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Ischemia Reperfusion Injury: Where to Interrupt the Damaging Process

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During the last five decades organ transplantation has developed from an experimental therapeutic approach to the gold standard therapy for irreversible end-stage organ failure. However, despite major advances in surgical techniques, perfusion solutions, immunosuppression and antibiotic prophylaxis, long-term survival does not always mirror the substantial short-term outcome improvements achieved [1]. Ischemia reperfusion injury (IRI) is crucially involved in this discrepancy.

The continuous efforts to increase the donor pool because of the chronic shortage of organs, have led to the implementation of transplantation of so called "marginal" or "extended criteria" donors as well as donation after cardiac death (DCD). However, the observation, that these organs are more prone to IRI related injuries, together with growing evidence that IRI influences not only short- but also long-term graft outcomes (contrasting with much better outcomes of kidneys from living donors), all highlight IRI as a crucial factor in influencing the fate of the graft.

On-going experimental basic and translational research describe a plethora of mechanisms participating in this graft injury, involving mitochondria [2], complement factors and Toll-like receptors [3], reactive oxygen [4] as well as reactive nitrogen species [5]. The close relationship between the innate and the adaptive immune system is also being increasingly unravelled [6], thereby explaining the observed higher incidence of acute rejections in organs suffering from IRI [7]. Microcirculatory derangements observed in IRI [8,9] highlight the role of endothelial cells [10,11]. Even though most of the promising results achieved *in vitro* and *in vivo* in experimental animal studies have not yet (and may never) reached human investigation, currently registered clinical trials regarding IRI are clearly based on these results.

The timeframe for therapeutic interventions against IRI ranges from donor management prior to organ retrieval to the time following graft reperfusion in the recipient. In fact, encouraging experimental results are achieved with post-conditioning strategies. Even though still not fully understood, previously transplanted organs or organs suffering from an ischemic insult which are subsequently re-exposed to controlled ischemic periods show decreased ischemic injury [12]. Mainly reported for cardiac ischemia, this strategy finds increasing support in transplantation surgery especially if it is applied in a remote organ, like hind limbs [13]. These findings are currently translated into a registered clinical trial with kidney transplant recipients, where a remote post-conditioning of the upper limb will be applied (clincaltrials.gov number NCT01363687). Other trials focus on perioperative recipient treatment with intraoperative nitric oxide inhalation in liver recipients (clincaltrials.gov number NCT00948194) or sevoflurane based anaesthesia in kidney recipients (clincaltrials.gov number NCT00337051). Both agents have been previously shown to decrease leukocyte as well as platelet adherence, hence, ameliorating IRI related microcirculatory derangements [14,15]. Even though results of these on-going studies are of major interest and still pending, it seems preferable to target IRI by interfering with the process at earlier stages, in order to prevent damage rather than repair it.

Recently, pulsatile organ reperfusion has been shown to decrease delayed graft function following kidney transplantation, with an even more accentuated protection in extended criteria grafts, if compared to standard cold organ storage [16,17]. First results of a newly developed hypothermic liver perfusion machine are also encouraging [18]. Ongoing clinical observation of these patients as well as a current clinical trial using hypothermic oxygenated perfusion (HOPE) in liver grafts (clincaltrials.gov number NCT00337051) will reveal, whether this strategy will have broad acceptance also in liver transplantation. Not only the optimisation of organ preservation but also the possibility of *ex-vivo* evaluation and *ex-vivo* organ re-conditioning represent major theoretical benefits of machine perfusion. This strategy has been successfully applied in lung transplantation with intra-airway delivery of adenovirus encoding the anti-inflammatory cytokine IL-10 [19,20], although, normothermic Extracorporeal Membrane Oxygenation (ECMO) was used in this study.

Changing the "dogma" to preserve in a normothermic rather than in hypothermic state, is a current debate in abdominal transplantation, especially in DCD donors, which are more inclined to develop severe IRI. The effectiveness of this preservation strategy was shown in a large animal study which demonstrates substantial benefits in transplanted DCD livers following normothermic ex-vivo perfusion compared to standard hypothermic preservation [21]. Normothermic perfusion solutions are oxygenated and supplied with nutrients that allow physiological metabolism to take place and thereby avoiding accumulation of metabolites during hypoxia which react with normothermic blood at the time of reperfusion. Recently, a clinical trial using Maastricht type 2 NHBD was published where ECMO was already started before organ procurement. Almost 10% of livers from this previously discharged donor pool were successfully transplanted and resulted in acceptable 1-year patient and graft survival [22]. Despite higher logistically demands due to different teams involved in recovering several organs, this study identifies another key time point for treatment of IRI related graft damage, i.e. before organ recovery.

There is evidence that transplanted grafts benefit from "aggressive" donor management [23] and pre-treatment of the donor in order to mitigate deleterious mechanisms during brain dead and the pre-final phase. In a prospective randomised controlled trial pre-treatment with methylprednisolone has been shown to decrease the initial innate inflammatory response and also acute rejection episodes following liver transplantation [24]. Similarly, pretreatment of the donor with dopamine – known to decrease reactive oxygen species occurrence and increase renal blood perfusion - has been shown to decrease delayed graft function incidence of transplanted kidneys [25]. However, the main drawback of these studies may be represented by the choice of the endpoint, which focused on a single organ only instead of accounting for all organs retrieved. Registered, currently patient-recruiting, clinic

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trials address this issue by expanding their inclusion criteria to all the abdominal organs, even including thoracic organs. In this regard the Donor Simvastatin Treatment Trial (clincaltrials.gov number NCT01160978) is of particular interest, since among their pleiotropic actions statins have been repeatedly shown to protect organs from IRI [26]. Another form of donor pre-treatment consists in ischemic pre-conditioning. This approach is controversially discussed in liver resection, since no evident clinical benefits were shown in patients undergoing repeated short ischemic times before major liver resections and fewer surgeons nowadays use the Pringle manoeuvre for liver resections. Similarly, for liver transplantation there is currently no recommendation for IP. Even though most studies show decreased parenchymal damage, paradoxically, one prospective study resulted in an even higher IRI degree, even though associated with less acute rejection episodes ("ischemic preconditioning paradox", [27]). Additionally, no clinical benefit regarding recipient and graft survival has so far been demonstrated. However, just as for the ischemic postconditioning, organs can be remotely pre-conditioned. This approach would avoid subjecting the retrieved organ to direct injury, however, it should benefit from an up-regulation of hypoxia induced factors following ischemia of a remote organ. In children undergoing cardiac surgery for congenital heart defects remote ischemic pre-conditioning of the hind limb prior to cardiopulmonary bypass has already been shown to reduce the infarcted size [28]. A current randomised controlled trial is testing this approach by evaluating the influence of a short period of blood flow occlusion of the lower extremity prior to organ recovery. In this study, initial organ function as well as recipient and graft long-term survival of kidney, liver and pancreas grafts will be analysed (clincaltrials.gov number NCT00975702).

While on the one hand findings of new pathways in experimental studies is of crucial importance to gain further insights in IRI associated mechanisms, a complete understanding of the underlying molecular mechanisms may not be an absolute prerequisite before starting a clinical trial, especially if clear benefits are shown in preclinical studies. There is an increasing effort to translate experimentally achieved knowledge into clinical trials addressing IRI following organ transplantation with trials of many different strategies designed to interfere with IRI at different time points of the transplantation process. Which of these strategies will provide the best results is an open question, and the question on synergistic effects of two or more strategies could add further benefits – these complexities remain to be addressed. This plethora of clinical trials, all with the goal to reduce IRI, is a conditio sine qua non to provide a solid foundation to build on for every transplanted organ.

References

- Lodhi SA, Lamb KE, Meier-Kriesche HU (2011) Solid organ allograft survival improvement in the United States: the long-term does not mirror the dramatic short-term success. Am J Transplant 11: 1226-1235.
- Hermann M, Kuznetsov A, Maglione M, Smigelskaite J, Margreiter R, et al. (2008) Cytoplasmic signaling in the control of mitochondrial uproar? Cell Commun Signal 6: 4.
- Damman J, Daha MR, van Son WJ, Leuvenink HG, Ploeg RJ, et al. (2011) Crosstalk between complement and Toll-like receptor activation in relation to donor brain death and renal ischemia-reperfusion injury. Am J Transplant 11: 660-669.
- Ma A, Qi S, Chen H (2008) Antioxidant therapy for prevention of inflammation, ischemic reperfusion injuries and allograft rejection. Cardiovasc Hematol Agents Med Chem 6: 20-43.
- 5. Shi Y, Rehman H, Wright GL, Zhong Z (2010) Inhibition of inducible nitric oxide

synthase prevents graft injury after transplantation of livers from rats after cardiac death. Liver Transpl 16: 1267-1277.

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- Murphy SP, Porrett PM, Turka LA (2011) Innate immunity in transplant tolerance and rejection. Immunol Rev 241: 39-48.
- Geddes CC, Woo YM, Jardine AG (2002) The impact of delayed graft function on the long-term outcome of renal transplantation. J Nephrol 15: 17-21.
- Schaser KD, Puhl G, Vollmar B, Menger MD, Stover JF, et al. (2005) In vivo imaging of human pancreatic microcirculation and pancreatic tissue injury in clinical pancreas transplantation. Am J Transplant 5: 341-350.
- Maglione M, Hermann M, Hengster P, Schneeberger S, Mark W, et al. (2006) Tetrahydrobiopterin attenuates microvascular reperfusion injury following murine pancreas transplantation. Am J Transplant 6: 1551-1559.
- Preissler G, Loehe F, Huff IV, Ebersberger U, Shuvaev VV, et al. (2011) Targeted endothelial delivery of nanosized catalase immunoconjugates protects lung grafts donated after cardiac death. Transplantation 92: 380-387.
- Taflin C, Favier B, Baudhuin J, Savenay A, Hemon P, et al. (2011) Human endothelial cells generate Th17 and regulatory T cells under inflammatory conditions. Proc Natl Acad Sci U S A 108: 2891-2896.
- Ambros JT, Herrero-Fresneda I, Borau OG, Boira JM (2007) Ischemic preconditioning in solid organ transplantation: from experimental to clinics. Transpl Int 20: 219-229.
- Zeng Z, Huang HF, Chen MQ, Song F, Zhang YJ (2010) Heme oxygenase-1 protects donor livers from ischemia/reperfusion injury: the role of Kupffer cells. World J Gastroenterol 16: 1285-1292.
- Chappell D, Heindl B, Jacob M, Annecke T, Chen C, et al. (2011) Sevoflurane reduces leukocyte and platelet adhesion after ischemia-reperfusion by protecting the endothelial glycocalyx. Anesthesiology 115: 483-491.
- Abu-Amara M, Yang SY, Seifalian A, Davidson B, Fuller B (2012) The nitric oxide pathway - evidence and mechanisms for protection against liver ischaemia reperfusion injury. Liver Int 32: 531- 543.
- Moers C, Smits JM, Maathuis MH, Treckmann J, van Gelder F, et al. (2009) Machine perfusion or cold storage in deceased-donor kidney transplantation. N Engl J Med 360: 7-19.
- Treckmann J, Moers C, Smits JM, Gallinat A, Maathuis MH, et al. (2011) Machine perfusion versus cold storage for preservation of kidneys from expanded criteria donors after brain death. Transpl Int 24: 548-554.
- Guarrera JV, Henry SD, Chen SW, Brown T, Nachber E, et al. (2011) Hypothermic machine preservation attenuates ischemia/reperfusion markers after liver transplantation: preliminary results. J Surg Res 167: e365-e373.
- Ingemansson R, Eyjolfsson A, Mared L, Pierre L, Algotsson L, et al. (2009) Clinical transplantation of initially rejected donor lungs after reconditioning ex vivo. Ann Thorac Surg 87: 255-260.
- Cypel M, Liu M, Rubacha M, Yeung JC, Hirayama S, et al. (2009) Functional repair of human donor lungs by IL-10 gene therapy. Sci Transl Med 1: 4ra9.
- Brockmann J, Reddy S, Coussios C, Pigott D, Guirriero D, et al. (2009) Normothermic perfusion: a new paradigm for organ preservation. Ann Surg 250: 1-6.
- Fondevila C, Hessheimer AJ, Flores E, Ruiz A, Mestres N, et al. (2012) Applicability and results of Maastricht type 2 donation after cardiac death liver transplantation. Am J Transplant 12: 162-170.
- Salim A, Velmahos GC, Brown C, Belzberg H, Demetriades D (2005) Aggressive organ donor management significantly increases the number of organs available for transplantation. J Trauma 58: 991-994.
- 24. Kotsch K, Ulrich F, Reutzel-Selke A, Pascher A, Faber W, et al. (2008) Methylprednisolone therapy in deceased donors reduces inflammation in the donor liver and improves outcome after liver transplantation: a prospective randomized controlled trial. Ann Surg 248: 1042-1050.
- Schnuelle P, Gottmann U, Hoeger S, Boesebeck D, Lauchart W, et al. (2009) Effects of donor pretreatment with dopamine on graft function after kidney transplantation: a randomized controlled trial. JAMA 302: 1067-1075.
- Abdul Rahman MN, Chetter IC (2010) Statins and ischaemia reperfusion injury: a molecular biological review. Curr Vasc Pharmacol 8: 831-835.

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- Koneru B, Shareef A, Dikdan G, Desai K, Klein KM, et al. (2007) The ischemic preconditioning paradox in deceased donor liver transplantation-evidence from a prospective randomized single blind clinical trial. Am J Transplant 7: 2788-2796.
- Cheung MM, Kharbanda RK, Konstantinov IE, Shimizu M, Frndova H, et al. (2006) Randomized controlled trial of the effects of remote ischemic preconditioning on children undergoing cardiac surgery: first clinical application in humans. J Am Coll Cardiol 47: 2277-2282.

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