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Ischemia and Reperfusion Injury in Reconstructive Transplantation

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Abstract

The reestablishment of blood supply to the ischemic tissue leads to a cascade of deleterious pathophysiological conditions that ultimately culminate in a vicious cycle termed ischemia reperfusion injury (IRI). This article reviews the pathophysiology of IRI in vascularized composite tissue allotransplantation (VCA).

Keywords: Ischemia reperfusion injury; Vascularized composite tissue allotransplantation

Introduction

Transplantation of foreign vascularized composite tissues may be considered as one of the recent adventurous leaps in medicine. The mastery of microsurgery not only provided surgeons with a feasibility that allowed them to rebuild injured body-parts with autologous tissues, but upon that, equipped them with a tool, that facilitated a surgical reconstruction with a foreign equivalent body-part, procured from a brain-dead human individual. This kind of transplantation - without doubt - represents the backbone of all modern reconstructive surgery and to date more than 200 patients worldwide have received a vascularized composite allograft (VCA), mainly a hand or a face [1].

However, what everybody has followed with enthusiasm is even so faced with grave challenges. Similar to solid organs, a VCA is predominantly confronted with two cross-linked problems after transplantation: Ischemia reperfusion injury and rejection [2]. Through the application of cold preservation solutions and immunosuppressive therapies, right from the start, treatment strategies to prevent undesirable outcomes are successfully called into service. However, the outcomes - although excellent - do not nurse the human thirst for further improvement.

Ischemia Reperfusion Injury

Ischemia reperfusion injury has a wide clinical relevance since it influences the outcome of graft and patient survival after reconstructive and transplant procedures [3,4]. In its classic manifestation, impaired arterial blood supply results in a severe imbalance of metabolic supply and demand, causing tissue hypoxia. Perhaps surprisingly, restoration of blood flow and reoxygenation is commonly associated with an exacerbation of tissue injury and profound inflammatory response [5]. Tissue can be either subjected to periods of cold or warm ischemia, depending on the clinical setting. Cold ischemia typically occurs in transplantation, where tissues are flushed and stored in ice-cold preservation solutions after procurement, whilst warm ischemia occurs during revascularization or following organ traumas such as stroke or myocardial infarction.

The first clue to the existence of ischemic injury was brought up in the 1960s, when it was recognized that the restoration of blood supply after the prolonged clamping of major arteries was followed by systemic shock and acidosis [6,7]. It is today appreciated that this shock is caused by more than just the "flushing out of toxic metabolites", that accumulate in ischemic tissues. Ischemia and reperfusion injury was first described in 1975 by Cerra et al. upon the findings that the restoration of blood flow to myocardial pedicles in dogs was followed by subendothelial hemorrhagic necrosis [8].

Recent advances in understanding the molecular and immunological consequences of ischemia and reperfusion has led to conclusion that even the exposure of a single organ to ischemia and reperfusion (e.g. liver) may subsequently induce an inflammatory response in another distant organ (e.g. intestine) eventually leading to multiorgan failure [9]. It is important to point out, that IRI can be a heterogeneous group of condition. Indeed there are important differences between a systemic reduction of the blood flow (e.g. during shock) compared to regional ischemia and reperfusion of a single organ.

The past decade has seen innovative experimental strategies to render tissues more resistant to ischemia and reperfusion-associated tissue inflammation; however, the challenge to integrate these new therapies into clinical practice remains ahead.

Mechanisms of Ischemia Reperfusion Injury

In fact, a plethora of pathological processes contribute to ischemia and reperfusion associated tissue injury. For example, hypoxia as occurs during ischemia is associated with impaired endothelial cell barrier function [10] due to a decrease of intracellular cAMP levels and an accompanying increase in vascular permeability and leakage [11]. In addition ischemia leads to an activation of several cell death programs including apoptosis, necrosis and autophagy associated cell death [12]. The ischemic period is in particular associated with significant changes in intracellular signaling activities subsequently resulting in alterations in the transcriptional control of gene expression. Reperfusion, however, is characterized by an increased production of reactive oxygen species (ROS) as well as cumulative episodes of autoimmune and innate immunologic responses [13]. There remains an urgent need to gain additional mechanistic insights into the molecular events that are triggered by IRI and that could be exploited therapeutically.

Implications for Reconstructive Surgery

With autologuous free flap transfer becoming more and more important in reconstructive surgery, it is probably important to consider ischemia reperfusion injury as a possible key factor that might influence

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a successful outcome of a reconstructive procedure [3]. Although free flap reconstruction is generally triumphant in 90%-95% of the cases [14,15] a small percentage of patients show signs of postoperative IRI. Sometimes this even results in partial or complete flap loss, which can be traumatic for the patient. Nevertheless, autologous tissue transfer is different from allogeneic tissue transplantation because the immunological reactions, which are in part amplified by IRI and ultimately promote acute and chronic rejection, do not occur [16,17].

However, with a scientific foundation in tissue regeneration, transplantation and stem cell biology reconstructive transplantation is uniquely poised to make the next major advances in medicine. By replacing missing body parts like the face, hand and foot, reconstructive transplantation can transform patients' lives in ways that could not have been imagined only recently.

Autologus tissue transfer and replantation

The reconstruction of severe tissue defects with autologus tissue can in fact be paralleled by a detrimental spectrum of IRI related problems. Especially the replantation of ischemic limbs can not only cause severe IRI related complications in the affected organ, but can accordingly lead to severe damage in distant organs due to acidosis, hyperkalemia, myoglubinuria and disseminated intravascular coagulation [18]. As expected there is a strong correlation between acute renal failure due to arterial occlusion and limb revascularization surgery [19]. Furthermore, replantation surgery can cause severe dysfunction of the respiratory system, since reactive oxygen species and cytokines, which are released upon reperfusion, can cause a severe capillary leakage within the microvasculature of the lung leading to pulmonary edema [20]. It has been shown that these effects can be so profound that replanted limbs had to be removed in an effort to overcome these problems [21].

In free flap surgery, IRI always occurs when a graft is transplanted from one area to another. This so-called "primary ischemia" can be succeeded by any circulation-compromising event (e.g. failure of the anastomosis resulting in thrombosis, external mechanical compression due to haematoma or tight wound closure or compression), which is then referred to as "secondary ischemia". Animal studies have confirmed that skin flaps are indeed less tolerant to secondary than to primary ischemia [15]. However, since secondary ischemia cannot be prevented except for training the surgeon's microsurgical skills, efforts are mainly aimed at reducing (primary) IRI.

Reconstructive transplantation

Interruption of oxygen and nutrient supply during ischemia is invariably associated with donor organ procurement in the process of reconstructive transplantation (RT). The reestablishment of blood supply after transplantation causes not only the resumption of respiratory and metabolic function but also implies a series of events, which culminate in severe injury to the different components of a vascularized composite tissue allograft. This ischemia reperfusion injury constitutes the first immediate threat to a graft and comprises a multitude of cellular and molecular events including loss of endothelial integrity and microcirculatory disorders. From solid organ transplantation we know that this plethora of adverse effects contribute to early graft dysfunction through the activation of the innate immune system and are even capable to trigger chronic rejection which ultimately leads to graft loss. Today we have to hypothesize that ischemia reperfusion injury also plays a dominant role in the emerging field of VCA. The experience in solid organ transplantation has provided evidence that cold ischemia thresholds are different for individual organs (Figure 1). If ischemia times extend beyond these limits graft function is adversely affected. In the field of VCA these thresholds could be different for individual tissue components (i.e. skin, muscles, nerves, blood vessels, bone marrow) of the allograft.

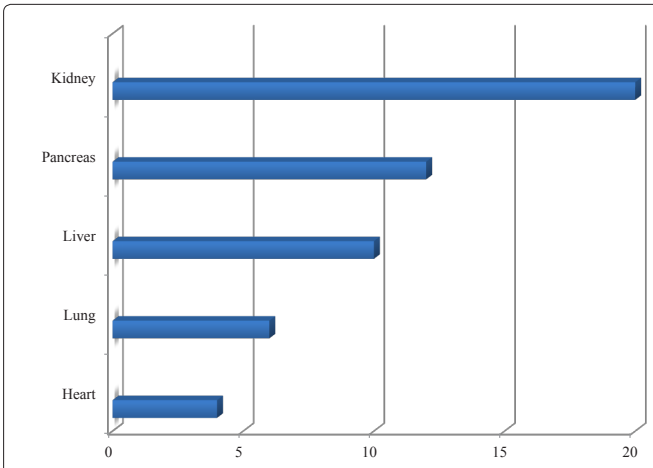

Figure 1: Cold ischemia time thresholds in solid organ allografts.

However, the world experience in hand transplantation over the past decade has confirmed that cold ischemia times have ranged between 2.5 and 13 hours, however a certain threshold has not been defined. It is therefore important to define these thresholds in VCA because of yet undetermined impact of cold and warm ischemia on immune and non-immune outcomes of the graft.

Conclusion

Ischemia and reperfusion injury has always been crucial for transplant outcome and the task to at least maintain the quality of the graft before transplantation has become even more important in the present era with increasing numbers of older, more marginal and non heart beating donors. The past decades have seen strong progress in understanding the underlying pathophysiological events of IRI, and a multitude of therapeutic options have emerged to render tissues more resistant to IRI. For example the use of cold storage preservation solutions, the application of cold machine perfusion and the introduction of ischemic preconditioning in specific clinical settings have indeed contributed to distinct advances in the field of organ preservation and transplantation. The relatively new domain of reconstructive transplantation already benefits from the recent advances made in solid organ transplantation, regarding tissue preservation; however RT is furthermore uniquely poised to make the next major advances in the field of tissue preservation.

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