Review

Structure and function of the type 1 insulin-like growth factor receptor

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Abstract. The type 1 insulin-like growth factor receptor (IGF-1R), a transmembrane tyrosine kinase, is widely expressed across many cell types in foetal and postnatal tissues. Activation of the receptor following binding of the secreted growth factor ligands IGF-1 and IGF-2 elicits a repertoire of cellular responses including proliferation, and the protection of cells from programmed cell death or apoptosis. As a result, signalling through the IGF-1R is the principal pathway responsible for somatic growth in foetal mammals, whereas somatic growth in postnatal animals is achieved through the synergistic interaction of growth hormone and the IGFs. Forced overexpression of the IGF-1R results in the malignant transformation of cultured cells; conversely, downregulation of IGF-1R levels can reverse the transformed phenotype of tumour cells, and may render them sensitive to apoptosis in vivo. Elevated levels of IGF-1R are observed in a variety of human tumour types, whereas epidemiological studies implicate the IGF-1 axis as a predisposing factor in the pathogenesis of human breast and prostate cancer. The IGF-1R has thus emerged as a therapeutic target for the development of antitumour agents. Recent progress towards the elucidation of the three-dimensional structure of the extracellular domain of the IGF-1R represents an opportunity for the rational assembly of small molecule antagonists of receptor function for clinical use.

Key words. Insulin-like growth factor; insulin; receptors; 3D structure; signalling pathways; apoptosis; cancer therapy.

Introduction

The insulin-like growth factors (IGFs) are essential for normal foetal and postnatal growth and development. Targeted ablation of the Igf-1 gene results in embryonic growth deficiency, manifested as dwarfism at birth, and impaired postnatal growth and infertility in mice [1, 2]. Functional inactivation of the Igf-2 gene also compromises embryonic growth but has little effect on relative growth rates following birth [3]. Two members of the same family of cell-surface receptors mediate the diverse cellular effects elicited by IGF-1 and IGF-2. The type 1 IGF receptor (IGF-1R), a member of a family of transmembrane tyrosine kinases that includes the insulin receptor (IR) and the orphan insulin receptor-related receptor (IRR), binds IGF-1 with high affinity and initiates the physiological response to this ligand in vivo [4]. The IGF-1R also binds IGF-2, albeit with lower affinity, and is in part responsible for the mitogenic effects of this polypeptide during foetal development [2]. Mice lacking functional IGF-1Rs are born weighing less than half the normal weight, and die soon
thereafter [1]. An alternately spliced form of the IR that lacks exon 11 and is expressed in many foetal tissues has recently been identified as binding IGF-2 with high affinity [5], confirming an earlier genetic study implicating the IR in the growth-promoting effects of IGF-2 [6]. A third receptor, the mannose-6-phosphate receptor, also binds IGF-2 and regulates its bioavailability by internalizing and targeting bound ligand for lysosomal degradation [7]. Finally, there exist at least six soluble IGF-binding proteins (IGFBPs), to which the majority of circulating IGFs are bound, that act to modulate the biological activity of both growth factors [8].

Endocrinologically, signalling through the IGF-1R has traditionally been viewed in the context of its impact on somatic growth, in particular the synergistic relationship with growth hormone (GH) that is essential for normal postnatal growth [9]. However, a number of experimental observations made earlier this decade have served to broaden the cellular roles played by this axis, under both normal and pathophysiological conditions. First, it was found that IGF-1 was effective in rescuing neuronal [10], haematopoietic [11] and fibroblast [12] cell types from programmed cell death (apoptosis), thereby establishing IGF-1 as a ‘cell survival factor’. Second, ablation of IGF-1R expression (apoptosis), thereby establishing IGF-1 as a ‘cell survival factor’. Second, ablation of IGF-1R expression significantly impaired the progression of fibroblasts through the cell cycle in serum-rich conditions, and significantly impaired the progression of fibroblasts [12] cell types from programmed cell death (apoptosis), thereby establishing IGF-1 as a ‘cell survival factor’.

First, it was found that IGF-1 was effective in rescuing neuronal [10], haematopoietic [11] and fibroblast [12] cell types from programmed cell death (apoptosis), thereby establishing IGF-1 as a ‘cell survival factor’. Second, ablation of IGF-1R expression (apoptosis), thereby establishing IGF-1 as a ‘cell survival factor’. Second, ablation of IGF-1R expression significantly impaired the progression of fibroblasts through the cell cycle in serum-rich conditions, and prevented entry into S phase in the presence of mitogenic growth factors [13]. These in vitro studies reflected the in vivo effects of the germline deletion of both Igf-1r alleles on embryonic growth, in that the severe growth retardation observed during the second half of gestation resulted principally from a deficit of cellular proliferation events. Finally, and perhaps most provocatively, fibroblast cell lines established from Igf-1r knockout mice were resistant to oncogenic transformation by a variety of viral and cellular oncogenes [13]. Conversely, overexpression of IGF-1Rs promoted the neoplastic transformation of normal fibroblasts in a ligand-dependent manner [14]. These observations have provided a foundation that has resulted in a wealth of knowledge about the role played by the IGF axis not only in normal cellular development, but also in malignant transformation [15]. As a result, the IGF-1R has emerged as a candidate therapeutic target for the treatment of human cancer.

IGF-1 receptor: discovery and sequence

The first evidence for the presence of an IGF receptor distinct from IR came in 1974 when 125I-labelled insulin and 123I-labelled NSILAs (soluble fraction of nonsuppressible insulin-like activity) were used to label distinct proteins in purified rat liver plasma membranes [16, 17]. The IGF-1R could be solubilized with nonionic detergents [18] and was subsequently shown by SDS gel electrophoresis to resemble IR in being a homodimer composed of two α and two β chains held together by disulfide bonds [19–21]. The solubilized IGF-1R and IR proteins could be selectively immunoprecipitated by the three monoclonal antibodies z1R-1, z1R-2 and z1R-3 [22]. When expressed in the presence of monensin, an inhibitor of posttranslational processing, the IGF-1R was shown to be synthesized as a 180-kDa precursor [23] which is glycosylated, dimerized and proteolytically processed to yield the mature αβ2 receptor. The next key discovery was the demonstration that IGF-1R, like IR, is a tyrosine kinase which is activated and autophosphorylated following IGF-1 binding [24, 25].

The complementary DNA (cDNA) for human (h) IGF-1R was cloned and sequenced in 1986 [26]. It consists of 4989 nucleotides and codes for a 1367-amino acid precursor (fig. 1). The preproreceptor includes a 30-residue signal peptide (residues −30 to −1) and an Arg.Lys.Arg.furin protease cleavage site at residues 708–711 which results in the production of an α chain (residues 1–707) and a β chain (residues 712–1337). The α chain and 195 residues of the β chain comprise the extracellular portion of the IGF-1R and contain 11 and 5 potential N-linked glycosylation sites, respectively [26]. There is a single transmembrane sequence (residues 906–929) and a 408-residue cytoplasmic domain containing the tyrosine kinase. The cDNA for the hIR and the third member of the IR family, hIRR, have been cloned and sequenced and are similarly organized [27–29]. The human IGF-1R gene is greater than 100 kb in size and contains 21 exons, 10 in the α chain and 11 in the β chain [30]. No evidence for an exon equivalent to the alternatively spliced exon 11 of hIR was found. An alternate human IGF-1R messenger RNA (mRNA) transcript has been reported, in which a 3-bp (CAG) deletion results in the substitution of Arg for Thr898Gly899 (fig. 1), eight residues upstream from the start of the transmembrane region of hIGF-1R [31]. The CAG+ isoform shows reduced internalization and enhanced signalling properties compared with the CAG− isoform [32].

The ligands (insulin, IGF-1 and IGF-2) share a common three-dimensional (3D) architecture [33] and can bind to each other’s receptor in a competitive manner. The hIRR ligand is unknown.