IGFBP motif (GCGCCXXC) that plays an important role in IGF binding. The C-terminal domain is also highly conserved, and supports an essential role in binding to IGFs. The linker domain is highly variable among members of the IGFBP superfamily. It has some sites of post-translational modification and proteolysis and coordinates with the IGF binding sites of both the N- and C-terminal domains. Further data indicate that the linker and C-terminal domains mediate IGF-independent actions [1,12,13].

IGFBP-rP1 was the first member of the IGFBP-related family of proteins to be identified; it also has the conserved N-terminal domain and an IGFBP motif (A^{30}CGCCPMCA^{38}). There are 12 conserved cysteine residues in the N-terminal domain, out of a total number of 18. It was originally called IGFBP-7 owing to its ability to bind IGFs via the N-terminal domain [14] (Fig. 2). Yamanaka et al. [15] demonstrated that the protein could bind to insulin and effectively inhibit the phosphorylation of the insulin receptor. They also suggested that the binding site of insulin might be at, or near, the IGF binding site. Sato et al. [16] identified the heparin-binding site K^{89}SRKRRKGK^{97} in IGFBP-rP1, which interacted with heparin sulfates on the cell surface. Homology modeling, docking analysis, interaction energy curve analysis and

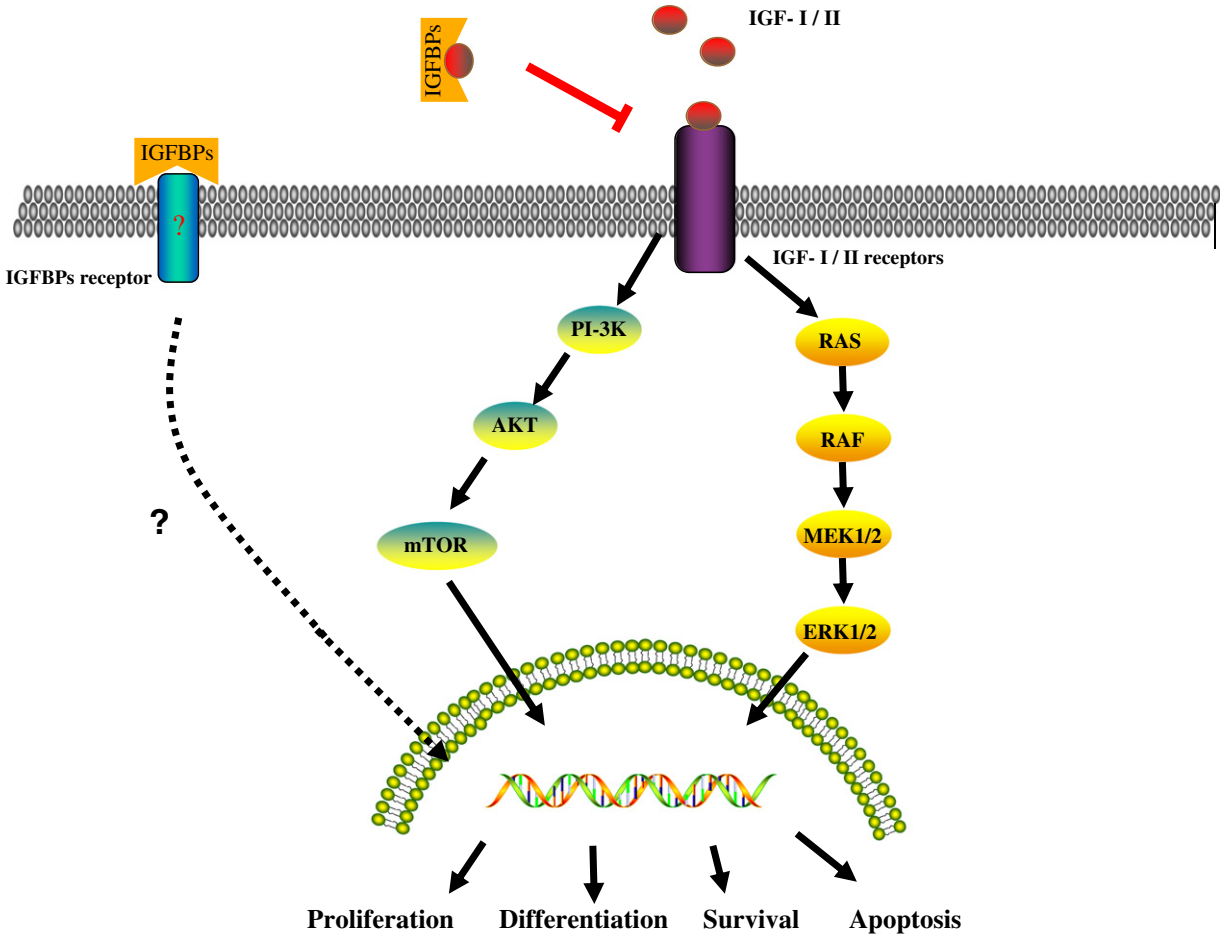

Fig. 1. IGF signaling pathway. By binding with IGFs, IGF receptors display tyrosine kinase activity and activate signaling pathways such as PI-3K/AKT and RAS/MAPK, thus resulting in the functions of proliferation, differentiation, survival and apoptosis. IGFBPs can interact with IGFs and block their actions. The biological effects of IGFBPs may be mediated by as yet uncharacterized cell membrane "IGFBP receptors". PI-3K, phosphatidylinositol 3-kinase; mTOR, mammalian target of rapamycin; MEK, mitogen-activated protein kinase kinase; ERK, extracellular signal-regulated kinase.