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Angiopoietin-1, Angiopoietin-2 and Myocardial Ischemia-Reperfusion Injury

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Prolonged periods of myocardial ischemia cause irreversible myocardium loss. Thus, early reperfusion is the paramount strategy for myocardial salvage. However, reperfusion itself also causes myocardial damage known as reperfusion injury [1]. Angiopoietin-1 (Ang-1) and angiopoietin-2 (Ang-2), initially implicated in embryonic vasculogenesis and angiogenesis [2,3], were shown to be involved in myocardial ischemia/reperfusion (I/R) injury in recent years [4,5].

Angiopoietins

Angiopoietins have been identified in the mid 1990s as a family of growth factors that are essential for blood vessel formation. There are four types of angiopoietins: angiopoietin-1 (Ang-1), angiopoietin-2 (Ang-2), angiopoietin-3 (Ang-3), and angiopoietin-4 (Ang-4). Angiopoietins are secreted glycoproteins with a dimeric molecular weight of approximately 75 kDa. The best characterized angiopoietins are Ang-1 and Ang-2 [2,3]. Very little is known about Ang-3 and Ang-4 [6]. Ang-1 is primarily expressed by mesenchymal cells. Ang-2 is almost exclusively expressed by endothelial cells where it is stored in Weibel-Palade bodies (WPB) [2,3]. Following endothelium activation, Ang-2 is rapidly released from WPB [7].

Angiopoietins are ligands binding to the tyrosine kinase receptor Tie-2, which is present on endothelial cells and neutrophils [2,3,6]. Ang-1 acts in a stimulating, agonistic manner on Tie2, whereas Ang-2 exerts antagonistic functions on Ang-1/Tie2 signaling [2,3]. Some studies also identified Ang-2 as an agonist of Tie2 [8]. It has been suggested that Ang-1 could also exert its activity in non-endothelial cells through integrins [5,9].

Pathophysiologic Mechanisms of Myocardial I/R Injury and the Relevance of Angiopoietins

Molecular and cellular events underlying I/R are complex. The inflammatory response partially mediates I/R injury [1]. Endothelial activation and injury increase vascular permeability, leading to interstitial edema and subsequently compounding myocardium loss [1]. Cellular adhesion molecules elicited by the injured endothelium (e.g., intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), E-selectin) promote tissue invasion by inflammatory cells. These infiltrating cells, including (and in particular) neutrophils, are directly toxic to the myocardium by secreting proteases, generating reactive oxygen species (ROS), and occluding the microvasculature [1]. Ang-1 has been shown to inhibit vascular permeability and exert anti-inflammatory effect via the Tie-2 receptor. Ang-1 attenuates thrombin-induced permeability in human pulmonary microvascular endothelial cells (HPMVECs) by enforcing the VE-cadherin organization [10]. Ang-1 could counteract the inflammatory effects of vascular endothelial growth factor (VEGF) on endothelial cells [11], ameliorate ROS-induced acute lung injury [12] and lipopolysaccharide-induced acute kidney injury [13] by reducing the induction of ICAM-1 and VCAM-1, causing a reduction in leukocyte adhesion and subsequent inflammation. While Ang-1 has been shown to have a protective effect against inflammation, Ang-2 has been shown to have the opposite effect. Ang-2 could sensitize thrombin-induced permeability in HPMVECs by destabilizing VE-cadherin junctions and increasing gap formation [10]. Overexpression of Ang-2 also sensitizes ICAM-1 and VCAM-1 expression in diabetic mouse hearts [14]. Osteoprotegrin (OPG) has been shown to up regulate Ang-2 in endothelial cells thereby sensitizing the cells to tumor necrosis factor-α (TNF-α) [15]. TNF-α is a pro-inflammatory cytokine which stimulates adhesion molecule up regulation.

Apoptosis has been observed in hearts subjected to either continuous ischemia or ischemia followed by reperfusion [1] Ang-1 promotes cell survival. Ang-1 binds to Tie2 on endothelial cells, leading to phosphorylation of phosphatidylinositol 3-kinase (PI3 K). PI3 K activates Akt, and stimulates the phosphorylation and thereby the inhibition of pro-apoptotic proteins, including BAD and procaspase-9 [16]. Additionally, Akt upregulates survivin, a classical apoptosis inhibitor, and thereby supports cell survival [17]. Ang-1 has also been shown to promote cardiac and skeletal myocyte survival through integrins[5]. Unlike a general agreement about the influence of Ang-1 on cell survival, there are conflicting results regarding the physiological roles of Ang-2 [18,19]. Ang-2 may promote both endothelial cell survival and apoptosis depending on VEGF concentrations.

Evidence from Animal and Human Studies

In order to investigate the participation of Angiopoietins in myocardial I/R, a previous study using a rat model of left anterior descending coronary artery (LAD) occlusion and reperfusion, has shown that expression of Ang2 increased after I/R in the ventricular myocardium, while the expression of Ang1 did not [4]. We investigated serum Ang-1 and Ang-2 levels in 85 patients with ST-segment elevation myocardial infarction (STMEI), and found that Ang-1, Ang-2 and Ang-2/Ang-1 ratio (Ang-2/1) were all significantly elevated. This study also showed that Ang-2 and Ang-2/1 were positively correlated with peak cardiac troponin T levels, suggesting that the extent of myocardial damage may be linked to circulating Ang-2 and Ang-2/1[20]. In the study by Lee et al. [5], shifting of the Ang-2/1 ratio to favor Ang-1 by administration of adenovirus expressing Ang-1 in a mouse I/R model could prevent vascular leakage through regulating VE-cadherin phosphorylation, increase cardiomyocyte survival and reduce infarct size [5].

In conclusion, Ang-1 has anti-permeability, anti-inflammatory

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and anti-apoptosis effects, and is protective in I/R injury. Further work is needed to better understand the pathological effect of Ang-2 on endothelial cell and cardiomyocyte survival. Human studies suggested that the extent of myocardial damage may be linked to circulating Ang-2 and Ang-2/1 in AMI patients. Therefore, further studies are needed to clarify the role of Ang-2 in I/R injury.

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