Best Practice & Research Clinical Endocrinology & Metabolism 29 (2015) 713–722

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

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Insulin-like growth factor binding proteins 4-6

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ARTICLE INFO

Article history:
Available online 27 June 2015

Keywords:
insulin-like growth factor
binding protein
protein structure
regulation
cellular action

Insulin-like growth factor binding proteins (IGFBPs) 4-6 have important roles as modulators of IGF actions. IGFBP-4 and IGFBP-6 predominantly inhibit IGF actions, whereas IGFBP-5 may enhance these actions under some circumstances. IGFBP-6 is unique among the IGFBPs for its marked IGF-II binding preference. IGFBPs 4-6 are found in the circulation as binary complexes with IGFs that can enter tissues. Additionally, about half of the circulating IGFBP-5 is found in ternary complexes with IGFs and an acid labile subunit; this high molecular complex cannot leave the circulation and acts as an IGF reservoir. IGFBPs 4-6 also have IGF-independent actions. These IGFBPs are regulated in a cell-specific manner and their dysregulation may play a role in a range of diseases including cancer. However, there is no clear clinical indication for measuring serum levels of these IGFBPs at present.

Insulin-like growth factor (IGF)-I and −II have essential roles in normal growth and development [1]. They are widely expressed in most tissues, circulate in nanomolar concentrations in human serum, and have endocrine, autocrine and paracrine actions. As well as promoting growth mainly through the IGF-I receptor, they have insulin-like actions as a result of their homology with proinsulin and ability to bind to the insulin receptor [2]. The IGF-II/mannose 6-phosphate receptor mainly regulates IGF-II clearance, although some IGF-II actions mediated by are this receptor. IGF-II also has mitogenic actions mediated by the IR-A isoform of the insulin receptor [3]. IGF actions are finely regulated by a family of six high affinity IGF binding proteins (IGFBPs) that share a high degree of sequence homology.

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http://dx.doi.org/10.1016/j.beem.2015.06.002
1521-690X/

Most IGFBPs have also been reported to have IGF-independent actions. The biology of IGFBPs 1-3 are covered in other chapters of this issue, so this chapter will focus on IGFBPs 4-6 (Table 1).

Insulin-like growth factor binding proteins

IGFBPs share a three-domain structure [4]. The N- and C-terminal domains are each highly conserved between IGFBPs and internally disulphide-linked, and both of these domains play a role in high affinity IGF binding. They are connected by a linker domain that is predominantly unstructured and is not conserved between IGFBPs. Linker domains do not directly contribute to IGF binding but contain sites for limited proteolysis that may be a mechanism for release of bound IGFs, as well as sites of post-translational modifications that modify IGFBP actions such as glycosylation and phosphorylation. Many of the IGF-independent actions of IGFBPs are mediated via interaction of their C-terminal and linker domains with glycosaminoglycans, specific membrane proteins including integrins, and importins.

IGFBP-3 accounts for more than 60% of circulating IGFBPs [5]. More than 90% of circulating IGFBP-3 is found in a high molecular weight ternary complex with IGF-I or IGF-II and an acid-labile subunit. This complex is unable to leave the circulation and prolongs the half-life of IGFs. As discussed below, IGFBP-5 is also found in ternary complexes, but it and other IGFBPs form binary complexes with IGFs that can enter tissues. IGFBPs bind over 99% of circulating IGFs.

In most circumstances, IGFBPs inhibit IGF actions. They bind IGFs with higher affinity than IGF receptors, and this sterically hinders IGF binding to IGF receptors at adjacent molecular surfaces. Some IGFBPs also enhance IGF actions in certain conditions. Although incompletely understood, it has been postulated that these IGFBPs may concentrate IGFs near receptors by binding to extracellular matrix or cell surfaces, and that decreased IGF affinity consequent upon IGFBP binding to glycosaminoglycans and/or local proteolysis may optimise IGF presentation to these receptors. Although the mechanisms of IGF-independent actions of IGFBPs are incompletely understood, different IGFBPs bind of to a range of non-IGF proteins and other biomolecules [6].

IGFBP-4

Structure

Mature human IGFBP-4 has 237 amino acids [7]. In addition to the 18 disulphide-linked cysteine residues that are conserved in the N- and C-domains of IGFBPs 1-5, it also has a disulphide-linked cysteine pair in its linker domain. The first 38 amino acids of the N-domain of IGFBP-4 form a rigid, disulphide bonded, ladder-like structure and the remaining residues form a globular high-affinity IGF binding site [8]. IGFBP-4 is found in a non-glycosylated 24 kDa form and a 28 kDa form that is N-glycosylated on Asn^{104}. Glycosylation of IGFBP-4 reportedly has no effect on IGF binding or its susceptibility to proteolysis [9].

Table 1
Features of IGFBPs 4-6.

IGFBP-4	• Predominantly inhibits IGF actions • Cleaved by PAPP-A • Possible IGF-independent actions
IGFBP-5	• Inhibits and potentiates IGF actions • IGF-independent actions • Binds to extracellular matrix • Nuclear localisation
IGFBP-6	• IGF–II binding preference • Predominantly inhibits IGF-II actions • IGF-independent actions • Nuclear localisation