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Insulin-like growth factor-1 signaling in cardiac aging

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ABSTRACT

Cardiovascular disease (CVD) is the leading cause of death in most developed countries. Aging is associated with enhanced risk of CVD. Insulin-like growth factor-1 (IGF-1) binds to its cognate receptor, IGF-1 receptor (IGF-1R), and exerts pleiotropic effects on cell growth, differentiation, development, and tissue repair. Importantly, IGF-1/IGF-1R signaling is implicated in cardiac aging and longevity. Cardiac aging is an intrinsic process that results in cardiac dysfunction, accompanied by molecular and cellular changes. In this review, we summarize the current state of knowledge regarding the link between the IGF-1/IGF-1R system and cardiac aging. The biological effects of IGF-1R and insulin receptor will be discussed and compared. Furthermore, we describe data regarding how deletion of IGF-1R in cardiomyocytes of aged knockout mice may delay the development of senescence-associated myocardial pathologies.

1. Introduction

The prevalence of cardiovascular disease (CVD) increases with aging. Aging affects the integrity of the cardiovascular system in the absence of any disease [1,2]. Cardiac aging is a slow, heterogeneous process characterized by the inability of the heart to maintain appropriate function in response to greater stress or workload, such as ischemia or exercise [3–5]. Cellular senescence was originally described as a process that limits cell division of normal human cells in culture [6], and its definition has been expanded to include growth arrest caused by diverse cellular stresses, including oxidative stress and DNA damage [7,8].

One of the most conserved signaling pathways involved in longevity is the insulin-like growth factor-1 (IGF-1)/insulin signaling pathway. Indeed, mutations in insulin-like receptor (daf-2), IGF-1 receptor (IGF-1R), insulin receptor (IR), and their downstream targets have been shown to prolong lifespan in invertebrates and vertebrates [3,9]. The hormone IGF-1 is a 70-amino acid peptide of 7.6 kDa, which has pleiotropic effects, including autocrine, paracrine, and endocrine effects. About 75% of IGF-1 is synthesized in the liver in response to growth hormone (GH) stimulation and it shares approximately 50% structural homology with pro-insulin and more than 60% homology with IGF-2. IGF-1 exerts negative feedback on the somatotropic axis, consisting of GH-releasing hormone (GHRH), GH, and IGF-1, in the peripheral circulation. However, some IGF-1 can also be produced in target tissues, including the heart, kidney, and cartilage. To control IGF-1, approximately 98% of circulating IGF-1 is bound to IGF binding protein (IGFBP) consisting of 6 subtypes with varying homology. For this particular review, we will focus on IGFBP3, the most abundant IGFBP, that binds with approximately 80% of circulating IGF-1 [10–13]. The IGF-1–IGFBP3 complex binds to a third protein termed acid labile subunit (ALS). This ternary complex has a half-life of 16 h. Conversely the half-life of free IGF-1 is less than 15 min [14,15]. As the concentration of free IGF-1 in normal subjects is less than 1% of the total IGF-1 concentration, formation of this tripartite complex results in most of the IGF-1 and IGF-2 in blood being present in a stable reservoir [16]. The second most abundant IGFBP is IGFBP2. IGFBP2 does not bind to ALS and the IGF-1–IGFBP2 or IGF-2–IGFBP2 complexes have much shorter half-lives of about 90 min [14,15]. A third IGFBP, IGFBP1, accounts for only a small percentage of the IGF carrying capacity. Like IGFBP2, IGFBP1 is generally unsaturated and, therefore, represents a potential regulator of free IGF-1 and IGF-2. IGFBP1 is suppressed by insulin [17]. IGFBP4, IGFBP5 and IGFBP6 are present in lower concentrations and appear to be less important for regulating free IGF concentrations in serum [14,15].

Extensive studies in cancer [18–20], diabetes [21,22], and CVD [23–25] have explored the area of IGF-1 signaling. Particularly in the heart, IGF-1 regulates a number of cellular processes, including senescence, apoptosis, growth, metabolism, and autophagy [10,26–28]. The cardiac effects of IGF-1 are coordinated by activation of plasma membrane IGF-1R, which belongs to the receptor tyrosine kinase family. IGF-1R comprises a α2β2 heterotetrameric complex of approximately

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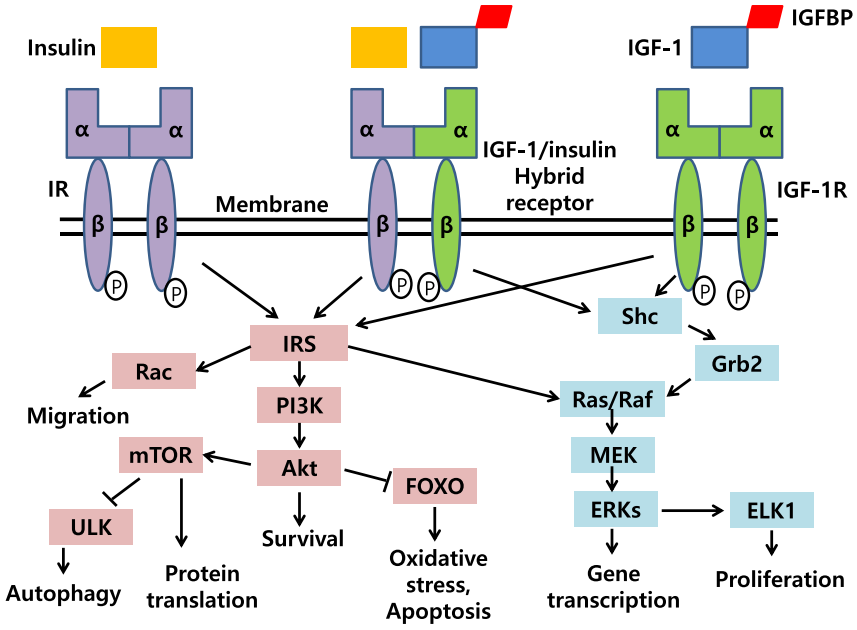

Fig. 1. Insulin-like growth factor 1 (IGF-1) and insulin signaling pathways in cardiomyocytes. Binding of IGF-1 to plasma membrane IGF-1 receptor (IGF-1R) and IGF-1/insulin hybrid receptor leads to receptor autophosphorylation in the intracellular β-subunits. IGF binding proteins (IGFBPs) modulate IGF-1 signaling. High affinity IGFBPs reduce the bioavailability of the ligand and thereby (indirectly) impact on receptor activation. Phosphorylated β-subunits provide docking sites for insulin receptor substrate (IRS), which mediates phosphatidylinositol-3 kinase (PI3K) activation and Akt phosphorylation. Activation of the PI3K and Akt pathway supports cell survival. Downstream targets of activated Akt include mammalian target of rapamycin (mTOR), which promotes protein synthesis and suppresses autophagy. Docking of growth factor receptor-bound protein 2 (Grb2) to the phosphorylated IGF-1R β subunits also induces extracellular signal-regulated kinase (ERK) phosphorylation through the Ras/Raf/mitogen-activated protein kinase (MEK) axis. The Ras/Raf pathway is critical for proliferative responses, whereas activation of Rac is important for cell migration. Phosphorylated ERK can translocate to the nucleus to regulate gene expression. IGF-1, insulin-like growth factor 1; IGFBP, IGF binding protein; IRS, insulin receptor substrate; PI3K, phosphatidylinositol-3 kinase; Akt, serine/threonine protein kinase; mTOR, mammalian target of rapamycin; FOXO, forkhead box O; Shc, Src homology and collagen domain protein; Grb2, growth factor receptor-bound protein 2; MEK, mitogen-activated protein kinase; ELK1, ETS transcription factor.

400 kDa (Fig. 1). Structurally, IGF-1R has two extracellular α-subunits, including the ligand-binding sites, and each α-subunit matches one of two transmembrane β-subunits, which cover an intracellular domain with intrinsic tyrosine kinase activity [10,29,30]. Binding of IGF-1 to its cognate receptor starts a complex signaling cascade in cardiomyocytes [31]. Activation is initiated by triggering the kinase domain in the β subunits, leading to receptor tyrosine phosphorylation and autophosphorylation of multiple substrates [29]. After these initial incidents, the activated signaling is transduced to a complex network of second messengers, intracellular lipids, and serine/threonine kinases that ultimately connect IGF-1 to the regulation of cardiomyocyte hypertrophy, proliferation, metabolism, differentiation, and protection from cell death [10].

In the current review, we discuss the mechanisms of cardiac and cellular senescence associated with IGF-1 signaling pathways. Moreover, we describe the long-term effects of IGF-1R inactivation on cardiac aging.

2. IGF-1 signaling in longevity

The GH and IGF-1 pathways have been shown to affect processes involved in longevity and aging. In *Caenorhabditis elegans*, mutations that reduce the activity of daf-2 result in a doubling of lifespan, and mutations affecting the downstream phosphatidylinositol 3-kinase (PI3K)/serine-threonine protein kinase (AKT) cascade also extend lifespan. Inhibition of IGF-1/insulin signaling extends lifespan through the heat-shock transcription factor (HFS-1), the forkhead box O (FOXO) transcription factor (DAF-16), and through a nuclear respiratory factor (Nrf)-like xenobiotic-response factor protein skinhead 1 (SKN-1) [32]. In concert these transcription factors regulate diverse genes that act cumulatively to produce large effects on lifespan [7,33]. The effects of the IGF-1/insulin pathway on lifespan have been evolutionarily conserved [9,34]. In Drosophila and *C. elegans* for example inhibiting a single IGF-1/insulin signaling pathway or increasing the activity of FOXO (i.e. dFOXO and DAF-16, respectively) extends lifespan [35]. In mammalian systems, growth and glucose metabolism are regulated by two related but also independent pathways, with IGF-1 and insulin having separate receptors, suggesting that their regulation is more complex. As mentioned above, the IGF-IR and IR are highly homologous in the tyrosine kinase domain (84%) but differ markedly in other regions (e.g., only 22–26% homology in the transmembrane domain and 45% homology in the COOH-terminal domain) [36,37], and this may contribute to the biological specificity of the two receptors [36]. Despite these similarities, the ligand binding specificity is strict. The IGF-1R has 1000-fold greater affinity for IGF-1 compared to insulin and the affinity of the IR is 100-fold greater for insulin than IGF-1. IGF-1R and IR densities vary widely among cell types i.e. mature differentiated adipocytes and hepatocytes have abundant IRs whereas they have almost no IGF-1Rs. By contrast, cell types such as vascular smooth muscle cells (VSMCs) have abundant IGF-1Rs and minimal IRs. This difference in receptor distribution accounts for many of the differences in IGF-1 and insulin actions [38]. Although some of the variation can be attributed to different hormone receptor affinities or subcellular localization or divergent tissue distribution, variation can also be explained by differences in the structural differences in the β-subunit (specifically in the C-terminus) or internalization of the receptors, which may cause to specific activation of signaling pathways and particular substrates [39].

Nevertheless, a series of genetic manipulations in the mouse have provided evidence that these pathways affect longevity in mammals. Mutations that result in GH deficiency or impair the GH receptor cause reduced body size, increased stress resistance, lowered IGF-1 and insulin levels, and extended lifespan [40]. Heterozygous deletion of the Igf1r gene in mice causes a modest reduction in size, improved stress resistance, and extended lifespan in females only [41,42]. Interestingly, tissue specific disruption of IR in adipose tissue in mice results in an extended lifespan in both sexes [43]. Knockout (KO) of the downstream signaling adaptor protein insulin receptor substrate 1 (IRS1), which is a major effector of both IGF-1 and insulin, also results in increased longevity in females only, irrespective of mild insulin resistance [44]. Intriguingly, IRS2 homozygous-null mice are short lived, whereas IRS1 heterozygous (+/−) and IRS2 heterozygous (+/−) mice of both sexes show a normal lifespan [44]. In humans, a 22-year-cohort study in Ecuadorian individuals with a mutation in GH receptor revealed that GH receptor deficiency is associated with a major reduction in prosenescence signaling, diabetes, and cancer, suggesting that pathways involved in the control of senescence and disease burden are evolutionarily conserved [45]. Furthermore, several studies in long-lived human populations lend support on the role of the GH receptor [46] and IGF-1R [47] mutations in longevity.