Review

Role of transforming growth factor-β in the progression of heart failure

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Abstract. Transforming growth factor (TGF-β) is a multifunctional peptide growth factor that has an important role in the regulation of cell growth, differentiation, and repair in a variety of tissues. In mammals, the cytokine has three isoforms, TGF-β1, TGF-β2, and TGF-β3. TGF-β1 is up-regulated by Ang II and induction of TGF-β1 causes cardiac fibrosis. The stimulus that triggers the expression of TGF-β1 may be repeated causing continual injury, which is associated with an increase in the activity of Ang II in heart tissue. The interplay between Ang II and TGF-β1 causes continued activation that may result in chronic hypertension and progressive myocardial fibrosis, leading to heart failure. The regulation of TGF-β1 secretion and action involves complex transcriptional events. Overproduction of TGF-β1 underlies tissue fibrosis. Understanding the actions and signaling transduction of TGF-β1 could lead to the development of therapeutic options that may be effective in inhibiting myocardial fibrosis triggered by TGF-β1 in heart failure.

Keywords. Transforming growth factor-β, signaling pathways, heart tissues, therapeutic options.

Introduction

Heart failure is a leading cause of disability and death, and an important contributor to the cost of health care [1–4]. Advances in cytokine biology have opened an avenue to the understanding of the molecular events underlying chronic heart failure. It has become clear that cardiac remodeling is attended by cardiac hypertrophy and interstitial fibrosis, leading to the loss of normal cardiac function and heart failure [5–7]. This dynamic structural remodeling is a milestone in the progression to heart failure [8–10]. A pivotal mediator in cardiac remodeling is the activation of cytokines in response to myocardial overload and injury. Several lines of evidence point to transforming growth factor-beta (TGF-β) as a powerful cytokine that initiates and terminates tissue repair and sustained production underlies the development of myocardial fibrosis [11]. Moreover, increased TGF-β1 expression has been identified in the myocardium during cardiac hypertrophy and heart failure [12–14]. Thus, TGF-β1 expression may directly participate in the progressive remodeling process in heart failure. This review discusses the biological actions of TGF-β, focusing its role in the progression of heart failure. Understanding the actions of TGF-β1 and its signaling transduction could lead to the potential development of antifibrotic drug as a therapy in addition to conventional treatments in heart failure.

TGF-β isoforms: structure, function and synthesis

Based on structural and biological similarities, the TGF-β superfamily can be subdivided into four major families: the Mullerian inhibitory substance (MIS) family, the
inhbin/activin family, the bone morphogenetic protein (BMP) family, and the TGF-β family [15]. MIS can induce regression of the Mullerian duct in male embryos [16]. The inhibins and activins were originally identified by their ability to regulate hormone secretion in pituitary cells [17]. BMPs were purified as factors that induce ectopic bone formation and they regulate various early developmental processes in invertebrates and vertebrates [18].

Five distinct members of TGF-β family have been identified in vertebrates; three structurally and functionally similar TGF-β isoforms are expressed in mammals (TGF-β1, 2, and 3) [15, 19]. The TGF-β1, TGF-β2, and TGF-β3 genes have been mapped by distinct genes on chromosomes 19q13.1-q13.3, 1q41 [20], and 14q23-24 [21], respectively. TGF-β is a prototypical, multifunctional peptide growth that was isolated from platelets and its characteristic was known just over two decades ago [11]. Distinguished initially for their ability to inhibit the growth of most epithelial and hematopoietic cells, and to regulate the production of extracellular matrix (ECM) by mesenchymal cells, these peptides are now known to control a great diversity of fundamental biological processes such as cell growth, differentiation, development, tissue repair, and apoptosis [22–24]. Virtually every cell in the body, including epithelial, endothelial, hematopoietic, neuronal, and connective tissue cells, produces TGF-β and has receptors for it. TGF-β1 mRNA is expressed in endothelial, hematopoietic, and connective tissue cells. Thus, it is the isoform most implicated in tissue fibrosis, including the fibrotic disease of the heart, kidney, liver and lung [11]. TGF-β2 mRNA is mostly expressed in epithelial and neuronal cell, and TGF-β3 mRNA primarily in mesenchymal cells [25].

Loss of function studies with TGF-β family ligands in mice has also demonstrated their multifunctional properties and revealed their important role during embryogenesis and in maintaining homeostasis during adult life [26]. TGF-β1 knockout animals have over 50% embryonic lethality associated with defects in early hematopoiesis and vasculature in the yolk sac [27]. Shull et al. [28] have shown that animals homozygous for the mutated TGF-β1 allele have no gross developmental abnormalities, but about 20 days after birth they succumb to a wasting syndrome accompanied by a multifocal, mixed inflammatory cell response and tissue necrosis, leading to organ failure and death. Moreover, Kulkarni et al. [29] have demonstrated that TGF-β1 null mice reveal an excessive inflammatory response with massive infiltration of lymphocytes and macrophages in many organs, but primarily in heart and lungs [29]. Mice deficient in the TGF-β2 gene die around birth and show developmental defects in areas including the heart, lung, limbs, spinal column, eye, inner ear, and urogenital system [30, 31]. The TGF-β3 knockout phenotype is characterized by cleft palate and delayed pulmonary development [32]. The distinct phenotypes of TGF-β1, 2, and 3 knockout mice provide evidence that these TGF-β isoforms play distinctive roles in embryonic growth and development [24].

In fibrotic diseases of all three isoforms, regions of increased matrix show increased of TGF-β, especially the isoform of TGF-β1 [11, 33]. The TGF-β1 encodes a 390-amino acid precursor molecule that contains a signal peptide, the active TGF-β1 molecule, and a latency-associated peptide (LAP) [34]. After removal of the signal peptide, the TGF-β1 gene product is proteolytically cleaved to form mature TGF-β1 and the latency associated peptide [35]. Before secretion, TGF-β1 non-covalently associates with LAP to produce an inactive latent TGF-β1 complex [36, 37]. TGF-β1 can be released from the latent complex, and thereby activated by changes in pH, by proteases such as plasmin and cathespin D, and by thrombospondin [38, 39]. Once activated, TGF-β1 is capable of binding a cell surface receptor, thereby initiating an intracellular signaling cascade (Fig. 1).

Molecular mechanism of TGF-β1 signal transduction

The pathway of TGF-β signaling is summarized in Figure 1. The three isoform of TGF-β are synthesized as precursor protein from TGF-β messenger RNA, which are biologically inactive or latent form [15, 40, 41] containing an LAP. Latent TGF-β undergoes activation with release of the LAP. TGF-β in turn binds to three high-affinity cell surface receptors known as types I, II, and III. Type III receptors are the most abundant type. They bind to TGF-β and then transfer it to its signaling receptors, the type I and II receptors. The expression of the TGF-β receptors represents another mechanism for regulating the activity of TGF-β activity [15]. Endoglin, another TGF-β receptor that is abundant on endothelial cells, contains a transmembrane region and a cytoplasmic tail homologous to the type III receptor.

Intracellular signaling of TGF-β occurs via two receptor serine/threonine kinases, type I and type II receptors. The active form of TGF-β binds to type II receptor, which is followed by the recruitment of the type I receptors to form tetrameric complexes with the type II receptors [42]. After receptor activation, the signal is propagated downstream through the recently identified Smad protein family [42, 43]. In the mammalian heart, Smads can be divided into three major groups: the receptor-regulated Smads (R-Smads: Smad 1, Smad 2, Smad 3, Smad 5, and Smad 8), common-mediator Smad (Co-Smad: Smad 4), and inhibitory Smads (I-Smad: Smad 6 and Smad 7) [42]. Smads 1, 5, and 8 serve principally as substrates for the BMP and anti-Mullerian receptors, and Smads 2 and 3 for the TGF-β, activin, and nodal receptors [44].