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Review

Insulin-like growth factors (IGFs), IGF receptors, and IGF-binding proteins: Roles in skeletal muscle growth and differentiation

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ABSTRACT

The insulin-like growth factor (IGF) signaling pathway consists of multiple IGF ligands, IGF receptors, and IGF-binding proteins (IGFBPs). Studies in a variety of animal and cellular systems suggest that the IGF signaling pathway plays a key role in regulating skeletal muscle growth, differentiation, and in maintaining homeostasis of the adult muscle tissues. Intriguingly, IGFs stimulate both myoblast proliferation and differentiation, which are two mutually exclusive biological events during myogenesis. Both of these actions are mediated through the same IGF-1 receptor. Recent studies have shed new insights into the molecular mechanisms underlying these paradoxical actions of IGFs in muscle cells. In this article, we provide a brief review of our current understanding of the IGF signaling system and discuss recent findings on how local oxygen availability and IGFBPs act to specify IGF actions in muscle cells.

1. Introduction

1.1. The IGF signaling pathway

1.1.1. The IGF ligands

Insulin-like growth factors (IGFs), including IGF-I and IGF-II, are evolutionarily conserved peptide structurally related to insulin. Mature IGF-I and IGF-II consist of A, B, C, and D-domains. The A- and B-domains of IGFs are homologous to those of insulin. Unlike in the case of insulin, the C-domain is not cleaved off in mature IGFs. IGFs contain an additional D-domain, which is not present in insulin (Le Roith et al., 2001).

IGFs are critical for growth and development in all vertebrates studied to date (Wood et al., 2005a). For example, the birth weight of IGF-I or IGF-II knockout mice is about 60% of their wild type littermates (Baker et al., 1993; Liu et al., 1993). Mice with null mutations in both IGF-I and IGF-II have a body weight 30% of their wild type littermates at birth and they invariably died shortly thereafter (Baker et al., 1993; Liu et al., 1993). Over-expression of IGF-I in mice increases the body weight by 30% (Mathews et al., 1988). Likewise, administration of IGF-I peptide to rats increases protein synthesis and body growth (Tomas et al., 1992). IGF-II over-expression resulting from loss of imprinting (LOI) is often associated with somatic overgrowth (Morison et al., 1996; Morison and Reeve, 1998).

In addition to their role in somatic growth, IGFs are important for the development and functional maturation of the central nervous system (CNS), skeletal tissues, and reproductive organs. In humans, a homozygous partial deletion of the IGF-I gene is associated with mental retardation and sensorineural deafness, in addition to severe growth retardation (Woods et al., 1996). In IGF-I knockout mice, there is a significant decrease in auditory neuron number and an increase in apoptosis of cochlear neurons (Camarero et al., 2001). Knockout of the IGF-I gene causes infertility (Baker et al., 1996), and characteristic underdevelopment of muscle tissue is observed in IGF-I null pups (Powellbraxton et al., 1993). Transgenic mice overexpressing IGF-I in the CNS have increased brain growth, neurogenesis, process outgrowth, synaptogenesis, and reduced neuronal apoptosis (D'Ercole et al., 2002). Over-expression of IGF-I in the osteoblasts of transgenic mice leads to improved bone structure, including increased bone density and mineralization (Zhao et al., 2000).

Abnormally high levels of IGFs are found in various tumor cells (LeRoith and Roberts, 2003). Epidemiological studies have suggested high levels of IGF-I as a risk factor in breast, prostate, colon, and lung cancer (LeRoith and Roberts, 2003). Reduced circulating

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IGF-I levels are associated with type 1 diabetes, and IGF-I treatment improved glucose and protein metabolism and attenuates diabetic cardiomyopathy (Carroll et al., 2000; Norby et al., 2002). Over-expression of IGF-I in mouse pancreatic β cells leads to improvement of type 1 diabetes (George et al., 2002). IGF-I treatment increases insulin sensitivity and improves glycemic control in patients with type 2 diabetes (Moses et al., 1996).

1.1.2. The IGF-I receptor

At the cellular level, IGFs induce a variety of cellular responses, including cell proliferation, differentiation, migration, and survival. IGFs exert these biological actions primarily through the binding and activation of the type I IGF receptor (IGF-IR). The IGF-IR has two α subunits and two β subunits linked by disulfide bonds. The α subunit contains a cysteine-rich ligand-binding site. The β subunit has tyrosine kinase activity. The IGF-IR exhibits high sequence and structural similarity with the insulin receptor (IR) (De Meyts and Whittaker, 2002). Given the significant structural similarity between IGFs and insulin, and their respective receptors, it is not surprising that these ligands can cross-activate the receptors when added at high concentrations in cell culture studies. IGF-1R-IR hybrid receptors have also been found, although their functional importance remains poorly understood (Taguchi and White, 2008).

Ligand binding of the IGF-IR induces its autophosphorylation. The activated IGF-IR in turn activates multiple intracellular signal transduction cascades, including the phosphatidylinositol 3-kinase (PI3K)-Akt cascade and the Raf-Mek-Erk1/2 cascade (Dupont and LeRoith, 2001; White, 2003), through the adaptor molecules. IRS-1, a well-studied adaptor protein, has multiple tyrosine residues, which are used as 'docking' sites for downstream signaling molecules. For instance, phosphorylation of these tyrosine residues results in the association of IRS-1 with the Src homology 2 (SH2) domains of other cytoplasmic signaling proteins, including PI3K and growth factor receptor-bound protein 2 (Grb2). Activated PI3K synthesizes membrane associated phosphorylated inositols, which in turn activate phosphoinositol-dependent kinases (PDKs). PDKs then activate other protein kinases including Akt/Protein Kinase B (Cianfarani et al., 2007). The activated IGF-IR also recruits the guanine-nucleotide-exchange factor Sos to IRS-1 through the SH2 domain of the adaptor Grb2 (Dupont and LeRoith, 2001). This leads to the activation of the small G-protein Ras, which activates the protein serine kinase Raf and the Erk signaling cascade (Fig. 1, left panel).

The new-born IGF-IR knockout mice weigh about 45% of their wild type littermates, and they die shortly after birth (Baker et al., 1993; Liu et al., 1993). IGF-IR conditional knockout in the liver decreased the capacity for liver regeneration (Desbois-Mouthon et al., 2006). Selectively disrupting the IGF-IR gene in mouse osteoblasts caused a significant decrease in bone volume, connectivity, and trabecular number (Zhang et al., 2002). Inactivation of the IGF-1R gene in the mouse brain impaired remyelination in re-

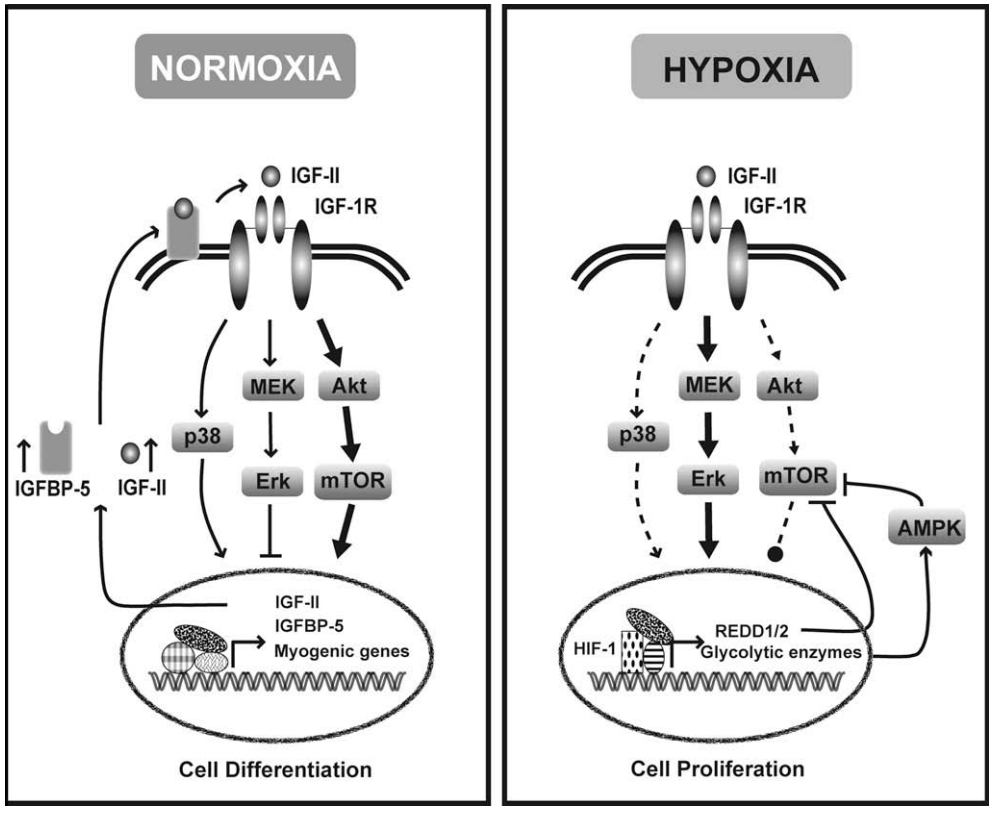

Fig. 1. A proposed model on how IGF signaling acts to stimulate myoblast differentiation and proliferation under normoxic and hypoxic microenvironments. Left panel: Under normoxia, differentiating muscle cells synthesize and secrete IGF-II and IGFBP-5 during myogenesis. IGFBP-5 is induced in early stages of myogenesis and is located on the cell surface. Cell-surface associated IGFBP-5 binds to IGF-II and targets IGF-II to the close proximity of the IGF-1R receptor, thereby enhancing IGF-1R-mediated signaling activity, leading to a further increase in IGF-II gene expression. Binding of the IGF-IR by IGF-II strongly activates the Akt-mTOR signaling pathway and the p38 MAPK pathway (bold line). Both Akt-mTOR and p38 MAPK positively contribute to myogenesis by up-regulating myogenic genes. The Erk1/2 MAPK signaling pathway is also activated by IGF-II, which results in a modest increase in cell number. Right panel: hypoxia alters the cellular response to IGF-II stimulation by suppressing the Akt-mTOR and the p38 MAPK signaling activities (broken lines). The expression of IGFBP-5 is also repressed under hypoxia. Hypoxia, through the activation of HIF-1 complex, up-regulates REDD gene expression, which inhibits mTOR activity. Hypoxia also activates AMPK, which in turn inhibits mTOR activity. Hypoxia/HIF-1 increases glycolysis by up-regulating several glycolytic enzymes. Under the hypoxic conditions, the binding of the IGF-1R by IGF-II preferentially activates the Erk1/2 MAPK signaling pathway. Activation of the Erk1/2 MAPK signaling pathway stimulates cell proliferation and suppresses differentiation in hypoxic microenvironments.