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Commentary

Ischemia/reperfusion injury: Effect of simultaneous inhibition of plasma cascade systems versus specific complement inhibition

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ABSTRACT

Ischemia/reperfusion injury (IRI) may occur from ischemia due to thrombotic occlusion, trauma or surgical interventions, including transplantation, with subsequent reestablishment of circulation. Time-dependent molecular and structural changes result from the deprivation of blood and oxygen in the affected tissue during ischemia. Upon restoration of blood flow a multifaceted network of plasma cascades is activated, including the complement-, coagulation-, kinin-, and fibrinolytic system, which plays a major role in the reperfusion-triggered inflammatory process. The plasma cascade systems are therefore promising therapeutic targets for attenuation of IRI. Earlier studies showed beneficial effects through inhibition of the complement system using specific complement inhibitors. However, pivotal roles in IRI are also attributed to other cascades. This raises the question, whether drugs, such as C1 esterase inhibitor, which regulate more than one cascade at a time, have a higher therapeutic potential. The present review discusses different therapeutic approaches ranging from specific complement inhibition to simultaneous inhibition of plasma cascade systems for reduction of IRI, gives an overview of the plasma cascade systems in IRI as well as highlights recent findings in this field.

1. Introduction

Ischemia is the clinical condition of an impaired circulation, which results in an undersupply of oxygen and nutrients in the affected tissue. Ischemia can occur through thrombosis or embolism, but can also be induced during surgery via tourniquet application as well as in transplantation. The absence of blood and oxygen causes time-dependent molecular and structural changes. In general, all organs and tissues are susceptible to ischemia, however susceptibility to an ischemic insult differs between organs. Brain tissue can cope with an ischemic burden for only a few minutes, whereas muscle tissue is able to withstand ischemia for 60–90 min without showing irreversible damage. Restoration of blood flow, termed as reperfusion, is the only effective treatment to prevent irreversible damage and necrosis of the ischemic tissue. Paradoxically, reperfusion activates a complex inflammatory response, which may finally lead to ischemia/reperfusion injury (IRI). Thus, not only prolonged ischemia itself, but also subsequent reperfusion of the affected tissue can result in irreversible cell damage or necrosis as well as microvascular and endothelial injury.

Already in 1960, Jennings et al. described the deleterious effect of reperfusion of ischemic tissue in a canine model of myocardial IRI [1]. As compared to the induction of permanent ischemia, the authors reported an acceleration of cellular necrosis after induction of transient ischemia and subsequent reperfusion [1]. Typically, myocardial ischemia followed by reperfusion manifests in arrhythmias, microvascular dysfunction, myocardial stunning as well as myocyte death. As seen in transplantation, IRI of the lung is characterized by non-specific alveolar damage, edema formation and hypoxemia. The clinical spectrum of lung IRI may range from mild hypoxemia to acute respiratory distress syndrome. As compared to other organs, the brain is particularly susceptible to ischemia, since it suffers irreversible neuronal damage after only 5 min of complete ischemia, which can be attributed to its high metabolic rate [2]. For brain ischemia, as occurring in stroke, induction of reperfusion through thrombolysis or thrombectomy seems to be only beneficial, if executed within three hours of the onset of ischemic stroke [3]. In the brain, induction of reperfusion by using thrombolytic agents, such as urokinase seems to be very critical, as patients may suffer cerebral reperfusion injury manifesting in intracranial hemorrhage as well as fatal cerebral edema formation [4]. Renal IRI typically occurs in the setting of transplantation, which is of particular importance. Renal failure may occur, which is characterized by an abrupt loss of the renal

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function to excrete wastes, concentrate urine, conserve electrolytes or maintain fluid balance resulting in high mortality rates [5]. The cortical-medullary region is the most susceptible region to tubular injury, inflammation and vascular alterations [6]. In comparison to brain, heart, lung and kidney, the liver has a clear advantage based on its unique dual blood supply coming from the hepatic artery and the portal vein, which can counterbalance arterial blood flow impairments. However, serious alterations in blood supply are found in clinical settings of portal vein obstruction, transplantation, surgical intervention or trauma, which cause high morbidity and mortality [7]. Reperfusion of the hepatic ischemic tissue leads to an increase of liver enzymes, biliary strictures and in severe cases to dysfunction or failure. Of particular importance is the deleterious effect of liver IRI on other organs, which occurs secondary to liver injury.

Not only organs can be crucially affected by ischemia, but also muscle tissue, which may become ischemic through tourniquet application during surgical intervention, trauma or thrombosis. Characteristic clinical signs of skeletal muscle IRI are edema formation, loss of muscle viability, as well as apoptosis and necrosis in the affected muscle tissue. In severe cases, IRI-induced rhabdomyolysis, the damage of muscle fibers, can result in compartment syndrome, a rise in pressure within the muscle fasciae due to edema formation, which in turn may lead to extensive microcirculatory impairment and consequently the loss of a whole limb. In addition, systemic complications can occur, such as distant organ damage due to myoglobin release and a generalized inflammatory reaction, cardiac arrhythmias, as well as disseminated intravascular coagulation [8].

Reperfusion of ischemic tissue initiates a complex inflammatory response without involvement of pathogenic triggers, known as sterile inflammation, whereby endogenous molecules may act as alarmins or danger-associated molecular patterns (DAMPs) [9]. The immune response is stimulated through self-antigens, which are functional components of intact cells but become stimulators of innate immunity when released through necrosis or secreted from injured cells [9]. In 1996, Weiser et al. described a novel mechanism for reperfusion injury that involves antibody deposition and activation of complement leading to an acute inflammatory response [10]. One decade later, Zhang and Carroll et al. introduced the concept of innate autoimmunity, which is based on the finding that circulating natural antibodies recognize self-antigens and elicit an acute inflammatory response involving the complement system [11]. However, the last years of extensive research in reperfusion injury have shown that also other plasma cascade systems, including the coagulation as well as the kinin systems, are of major importance. Therefore, therapies targeting the plasma cascade systems seem to be promising for attenuation or even prevention of IRI. The following overview aims to give a brief overview of the mechanisms of IRI and mainly focuses on the role of the plasma cascade systems in reperfusion injury.

2. Vascular barrier changes in ischemia/reperfusion injury

Impairment of the vascular barrier can cause changes in endothelial permeability, leading to edema and increased interstitial pressure. In skeletal muscle, this may result in the compartment syndrome and altered tissue perfusion. In a homeostatic situation the inner lining of blood vessels, the endothelium, maintains an anti-coagulatory and anti-inflammatory environment (Fig. 1). This is, amongst others, upheld by the protective layer of the glycocalyx, which is a negatively charged and tight mesh consisting of proteoglycans, such as syndecans, glypicans or perlecans, glycosaminoglycans including heparan sulfate, chondroitin sulfate, dermatan sulfate, keratan sulfate, associated plasma proteins and hyaluronan. The glycocalyx shields the endothelium and its adhesion molecules on the luminal side and also prevents the interaction of inflammatory cells with the

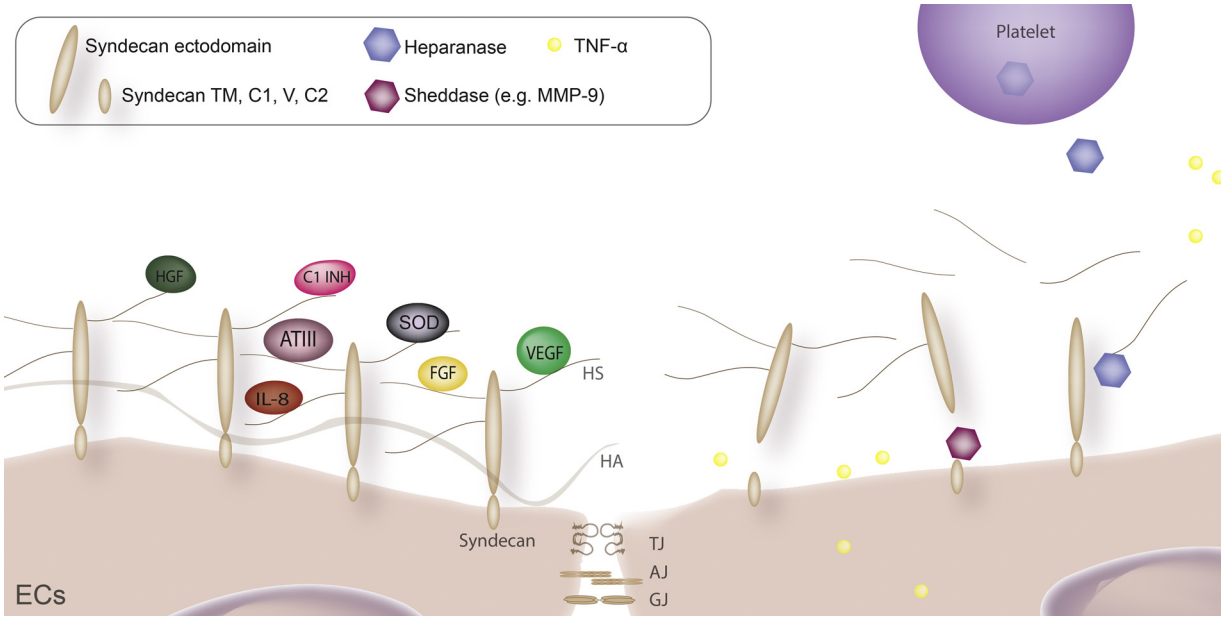

Fig. 1. Shedding of the glycocalyx. In a homeostatic condition, the intact glycocalyx binds a myriad of proteins (mainly via heparan sulfates), which in total maintain an anti-inflammatory and anti-coagulant state (left cell). However, during an ischemic event and subsequent reperfusion this state is rendered into a pro-inflammatory and pro-coagulant one, since shedding of proteoglycans (syndecans), and HS occurs (right cell). HS can be cleaved from syndecans via the endoglycosidase heparanase, which is secreted by activated platelets. The ectodomain of syndecans can be cleaved from its intracellular domain via different mechanisms. TNF-α, secreted by endothelial cells or by neutrophils can cause changes in the glycocalyx either dependent or independent of leukocyte adhesion, as it up-regulates endothelial-derived matrix metalloproteases and may cause endothelial release of superoxide, both resulting in shedding. MMPs are known sheddases of syndecans. AJ, Adherens junction; ATIII, antithrombin III; C1, conserved domain 1; C1 INH, C1 esterase inhibitor; C2, conserved domain 2; ECs, endothelial cells; FGF, fibroblast growth factor; GJ, gap junction; HA, hyaluronic acid; HGF, hepatocyte growth factor; HS, heparan sulfate; IL-8, interleukin-8; MMP-9, matrix metalloprotease-9; SOD, superoxide dismutase; TJ, tight junction; TM, transmembrane domain; TNF-α, tumor necrosis factor-alpha; V, variable domain; VEGF, vascular endothelial growth factor. This illustration is not drawn to scale.

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