Progress in the Research of Insulin-like Growth Factors and the Binding Proteins

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Abstract: Insulin-like growth factors are the very important growth factors. They interact with the receptors and the binding proteins. Insulin-like growth factors play very important regulated roles in the cell proliferation, growth and pathogenesis of cancers. In this paper we summarized progress in the research of Insulin-like growth factors and the binding proteins. [Nature and Science. 2007;5(3):82-86]. (ISSN: 1545-0740).

Keywords: Insulin-like growth factors; mitogenic; binding proteins

1. Introduction

In 1957, Salmon and Daughaday[1] first found that IGF-1 and IGF-2 could promote the cartilage to absorb 35s in sulphate. They named them as sulphation factors. In 1963, Froesch[2] described them as NSILA1 and 2.

In 1972, they were named as Somatomedin [3] in 1976, Rinderknecht and Humbel[4] isolated two active factors. They shared high degree of structural homology with insulin. They renamed them as insulin-like growth factor-1 and insulin-like growth factor-2 (IGF-1 and IGF-2). In 1978, Rinderknecht and Humbel identified the structure and characteristic of IGF-1 and IGF-2[5].

The IGF system is a complex network, consisting of the two IGF peptides (IGF-1 and IGF-2), two IGF receptors, eight well characterized IGF binding proteins (IGFBPs). In this article, we summarized the progress in the research of Insulin-like growth factors system..

2. Insulin-like growth factors family

Insulin-like growth factors (IGFs) consist of IGF-1 and IGF-2. Because they have high degree homology to insulin, they were called insulin-like growth factors. IGF-1 has 49% homology to insulin. IGF-2 has 47% homology to insulin. IGF-1 has 62% homology to IGF-2 in human. The IGF system is extremely complex.

IGFs have two forms[6] in serum in vivo: the protein complex, IGFs combine with IGF binding proteins, and the free form. IGFs can synthesize in different period and different tissues. The mainly resource is in liver, about 90% of total IGFs. Insulin-like growth factors play very important regulating roles in the cell proliferation, growth and pathogenesis of cancers with autocrine and paracrine two manners. They can promote cells from cell cycle G1 to S[7], and involve in the proliferation of cancer cells[8].

IGF-I and IGF-II play essential roles in cell metabolism, proliferation and differentiation and to this extent have major effects on fetal and postnatal development and organogenesis in mammals [9,10].

IGFs have the same function as insulin: cellular hypertrophy. But the consequences are different. The IGFs enhance the cell hypertrophy is requisite for cell survival, hyperplasia, and differentiation, and insulin enhances cell hypertrophy primarily as a means to increase nutrient stores[11]. They have distinct roles in regulating nutrient utilization. They have different receptor locations. These hormones can differentially regulate metabolism.

The activity IGFs is controlled by several inputs, such as energy intake, protein intake, body temperature, environment temperature, environment stress micronutrient[11] etc. These inputs not only regulate IGF secretion but also localization and circulating half-life by regulating IGFBPs levels.

2.1 IGF-1 and its biological function

Insulin-like growth factor-1 (IGF-1) is a single-chain polypeptide with 70 amino acid. The weigh of it is 7649Da[12]. Human IGF-1 locates on chromosome 12,and it has five extrons. IGF-1 has four domains,

they are domain B,C,A and D. It has highly conservation in mammal animals. IGF-I is growth hormone dependent, produced by the liver and extra hepatic tissues[13] . It stimulates DNA synthesis as a progression factor in the cell cycle[14]. IGF-1 plays an essential role in growth, differentiation, regeneration, and metabolism in all vertebrates[15].

In vivo, IGF-1 mimics the effects of growth hormone. IGF-1 is considered to be the major somatomedin in humans. In cells, IGF-1 mediates either short-term, insulin-like effects, which include metabolic effects such as stimulation of glucose uptake, glycogen, and lipid synthesis, or long-term mitogenic effects such as stimulation of protein, RNA, and DNA synthesis[16]. IGF-1 promotes mesoderm, adipocyte, neuron, oligodendrocyte, ovary, and testicular cell differentiation.

2.2 IGF-2 and its biological function

Insulin-like growth factor-2 (IGF-2) is a protein with 67 amino acid. The weigh of it is 7471Da. Human IGF-1 locates on chromosome11 and close to insulin. It has nine extrons and four promoters (Figure 1). IGF-2 also has four domains, they are domain B,C,A and D.

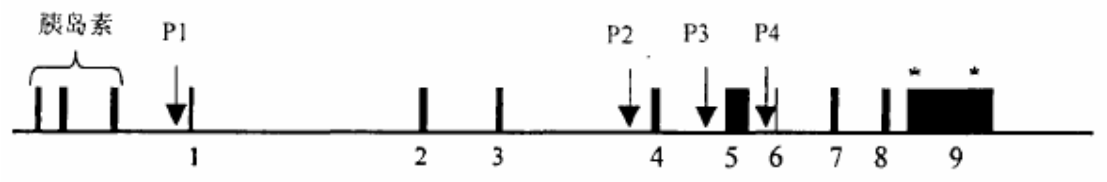

Figure 1. Insulin-like growth factor-1 (IGF-1)

The main function of IGF-2 in humans is not clear. In rodents, IGF-2 may function as a fetal growth factor; the levels of IGF-2 in fetal rat plasma are high and decline after birth[17]. IGF-2 values in adults are about four times higher than those of IGF-I[18].

The secretion of IGF-2 is usually high in the fetus. The concentration of IGF-2 will decline to different degrees after birth. It is synthesized primarily by the liver, but it is also produced locally by many tissues, where it acts an autocrine or paracrine manner.

IGF-2 stimulates glycogenesis in 18-day-old fetal hepatocytes cultured in the presence of glucocorticoids and this stimulation is regulated by secreted IGFBPs, especially IGFBP-1, which is the predominant IGFBP secreted by these cells[19]

Recently, the researches on IGF-2 are related to its imprinted gene. Genomic imprinting is a method of gene regulation whereby a gene is expressed in a parent-of-origin dependent fashion[20]. Paternally expressed IGF-2 encodes for a critical fetal mitogen, and mice deficient in this growth factor have a dwarf phenotype

IGF-2 and H19 (Figure 2) are closely linked imprinted genes lying at the centromeric end of a 1Mb imprinted domain on mouse chromosome7[21]. They are expressed only from the paternal and the maternal allele, respectively.

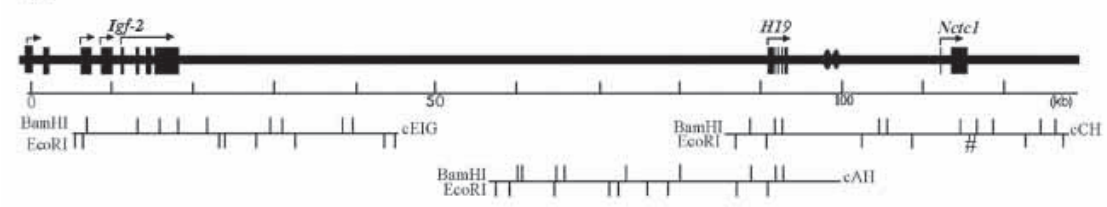

Figure 2. Insulin-like growth factor-2 (IGF-2)

3. Insulin-like growth factor binding proteins

In biological fluids, IGFs are normally bound to specific binding proteins, insulin –like growth factor binding proteins, IGFBPs[22]. They are belong to a structurally related secreted proteins family which has 8 members. IGFBPs specifically bind IGFs and modulate IGF bioactivity in different tissue[23]. They have two mechanisms: inhibitory mechanism and enhancing mechanism.

The IGFBPs deliver the IGFs to the cell surface, endowing the capability to IGF activity. IGFBPs and IGFs adhere to cell surfaces, their affinity drops and IGFs are released. The concentration of free IGFs

increased on the cell surface. It increases the potential for the cativation of IGF receptors and then expedites IGF activity.

Recently, multivalent cations were found [24] to control the adherence of IGFBP to cell surfaces. Both Zn2+ and La3+ (but not Mn2+) retain specific IGFBP on cell surfaces: IGFBP-3 on human GM-10 fibroblasts, IGFBP-3 on bovine MDBK kidney epithelial cells [24]. Zn2+ is also an important cation that controls IGFs access to cell. Some researches showed that the growth rate would decrease during Zn deficiency[25].

IGFBP-1, 25 to 34 kDa, is growth hormone-independent. It is the most important binding protein in amniotic fluid. Hepatic IGFBP-1 expression increases with stage of development, with a peak around birth[26], and is strongly enhanced in the presence of glucocorticoids[27]. IGFBP-1 is expressed largely in the liver and endometrium, suggesting that it plays some specific role in each organ [28.29].

IGFBP-2 , 32 to 34 kDa, is present in human cerebrospinal fluid, seminal plasma and lymph, in rat amniotic and cerebrospinal fluid.

The ability of IGFBP-1 and IGFBP-2 to expedite IGF activity requires a serum-derived factor [30]. The ability to expedite activity was directly related to the ability of these IGFBP to adhere to cell surfaces[30.31] . IGF-binding protein-2 was the predominant binding protein secreted by neonatal rat vascular smooth muscle cells. The predominant expression of IGFBP-2 in vascular smooth muscle cells from neonatal rats suggests that this protein may play a role in the development or growth of the vasculature and is consistent with the observation that IGFBP-2 is a major binding protein in fetal serum and fetal brain [32]. Generalized overexpression of IGFBP-2 in transgenic mice results in a 10–13% reduction of total body weight in adult animals[33].

IGFBP-3, 53kDa，is the most important binding protein. binds to IGF-1 or -2 with high affinity, can function as an inhibitor or activator of IGF-1 stimulated DNA synthesis. IGFBP-3 is a dominant binding protein in the blood in 40 times higher concentration than IGFBP-1 and with higher affinity to IGF-1. The majority of circulatory IGF-1 is bound to IGFBP-3[34]. Pioneer work by Harel and co-workers suggested that IGFBP-3 was also capable of inhibiting cell growth independently of its binding to IGFs [35].

IGF-binding protein-4 was most prevalent in adult vascular smooth muscle cells coincident with increased IGF-binding protein-4 protease activity[36].

IGFBP-5, 23 kDa, was purified by Andress and Birnbaum[37] from human osteoblast-derived culture. It stimulates osteoblast mitogenesis.

IGFBP-6, 30 to 32 kDa, was isolated from the human cerebrospinal fluid. It has high affinity to IGF-2 to IGF-1 about 10 times.

IGFBP-7,-8 have no affinity to IGFs, but have high affinity to insulin.

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