An important aspect of cardiac IRI is an inflammatory response. This begins in the peri-reperfusion period and may continue for the ensuing hours and days. A self-perpetuating cycle of ongoing activation is driven by chemokine signaling, cytokine release, complement activation, release of reactive oxygen species and neutrophil infiltration. Nuclear Factor κB plays a critical role in regulating these multiple parallel processes in the post infarction inflammatory milieu. The earliest inflammatory pathway to be activated involves the innate immune system. Even though cardiac IRI is a sterile process, this inflammatory response has many similarities to that seen in microbial ligand-pattern recognition receptor interactions during infections. In the case of IRI the analogous ligands are termed “damage-associated molecular patterns”. Ischemic damage to endothelial cells results in changes in surface molecule expression and the formation of neoantigens that are the target of naturally occurring antibodies (NAbs). Nonmuscle myosin heavy chain II is one such neoantigen exposed during IRI in intestinal, skeletal and myocardial murine models. A number of other relevant neoantigens have been identified and include annexin IV and oxidized phosphatidylcholine.

Natural antibodies are germline encoded and produced primarily by B1 B lymphocytes in the absence of external antigen stimulation. Despite low affinity and restricted epitope specificities they bind to these altered and exposed neoantigens, which results in complement activation, through the lectin pathway. Evidence supporting NAb amplification of inflammatory tissue injury is derived from studies in antibody deficient Rag-1/-/- mice. These mice are protected from IRI with injury restored through reconstitution by IgM obtained from normal mouse sera. Based upon these concepts the current paradigm of cardiac IRI comprises intrinsic cellular ischemic injury and an extrinsic inflammatory response initiated by the innate immune system and NAbs.

Beta 2 Glycoprotein I (β2GPI) is an abundant 43kDa circulating plasma protein that plays an important role in vascular biology and may provide another link between the innate immune system and tissue injury during IRI. It is highly conserved across species suggesting it has important functions. It is an integral part of the innate immune system and plays a physiological role that includes binding to damaged endothelial anionic phospholipids and the binding to, and clearance of, apoptotic cells. β2GPI consists of 5 domains (domains I-V); Domain V is unique and contains the anionic phospholipid binding site that is identical in all mammals. In contrast Domain I contains the antibody binding site which is cryptic due to the fact that β2GPI likely circulates in a circular configuration with Domain I interacting with Domain V. Domain I is exposed only after Domain V binds to its ligand(s) on damaged cell surfaces.

The role of β2GPI in cardiac IRI has not been explored to date, however, its relevance is supported by a previous human autopsy study. In patients who died within 14 days of an acute myocardial infarction there was evidence of endogenous β2GPI deposition within the area of cardiac ischemia. β2GPI deposition was not seen in non-ischemic myocardial samples from patients who died from other causes.

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**Abstract**

The World Health Organization has estimated that 48% of all deaths due to non-communicable disease in 2008 (17 million deaths worldwide) resulted from cardiovascular disease. A significant proportion of these deaths are due to acute myocardial infarction as a consequence of atherothrombotic coronary artery occlusion. Prognosis after acute myocardial infarction is primarily dependent upon the amount of myocardium that is subjected to irreversible injury. Timely reperfusion is the gold standard treatment, however restoration of coronary flow and re-oxygenation is associated with an exacerbation of tissue injury termed ‘ischemia reperfusion injury’ (IRI). It is recognized that IRI may contribute up to 50% of final infarct size during acute coronary occlusion with reperfusion.

The role of β2GPI in cardiac IRI has not been explored to date, however, its relevance is supported by a previous human autopsy study. In patients who died within 14 days of an acute myocardial infarction there was evidence of endogenous β2GPI deposition within the area of cardiac ischemia. β2GPI deposition was not seen in non-ischemic myocardial samples from patients who died from other causes.

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**Therapies To Prevent Cardiac Ischemia Reperfusion Injury Based On Peptides Derived From Beta 2 Glycoprotein I A Major Plasma Protein**