EBioMedicine xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Review

Ischemia-Reperfusion Injury Reduces Long Term Renal Graft Survival: Mechanism and Beyond

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ARTICLE INFO

Article history:
Received 7 December 2017
Received in revised form 18 January 2018
Accepted 20 January 2018
Available online xxxx

Keywords:
Ischemia-reperfusion
Graft survival
Renal transplantation
Acute rejection
Th cells: T helper cells

ABSTRACT

Ischemia-reperfusion injury (IRI) during renal transplantation often initiates non-specific inflammatory responses that can result in the loss of kidney graft viability. However, the long-term consequence of IRI on renal grafts survival is uncertain. Here we review clinical evidence and laboratory studies, and elucidate the association between early IRI and later graft loss. Our critical analysis of previous publications indicates that early IRI does contribute to later graft loss through reduction of renal functional mass, graft vascular injury, and chronic hypoxia, as well as subsequent fibrosis. IRI is also known to induce kidney allograft dysfunction and acute rejection, reducing graft survival. Therefore, attempts have been made to substitute traditional preserving solutions with novel agents, yielding promising results.

Contents

Abbreviation: IRI, ischemia-reperfusion injury; MMP, matrix metalloproteinases; DAMP, Damage associated molecular pattern; MHC, major histocompatibility complex; IL-1, Interleukine-1.

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https://doi.org/10.1016/j.ebiom.2018.01.025

1. Introduction

Renal grafts inevitably experience ischemia from the moment they are separated from the donor blood supply. The insult begins following a period of transient surgical warm ischemia during donor organ extraction, followed by a lengthy cold ischemic period in hypothermal preserving solution before ending with warm ischemia during implantation in the recipient. After revascularization, blood flow in post-ischemic kidneys activates a sequence of events that aggravates renal injury. This pathological phenomenon is described as ischemia-reperfusion injury (IRI) and contributes to a high rate of morbidity. The severity of renal insult correlates strongly with early renal graft failure. However, most transplant patients completely recover from the initial IRI period. Clinical evidence demonstrates that transplanted kidneys with prolonged ischemic time are more susceptible to long-term deterioration. We review clinical studies, in order to elucidate the association between early IRI and later graft loss, and discuss important concepts relating to the pathology and prevention of graft dysfunction.

2. Survival of the Renal Grafts

With the introduction of potent immunosuppressive drugs such as calcineurin inhibitors, acute rejection rates have fallen dramatically, whilst allograft survival rates have risen steadily. Hariharan et al. (2000) analyzed graft survival for 93,934 renal transplantations performed in the USA between 1988 and 1996 and reported a marked improvement in the long-term survival of renal grafts from both living and cadaveric donors. Over this period, the half-life of living donor grafts increased from 12.7 to 21.6 years, and the half-life of cadaveric grafts increased 7.9 to 13.8 years. These significant improvements in graft survival have been attributed to refinement in kidney preservation and improvements in peri-operative care and immunosuppressive medication.

Despite the continuous progress in immunosuppressive and supportive therapy, improvement in graft survival has reached a plateau. The majority of grafts eventually develop chronic dysfunction which limits long-term graft survival (Chapman et al., 2005). Histologically, chronic failure is characterized by intimal thickening of arteries, glomerulosclerosis, tubular interstitial fibrosis, and tubular atrophy. Renal functional impairment is often found in combination with proteinuria and aggravation of de novo hypertension. These histological changes are thought to be the end result of cumulative damage to renal grafts associated with both immune and non-immune factors, however the precise etiological factors underlying these changes remain to be elucidated (Nankivell and Chapman, 2006). Renal graft IRI may be one of the critical factors contributing to deterioration in long-term graft survival.

3. Impact of IRI on Renal Graft Survival: Clinical Evidence

3.1. Ischemia Reperfusion Injury and Marginal Donor Organs

There are three main types of kidney donors: donation after brain death (DBD) donors, donation after cardiac death (DCD) donors and living donors. Another donor source is expanded criteria donation (ECD), which includes DCD donors and those with particular co-morbidites such as arterial hypertension or an age > 60 years (Iordanous et al., 2009).

DCD donors are commonly patients who have been unsuccessfully resuscitated or are awaiting cardiac death (Doyle et al., 2015). The commonest type of organ transplantation in the UK is donation after brain death (DBD), which is characterized by total and irreversible loss of brain function (Robey and Marcolini, 2013). DBD is generally preferred over DCD because the graft is perfused until the point of organ retrieval. Whilst organs from DCD donors are subject to prolonged warm ischaemic times, they may have a theoretic advantage. In DBD donors, also known as heart-beating brain dead donors, brain death results in a systemic inflammatory 'cytokine storm' (Vergoulas et al., 2009). The body responds by increasing the release of circulating catecholamines, resulting in a subsequent autonomic storm. This can precipitate pulmonary oedema, hypertension, severe myocardial damage and microvascular and parenchymal damage to the renal graft. Following this period of intense autonomic activity, there is a dramatic fall in circulating catecholamines, resulting in vasodilation, bradycardia and tissue hypoxia. Whilst DCD donors are also susceptible to this inflammatory response, due to the rapidity of neuronal damage this is often to a smaller extent than DBD donors (Mckeown et al., 2012). Due to a lack of donors and the prevalence of graft failure, there has been an increased use of marginal donors, such as DCD donors. Therefore, it is important to understand if there is a distinction between the vulnerability of DCD and DBD grafts to ischemia and reperfusion.

Summers et al. (2010) performed a retrospective analysis of the UK Transplant Registry in order to assess the factors that affect outcomes following kidney transplantation of 9134 deceased donor kidney transplants performed between January 1, 2000 and December 31, 2007 (Summers et al., 2010). 8289 (90.7%) were from DBD donors, and the remaining 845 transplants (9.3%) were extracted from donation after cardiac death (DCD) donors. The cohorts demonstrated no significant difference in 5-year kidney graft survival (76.4% DBD vs 76.2% DCD) or primary non-function rates (3% each). However, the incidence of delayed graft function (DGF: 24% DBD vs 49% DCD, $P < 0.0001$) was significantly higher in DCD grafts. DGF is a type of acute renal failure that causes post-transplantation oliguria, increased allograft immunogenicity and also increases the risk of acute rejection episodes (Gueler et al., 2015). Similarly, Gagandeep et al. also undertook an analysis of clinical outcomes but from US national data (Gagandeep et al., 2006). The authors reported that both allograft and recipient survival were similar between DCD and DBD cohorts. However, the risk of delayed graft function (DGF) was found to be 42 to 51% in DCD recipients in comparison to 24% in DBD grafts. Likewise, Doshi and Hunsicker also found no significant difference in 5-year patient survival (DCD vs. DBD 81.3 vs. 81.8%; $P = 0.70$) or allograft survival rates (DCD vs. DBD, 66.9 vs. 66.5%; $P = 0.52$). The risk of DGF, however, was higher in DCD grafts (DCD vs. DBD, 41 vs. 24%; $P < 0.001$). Therefore, studies have consistently demonstrated the increased prevalence of DGF in DCD kidney graft recipients. In the US, between 1985 and 1999, the rate of DGF was reported at 14.7% (Ojo et al., 1997). The incidence of DGF rose to 23% between 1998 and 2004 and was concurrent with the increased use of ECD (Tapiawala et al., 2010). DGF continues to be a major barrier for allograft survival and requires the compulsory return of the patient to dialysis.

Whilst both DCD and DBD grafts seem to possess similar rates of allograft survival and patient survival, higher rates of DGF in DCD organs may be due to these grafts being more susceptible to ischemia reperfusion injury (Gobe et al., 1999). Experimental studies have demonstrated

Please cite this article as: Zhao, H., et al., Ischemia-Reperfusion Injury Reduces Long Term Renal Graft Survival: Mechanism and Beyond, EBioMedicine (2018), https://doi.org/10.1016/j.ebiom.2018.01.025