Binding Proteins of Somatomedins and their Functions

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One variable that provides insulin-like growth factors (IGFs) control at the extracellular level is the presence of high-affinity, soluble insulin-like growth factor binding proteins (IGFBPs). Their ability to form complexes with IGFs influences IGFs transport to receptors on cell surfaces and so also IGFs effects on cell proliferation (1). IGFBPs are proteins with different size, they are produced by many different tissues and they bind to IGF-I, IGF-II, but not to insulin. There are 8 well characterized forms of IGFBPs with different molecular weight, amino acid composition, binding properties and distribution in biological fluids. Growth hormone-independent IGFBP-1 obtained from human amniotic fluid was originally isolated from human placenta as placental protein 12 (2). Non-phosphorylated and phosphorylated forms of IGFBP-1 have already been found in human amniotic fluid, fetal serum and decidua (3). Busby et al. (4) have isolated two forms of IGFBP-1 (31 kDa) from amniotic fluid with different biological effects: the first one had inhibitory effect on ^{3}H-thymidine incorporation into smooth muscle cell DNA and the second one worked as activator. In animals (sheep and goats) there are besides IGFs also proteins with higher molecular weight, which are mitogenically active in BP-A31 cell culture (5). It seems that their properties are the same or very similar to that of human IGFBP-1 and IGFBP-3 (6). IGFBP-2 (32–34 kDa) is present in human cerebrospinal fluid, seminal plasma and lympha, in rat amniotic and cerebrospinal fluid, in chicken vitreal fluid (7) and in porcine follicular fluid (8). High concentrations of IGFBP-2 in rat fetal tissues and in porcine fetal serum decrease in postnatal life (9, 10). In preference IGFBP-2 binds to IGF-II, which is the important regulator in fetal growth (11). IGFBP-3 (53 kDa) is growth hormone-dependent, binds to IGF-I or -II with high affinity, can function as inhibitor or activator of IGF-I. IGFBP-3 is the dominant binding protein in blood in 40-fold higher concentration than IGFBP-1 and with higher affinity to IGF-I (1). Other IGFBPs (-4,-5,-6,-7,-8) are different from each other similarly as above mentioned by molecular weight, distribution in tissues and amino acid composition (12, 13, 14). Moreover IGFBP-7 and -8 in contrast to others have low affinity to IGFs. IGFBP-8 is probably connective tissue growth factor (15). IGFBPs carrier IGFs in circulatory system, they can cause inhibition of IGFs effects or total inactivation of growth factor. In certain situation they are able to potentiate the IGFs effects. 75–90 % of total IGF-I (1mg/ml in human adults) in serum are bound to ternary protein complex with molecular weight about 150 kDa and with long half-life (12–16 hours). 10–25 % of total IGFs form binary complex with molecular weight 28–35 kDa and with short half-life (about 30 minutes) (16,17). Less than 1 % of total IGF-I circulate in free form and its half-life is about 10 minutes (1). Potentiation phenomenon of IGFs effects by IGFBPs is characterized by phosphorylation, then association to cell surface or to extracellular matrix and proteolysis. Proteolysis of IGFBP-3, -4 and -5 decreases their affinity to IGF-I for 50–100-fold. Binding of IGFBPs to IGFs inhibits IGFs association to target cells and so IGFs effect is weak (9). IGFBP-1 inhibits IGF effect on human osteosarcoma cells. Increased concentration of IGFBP-3 inhibits the proliferation of breast cancer cell line MCF_7 either directly or by competition for IGF receptors. Maybe IGFBPs work as antimitogens and IGFs are potential promotors of cancer growth.

Acknowledgements. This work was supported by RVT Grant RVO6O6 and VEGA Grant No.1/5150-98.

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