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Apoptosis and the cardiac action of insulin-like growth factor I

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Abstract

In both cardiac surgical and cardiological settings, clinical interventions used to reperfuse the ischemic heart are associated with myocardial damage that is likely to influence long-term functional recovery. Ischaemia and reperfusion trigger cardiomyocyte death by necrosis and apoptosis. Therefore identifying potent cardioprotective agents remains an important goal in cardiac research. In a variety of tissues, insulin-like growth factor I (IGF-I) stimulates cellular proliferation, somatic growth, and differentiation. In addition, IGF-I inhibits apoptotic cell death and therefore plays an important role as a cell survival factor. This characteristic would provide an opportunity to both protect (rescue) the cardiac myocytes during (after) cardiac insults. In this review, we shall (i) describe the characteristics of apoptotic cell death with particular emphasis on the heart, (ii) discuss the IGF system with emphasis on the cardiac actions of IGF-I under normal and pathological conditions, (iii) elaborate on the potential role of IGF-I in myocardial protection, and finally (iv) describe how an improved understanding of the cardiac actions of IGF-I may lead to better protective clinical strategies in the future. We discuss work by ourselves and others in these areas and also consider recent work describing the cellular signaling associated with the IGF-I receptor (IGF-IR) in the heart and its potential role in regulating excitation–contraction coupling.

Keywords: Insulin-like growth factor; Apoptosis; Myocardium; Ischaemia; Reperfusion injury; Signaling

Abbreviations: ARC, apoptotic repressor with CARD; ATP, adenosine triphosphate; bFGF, basic fibroblast growth factor (also known as FGF2); BAK, Bcl-2 antagonist/killer protein; BAX, Bcl-2 associated X protein; Bcl-2, B cell leukemia/lymphoma-2; BID, BCL-2 interacting domain; CARD, caspase recruitment domain; Caspase, cysteine-dependent aspartate-directed protease; CREB, cAMP response element-binding protein; Cyt *c*, cytochrome *c*; dATP, deoxy adenosine triphospahte; DISC, death inducing signaling complex; ERK, extracellular regulated kinase; FADD, Fas-associated death domain; H+E, haematoxylin and eosin; IGFBP, insulin-like growth factor binding protein; IGF-I, insulin-like growth factor I; IGF-IR, insulin-like growth factor I receptor; IRS, insulin receptor substrate; MAPK, mitogen-activated protein kinase; MSA, multiplication stimulatory activity; NSILA, nonsuppressible insulin like activity; PARP, poly ADP-ribose polymerase; PI3K, phosphatidylinositol 3-kinase; PKB, protein kinase B (also known as Akt); PKC, protein kinase C; TNF, tumour necrosis factor; TUNEL, terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate [UTP]-biotin nick end-labelling.

Contents

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1. Introduction

The excitation–contraction–relaxation cycle in cardiomyocytes is under tight control as disruption to this cycle can trigger cellular death and ultimately the demise of the afflicted individual. Therefore, in order to cope with changing functional demands, a multitude of intracellular signaling cascades provide the regulatory control. These include phosphatidylinositol 3-kinase (PI3K), Akt or protein kinase B (PKB), and Ca^{2+} (Lai et al., 2003; von Lewinski et al., 2003; Khoynezhad et al., 2004; Latronico et al., 2004; Leblais et al., 2004; Catalucci & Condorelli, 2006; Kamp & Chiamvimonvat, 2006; Sun et al., 2006). Insulin-like growth factor I (IGF-I) is one important extracellular effector responsible for triggering the interaction between these factors. It is also an important survival factor with known antiapoptotic effects. Therefore a better understanding of the cardiac actions of IGF-I may provide new strategies for protecting the myocardium against cardiac insults including ischaemia and reperfusion.

Myocardial ischaemia describes a condition where reduced coronary blood flow results in a decrease in the supply of oxygen and nutrients to the heart (reviewed in Suleiman et al., 2001). This in turn provokes a fall in energy production by the mitochondria, which is quickly followed by abnormal accumulation (e.g., lactate) and depletion (e.g., adenosine triphosphate [ATP]) of several metabolites. These metabolic changes lead to a decrease in intracellular pH and an increase in the intracellular concentrations of Na^{+} and Ca^{2+}. Several membrane ion pumps and ion channels are disrupted, leading to membrane depolarization and loss of excitability. If coronary flow is restored quickly, then metabolic and ionic homeostasis are re-established, the plasma membrane repolarises and recovery occurs. However, ischaemia, if prolonged, or indeed reperfusion may independently cause irreversible damage. Indeed, metabolic and ionic changes during ischaemia predispose the heart to damaging effects upon reperfusion. The main causes of reperfusion injury are intracellular Ca^{2+} loading and generation of reactive oxygen species. Consequences of reperfusion injury include ventricular fibrillation, myocardial stunning, and loss of intracellular proteins (Jennings & Reimer, 1994; Jennings et al., 1995). Clinical implications for reperfusion injury are seen in situations where attempts are made to reestablish blood flow to an area of the heart deprived as a result of coronary disease. Such interventions include thrombolysis, percutaneous coronary angioplasty, or coronary bypass surgery. In addition, during open heart surgery blood flow to the heart is totally stopped and must be restarted after surgery, with consequent reperfusion injury.

One of the consequences of ischaemia and reperfusion is the death of cardiac myocytes. Like other cells, cardiac myocytes can die from necrosis or apoptosis. During necrosis, there is cell swelling, disruption to cell membranes, lysis, and release of cytoplasmic materials, which trigger an inflammatory response and thus damage to neighbouring cells, and ultimately scarred tissue is formed. In contrast, apoptosis is associated with shrinkage of cells without release of intracellular material, and it therefore does not stimulate an inflammatory response or scarring but can lead to tissue loss. Recent experimental and clinical studies have indicated that reduced apoptosis is cardioprotective. With this in mind, IGF-I, a well-established survival and antiapoptotic factor, may be beneficial in situations of reperfusion injury.

In this article we present a detailed description of the involvement and the importance of death by apoptosis in the myocardium and an overview of the physiological significance of the IGF system, with particular emphasis on the cardiac role of IGF-I, and the potential mechanisms underlying its action, as well as its potential use in cardiac repair.

2. Death by apoptosis

2.1. Apoptosis versus necrosis

Apoptosis (Kerr et al., 1972) is a process of cell death that occurs in response to a physiological stimulus that triggers a predetermined series of events that culminate in the demise of the cell (reviewed in Lockshin et al., 2000. This is a tightly regulated process that is characterised by cell shrinkage and cytoplasmic condensation. DNA fragmentation (elicited by endonucleases) is accompanied by cellular blebbing and its decomposition into several membrane bound vesicles, known as apoptotic bodies, which are engulfed by neighbouring cells or macrophages (Schwartzman & Cidlowski, 1993). These