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Role of Fibrinogen in the Attenuation of the Ischemic Reperfusion Injury and in Remote Ischemic Preconditioning

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Abstract

Background: Ischemic reperfusion injury (IRI) is a common hazard involved in many human diseases, such as cerebral stroke, heart infarction, solid organ transplant dysfunction or failure, and vascular diseases. Understanding the molecular bases of this injury is essential for the prevention and control of these life-threatening conditions. Ischemic and remote ischemic preconditioning techniques (IPC and RIPC, respectively) have increasing importance in the clinical practice to protect against the IRI, however, the exact mechanisms of these techniques are not fully understood, which renders their clinical application query.

Possible effectors: Nitric oxide (NO) has been reported by multiple studies to be an important mediator of the protective effects of those techniques. While the physiological concentrations of NO and fibrinogen is known to antagonize each other, the circulating levels of both effectors increase in response to RIPC.

Hypothesis: While NO has potential anti-inflammatory effects, non-soluble fibrinogen plays a pro-inflammatory effects. However, the soluble fibrinogen (sFB) may have the potential to act synergistically rather than antagonistically with NO towards the attenuation of the IRI.

Conclusion: While FB is a risk factor for cardiovascular and inflammatory diseases that is also able to decrease the efflux of NO, and increase the NO oxidative metabolites and S-nitroglutathione, the increased sFB during the acute phase reaction might have other protective aspects that should be carefully investigated.

Keywords: Ischemic reperfusion injury; Fibrinogen; Nitric oxide; Ischemic conditioning; Solid organ transplant

Introduction

Fibrinogen (FB) is a gylcoprotein, which is a hexamer, containing two sets of three different chains (α, β, and γ), linked to each other by disulfide bonds. FB plays an important role in coagulation cascade, where it can form bridges between platelets, by binding to their GpIIb/IIIa surface membrane proteins, in addition to the major role, where prothrombin is converted into thrombin, which then converts the soluble FB (sFB) into insoluble fibrin strands that are then cross-linked by factor XIII to form the blood clot [1].

Role of Fibrinogen in the Pathogenesis of Diseases

Fibrinogen plays a significant role in the pathogenesis of many diseases, mainly the diseases of cardiovascular and inflammatory backgrounds.

Role of fibrinogen in cardiovascular diseases

There is a confirmed agreement that FB is an important contributor to the cardiovascular events, including myocardial infarction and cerebral stroke. In addition to the traditional cardiovascular risk factors, FB has been identified as an additional risk factor that could predict new events within 10 years [2]. This may refer to the traditional role of FB in blood clotting and platelet aggregates formation.

Role of fibrinogen in inflammatory diseases

Many studies have confirmed FB as a pro-inflammatory effector. In addition to its ability to stimulate the proliferation of B-lymphocytes, T-lymphocytes and monocytes [3], immobilized FB and fibrin have high affinity to macrophage antigen 1 (MAC-1) and can activate neutrophiles and monocytes [4-6]. In neutrophiles, FB/MAC-1 interaction activates the NF-κB pathway, which is an anti-apoptotic and inflammatory cytokine-inducing pathway [4].

Ischemic and Remote Ischemic Preconditioning

Ischemic preconditioning (IPC) is a technique, where prior application of repeated short cycles of ischemia and reperfusion is able to attenuate the severity of the subsequent ischemic reperfusion injury (IRI). Remote ischemic preconditioning (RIPC) describes the ability of the technique to function through distance. For example, the application of short, repetitive ischemia-reperfusion cycles of the limb would protect distant organs like heart, kidney, brain and liver during subsequent IRI. Both phenomena indicate the involvement of local, paracrine as well as remote, circulating mediators [7]. IPC showed ability to significantly reduce the DNA fragmentation and the apoptotic death of the myocytes, usually associated with IRI [7].

During limb ischemia, the diminished flow and shearing stress is associated with inhibition of Na^+/K^+ ATPase and the inward driving K^+ channels. This leads to increased Na^+ influx and persistent membrane depolarization. The increased intracellular Na^+ activates Na^+/Ca^{++} exchanger to let Na^+ out and Ca^{++} in. In addition, the inhibition of K^+ channels results in the activation of T type Ca^{++} channels, leading to increased Ca^{++} influx into the endothelial cells. Increased intracellular

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Ca^{++} activates Ca^{++} - dependent endothelial nitric oxide synthase (eNOS), which results in increased NO production [8,9].

Xanthine oxidoreductase (XOR) is a complex molybdoflavin protein, which catalyzes the terminal two reactions in purine degradation (hypoxanthine → xanthine → uric acid) in primates. In humans, hypoxia and the inflammatory cytokines TNF-α, IL-1β, and IFN-γ induce XOR expression in vascular endothelium, where it can be released into the circulation [10,11]. XOR is transcribed as a single gene product in the xanthine dehydrogenase (XDH) form, in which the enzyme exists intracellular, where substrate-derived electrons reduce nicotine amide adenine dinucleotide (NAD^+) to NADH. However, during ischemia and inflammation, reversible oxidation of critical cysteine residues (535 and 992) and/or limited proteolysis converts XDH to xanthine oxidase (XO) [12].

In the oxidase form, the affinity for oxygen is significantly enhanced, resulting in univalent and divalent electron transfer to O_2 generating O_2^- and hydrogen peroxide (H_2O_2), respectively [13]. Moreover, the inhibition of ATP-sensitive potassium channels, and the persistence of cell membrane depolarization result in increased activity of NADPH oxidase (NOX_2), and dysfunction of mitochondrial respiration, leading to more increase in the production of the reactive oxygen species (ROS) [7,9]. Increased production of both NO and ROS results in NO oxidation to produce nitrite (NO_2^-).

Role of NO to Protect the Vascular Endothelium during IRI

NO contributes to vessel homeostasis by inhibiting vascular smooth muscle contraction and growth, platelet aggregation, and leukocyte adhesion to the endothelium. NO acts through the stimulation of the soluble guanylate cyclase, which is a heterodimeric enzyme with subsequent formation of cyclic-GMP. Cyclic-GMP activates protein kinase G, which causes reuptake of Ca^{2+} and the opening of calcium-activated potassium channels that play an important role in the protection against IRI [14,15].

Several studies documented the important role of NO in mediating the protective effect of IPC and RIPC. While the locally produced NO can exert its action in case of IPC, it can't be accused for RIPC protective effect because of its short blood half-life (≤ 2 milliseconds) [16]. However, it was observed that NO inhalation in human provides protection against IRIs, while being associated with a significant increase in the circulating levels of nitrite. In addition, NO_2^- showed the ability to protect against IRI, to exert cytoprotective effects, and to decrease the infarction size similar to NO [17-24]. Moreover, it has recently been confirmed that the application of brachial artery RIPC results in the activation of eNOS and increased plasma NO_2^- levels [25].

In the heart, NO_2^- can be reduced to NO and N_2O_3 by myoglobin. In addition, mitochondrial amidoxime reducing components (mARC1&2) reduce NO_2^- to NO in various tissues [26,27]. NO and S-nitrosothiols formed from nitrite inhibit complex I of the respiratory chain during reperfusion. This attenuates the increased production of ROS in response to IRI, and indirectly improves the functionality of complex II [28,29].

In the vascular endothelium, at low concentrations, NO reacts with certain target proteins mainly through post-translational S-nitrosylation, thus regulating cell survival, smooth muscle tone and immune signaling [30]. Nevertheless, NO reactions in the setting of apoptosis appear to be double-faced. The nitrosative stress, similar to the oxidative stress, can potentially trigger cell death processes such as DNA fragmentation and lipid oxidation [31]. However, it can also have a protective role involving nitrosation of caspases and Poly-ADP-ribose-Polymerase, leading to inhibition of apoptosis [32].

Role of Fibrinogen

On the contrary to the proinflammatory effects of immobilized FB/fibrin, sFB has the ability to inhibit lymphocytic antigen 1-dependent binding to ICAM-1 through a direct interaction with ICAM-1 [7], and to reduce IL8-activated neutrophils binding to ICAM-1-expressing cells, in addition to reducing the binding of neutrophils to TNFα-activated endothelium to 40%, under flow conditions [33].

In addition, the interaction between FB and αM βII-integrin receptor has been reported to result in the activation of Rap-1, Talin-1 and CaMKII signalling. Rap1 is activated by adenosine diphosphate, hyperosmotic and cold stresses, interleukin-1, adenosine, and TNFα, where its active form bind to GTP [34]. The increased expression/activity of Rap-1 leads to NF-κB induction, while Rap-1 depletion leads to NF-κB decreased activity as Rap-1 is also important for the phosphorylation of p65 subunit of NF-κB. Remarkably, similar to inhibiting NF-κB, knockdown of Rap-1 sensitizes some cells to apoptosis [35-37].

While Talin-1 interacts with Rap-1 and is essential for adhesion, migration and phagocytosis, NF-κB activity is enhanced by ROS, TNFα, and interleukin 1-beta (IL-1β). Active NF-κB turns on the expression of genes that keep the cell proliferating and protect the cell from the conditions that would otherwise initiate apoptosis. Defects in NF-κB results in increased susceptibility to apoptosis leading to increased cell death. This is because NF-κB regulates anti-apoptotic genes especially the TRAF1 and TRAF2 and, therefore, checks the activities of the caspase family of enzymes, which are central to most apoptotic processes [38,39]. In conclusion, FB has the potential to play an anti-apoptotic role, especially during increased ROS production and inflammation.

CaMKII is activated by Ca^{++} and phosphorylation of its Thr287. Its inactivation is achieved through the physphorylation of Thr 306/307. Independently of Ca^{++}, it can also be activated by ROS via O-linked glycosylation of Ser280 by O-linked N-acetylglucosamine and via NO-dependent nitrosylation of Cys116, Cys273, or Cys290. When activated, it activates L Type Ca^{++} channels, slows the inactivation of Na^+ channel and activates K^+ channels [9]. The activation of K^+ channels has been strongly suggested to be a key protective mechanism against IRI.

Taken together, NO and the circulating nitrite, which can be reduced to NO, have been reported to be involved in mediating the action of the IPC and RIPC techniques, and have potential anti-apoptotic activities. However, according to the above discussed findings, the activation of Rap1-NF-κB and CaMKII signaling, by sFB during inflammation (acute phase), has potential anti-inflammatory and anti-apoptotic activities, in addition to the ability to activate K^+ channels, which are protective against IRI.

The Interaction between NO and FB

While the vascular endothelial uptake of FB was reported to increase by the inhibition of NO, this effect seems to be related to the secondary induced hypertension as the effect was not reproducible when the inhibition of NO didn't alter the normotensive status [40]. In addition, the exposure of FB to ProliNONOate, a donor of NO, affects the structural formation of the fibrin clot, resulting in lower density, but thicker fibers [41]. Such structural variations can have significant

impact on embolization and fibrinolysis, where the platelets can retract low density more than high density fibrin fibres [42]. On the other side, FB has been reported to decrease the efflux of NO from the erythrocytes, and increase the NO oxidative metabolites and S-nitroglutathione [43].

Conclusion

While FB is a risk factor for cardiovascular and inflammatory diseases that is also able to decrease the efflux of NO, and increase the NO oxidative metabolites and S-nitroglutathione, the increased sFB during the acute phase reaction might have other protective aspects that should be carefully investigated. Determining the exact signalling and functions of sFB, and the incorporated functional domains responsible for various actions, has the potential to open the gate for new pharmacological innovations to protect and or treat certain vascular and inflammatory diseases.

Conflicts of Interest

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