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Review article

Osteopontin: At the cross-roads of myocyte survival and myocardial function

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ABSTRACT

Heart failure represents a major cause of morbidity and mortality in Western society. Cardiac myocyte loss due to apoptosis plays a significant role in the progression of heart failure. The extracellular matrix (ECM) maintains the structural integrity of the heart and allows the transmission of electrical and mechanical signals during cardiac contraction and relaxation. Matricellular proteins, a class of non-structural ECM proteins, play a significant role in ECM homeostasis and intracellular signaling via their interactions with cell surface receptors, structural proteins, and/or soluble extracellular factors such as growth factors and cytokines. Osteopontin (OPN), also called cytokine Eta-1, is a member of the matricellular protein family. The normal heart expresses low levels of OPN. However, OPN expression increases markedly under a variety of pathophysiological conditions of the heart. Many human and transgenic mouse studies provide evidence that increased OPN expression, specifically in myocytes, is associated with increased myocyte apoptosis and myocardial dysfunction. This review summarizes OPN expression in the heart, and its role in myocyte apoptosis and myocardial function.

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Contents

Introduction

Heart failure represents a major cause of morbidity and mortality in Western society, affecting nearly 5 million Americans. In the United States, an estimated 400,000 to 700,000 new cases of heart failure are diagnosed each year. Heart failure, more common in people over the age of 65 years, is a progressive disease in which the heart loses the ability to pump enough blood to meet the metabolic demands of the body. Myocytes, a major cell-type of the heart, are responsible for the pumping ability of the heart. Adult cardiac myocytes are generally considered terminally differentiated (Cheng and Force, 2010). Myocyte loss, either acute substantial loss or chronic low levels of apoptosis, is considered a major contributing factor towards the development of heart failure.

Myocyte loss can occur due to autophagy, necrosis and/or apoptosis. All these types of cell deaths are observed in the heart during the

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progression of heart failure (Whelan et al., 2010). Autophagy, activated during nutrient deprivation, is a highly conserved process for the degradation of proteins and organelles. It involves the formation of double-membrane-bound structures known as autophagosomes which fuse with lysosomes to form autophagolysosomes and their contents are then degraded by acidic lysosomal hydrolases (Mizushima et al., 2002). Autophagy is a critical process for the maintenance of cellular and whole-body homeostasis. Increased autophagy is observed in a variety of pathologic conditions of the heart including cardiac hypertrophy, ischemia/reperfusion (I/R) injury and myocardial infarction (MI). Transgenic mouse studies provide evidence that enhanced autophagic flux may contribute to cardiac dysfunction (Whelan et al., 2010). Necrosis occurs when cells are exposed to excessive stress or environmental conditions such as lack of oxygen and essential nutrients during an ischemic event (e.g. MI or stroke), elevated temperature and mechanical strain (e.g. trauma). It can also occur as a result of an incomplete execution of apoptosis (Formigli et al., 2000). Myocyte necrosis is a major contributor of heart failure associated with several cardiac pathologies (Whelan et al., 2010; Tavernarakis, 2007). Apoptosis is a highly regulated and energy-requiring process in which activation of signaling cascades induces cell death (Orogo and Gustafsson, 2013). Myocyte loss due to apoptosis is recognized as an important determinant of structure and function of the heart, and is suggested to play a significant role in the progression of heart failure. Myocyte apoptosis occurs in the myocardium of patients during heart failure and in animal models of myocardial hypertrophy and failure (Whelan et al., 2010; Tavernarakis, 2007; Orogo and Gustafsson, 2013).

Extracellular matrix (ECM) modulates many cellular functions including cell adhesion, migration, differentiation, and survival (Bowers et al., 2010). The components of ECM include basic structural proteins such as collagen and elastin, and specialized proteins such as fibronectin, proteoglycans and matricellular proteins. Matricellular proteins are a class of non-structural ECM proteins exerting regulatory functions, most likely through their interactions with cell surface receptors, the structural proteins, and soluble extracellular factors such as growth factors and cytokines. Their expression is generally induced following an injury (Frangogiannis, 2012). Osteopontin (OPN) is a member of the matricellular protein family. The heart expresses low basal levels of OPN. However, the expression of OPN increases markedly in the heart under a variety of pathophysiological conditions (Singh et al., 2010a). Evidence has been provided that increased OPN expression, specifically in myocytes, is associated with increased myocyte apoptosis and myocardial dysfunction (Subramanian et al., 2007; Renault et al., 2010; Dalal et al., 2014). While lack of OPN is associated with reduced fibrosis in different models of myocardial hypertrophy and failure (Trueblood et al., 2001; Subramanian et al., 2007; Sam et al., 2004; Matsui et al., 2004), this review summarizes OPN expression in the heart, and its role in the induction of myocyte apoptosis and myocardial dysfunction.

OPN: a multifunctional protein

OPN (also called cytokine Eta-1) is a glycosylated phosphoprotein with high acidic amino acid content (Singh et al., 2010a; Wolak, 2014). While first isolated from mineralized bone matrix in 1986 (Oldberg et al., 1986), OPN has since been shown to be synthesized by a variety of tissues and cell-types and secreted into body fluids (Wang and Denhardt, 2008; Singh et al., 2010a). OPN is a hydrophilic protein with isoelectric point of ~3.5. The predicted molecular weight of human full-length OPN is ~35 kDa. It consists of 314 amino acid residues with 42 serine, 48 aspartic acid and 27 glutamic acid residues. 27 out of 42 serine residues can undergo phosphorylation. It has calcium and heparin binding domains, and undergoes O-linked and N-linked glycosylation. Due to the presence of acidic amino acid residues and extensive post-translational modifications, apparent molecular weight of OPN on SDS-PAGE can range from 45 to 75 kDa. Although OPN is generally described as a cell-secreted protein, an alternative translation of a non-AUG site downstream of the canonical AUG sequence is suggested to generate an intracellular isoform (iOPN) (Wang and Denhardt, 2008). OPN has RGD (Arg–Gly–Asp) cell-binding sequence and interacts with $\alpha v\beta 1$, $\alpha v\beta 3$, $\alpha v\beta 5$ and $\alpha 8\beta 1$ integrins in an RGD-dependent manner (Kazanecki et al., 2007; Scatena et al., 2007). The SVVYGLR (Ser–Val–Val–Tyr–Gly–Leu–Arg) sequence, which becomes accessible upon cleavage of OPN by thrombin, interacts with $\alpha 9\beta 1$ and $\alpha 1\beta 1$ integrins. Variants of hyaluronan receptor, CD44, have also been identified as a receptor for OPN.

OPN is described as a protein with diverse biological functions including bone resorption and calcification, tumorigenesis, immunemodulation, wound healing, cell adhesion, chemotaxis, cell survival, apoptosis, etc. (Wang and Denhardt, 2008; Singh et al., 2010a; Singh et al., 2010b; Kahles et al., 2014). Acting as a cytokine, OPN is shown to play a key role in immune cell recruitment and type-1 (Th1) cytokine expression at sites of inflammation. With respect to cardiovascular disease, OPN is suggested to play a critical role in atherosclerosis, valvular stenosis, hypertrophy, myocardial infarction (MI) and heart failure (Singh et al., 2007; Scatena et al., 2007; Wolak, 2014). The diverse biological functions of OPN can be attributable to its structural features, post-translational modifications, interaction with multiple receptors, and different isoforms. Matrix metalloproteinases (MMP) cleave OPN, thereby affecting migratory and adhesive properties of OPN (Scatena et al., 2007).

OPN: cell survival or death

In tumor cells, OPN is accepted as a pro-survival signal (Cao et al., 2012; Wai and Kuo, 2008). It is also shown to inhibit apoptosis in endothelial cells (Scatena et al., 1998) and melanocytes (Geissinger et al., 2002). In addition, mice lacking OPN exhibit significantly higher apoptosis in both tubular epithelium and interstitium during the injury phase of post-ischemic acute renal failure (Persy et al., 2003). Most of the anti-apoptotic actions of OPN are attributed to its interaction with $\alpha V\beta 3$ integrins and activation of NF-kB. In IL-3-dependent cells, the anti-apoptotic actions of OPN are demonstrated via its interaction with CD44 receptor and activation of PI-3-kinase/Akt cascade (Lin and Yang-Yen, 2001). In contrast, chondrocyte apoptosis was lower in mice lacking OPN in an experimental model of rheumatoid arthritis (Yumoto et al., 2002). Mice lacking OPN also exhibited decreased apoptosis in their spleen and thymus in response to hindlimb-unloading by tail suspension (Wang et al., 2007). Cardiac fibroblasts isolated from the myocardium of mice lacking OPN exhibited enhanced necrosis, but decreased apoptosis, in response to H_2O_2 treatment when compared to their wild-type (WT) counterparts (Zohar et al., 2004). In vascular smooth muscle cells, treatment with OPN stimulated autophagy via the involvement of integrin and CD44 pathways (Zheng et al., 2011). In a recent study, knockdown of OPN inhibited breast cancer metastasis by regulating $\alpha v\beta 3$ integrin expression and inducing autophagy (Zhang et al., 2014). Collectively these studies suggest involvement of OPN in all three types of cell death. However, the cell death or survival response appears to vary with different cell types and tissues.

OPN expression and myocardial dysfunction

The normal adult heart expresses only low levels of OPN. Cell types of the heart, i.e. myocytes, fibroblasts and microvascular endothelial cells, express low basal levels of OPN. Stimuli, such as angiotensin II (Ang II), glucocorticoid hormone and cytokines (interleukin-1β + interferon-γ) increase OPN expression in different cell-types of the heart (Singh et al., 2010a,b). Neonatal cardiac myocytes also express OPN where endothelin-1 and norepinephrine increased OPN expression (Graf et al., 1997). OPN expression increases markedly in the heart under a variety of pathophysiological conditions of the heart (Singh et al., 2010a,b). OPN mRNA levels were readily detectable in the hypertrophied ventricles of rats subjected to the clipping of the renal