Forewarned is forearmed: arm with HIF activation

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Summary of key findings

Patients suffering from end-stage kidney disease (ESKD) have three treatment options: haemodialysis, peritoneal dialysis and kidney transplantation. While a successful kidney transplant provides a good quality of life, the supply of organs for donation is always less than needed, prompting major efforts to improve early and late graft function to ensure the best use of donated organs. Hypoxia-inducible factor (HIF) is a master gene switch of a number of adaptive responses against ischaemia [1]. Kai-Uwe Eckardt’s group opened a new avenue in this field through their success in inducing an array of endogenous protective mechanisms regulated by HIF before initiation of the acute injury associated with transplantation [2].

Review of the field

Using an allogenic Fisher-Lewis rat kidney transplant model, Eckardt’s group investigated the effect of a small molecule, prolyl hydroxylase domain-containing protein (PHD) inhibitor, in organ donors. In normoxia, HIF-α undergoes proteasomal degradation, which is triggered by hydroxylation at one or two conserved proline residues. Inhibition of the initial hydroxylation by PHDs therefore leads to normoxic expression and activation of HIF. The HIF stabilizer was given to donor animals 6 h before kidney transplantation.

In the first set of experiments in the acute model (short-term follow-up of 10 days), pretreatment with the HIF stabilizer protected the donated organ and allowed better survival of the recipient animals. Because a reagent was given prior to kidney transplantation, this method may be considered ‘preconditioning’. The original preconditioning was the phenomenon that brief ischaemic treatment before the subsequent insult induced a state of resistance by initiating a cascade of biochemical events, which allowed for the upregulation of the cellular protective genes in the tissue [3]. Dating back to 2003, we reported that pharmacological preconditioning to activate HIF was effective in an ischaemia-reperfusion model of acute kidney injury [4]. Since then, we and others have confirmed successful preconditioning against ischaemia-reperfusion injury using various modalities to activate HIF [5, 6]. Carbon monoxide (CO) is a powerful activator of HIF, and previous reports have also shown a protective effect of continuous CO exposure [7] or administration of a CO donor at the time of reperfusion [8] in an acute model of kidney transplantation. In their recent study, Bernhardt and colleagues showed the preconditioning effects of pharmaceutical HIF activation in an acute model of kidney transplantation.

In the case of ischaemic preconditioning, a biphasic temporal relationship exists between organ (cardiac) protection and the duration of reflow. Maximum protection
of ‘classic’ preconditioning is achieved when the sustained ischaemic challenge is initiated within 30 min after the final bout of ischaemia, but rapidly wanes if the duration of intervening reflow is extended to 1 h. If the period of intervening reperfusion is further protracted to 24–72 h, a second window of milder protection emerges (‘delayed’ preconditioning). An advantage of pharmacological preconditioning is that the effective window may be wider than that with classic preconditioning, and is determined by the half-life of the reagent.

What really distinguishes this paper from previous reports is that the authors were able to show a long-term effect of preconditioning in a chronic model of kidney transplantation (Figure 1). The advent of potent immunosuppressive reagents has dramatically reduced the incidence of acute rejection, and today more than 90% of kidneys are still functioning at 1 year. Rates of graft loss after the first year have changed little, however, and long-term graft survival in the present era shows little sign of improvement. Causes of long-term loss are multifactorial, including both immune and non-immune mechanisms. In their second set of experiments, the authors showed that the short-term protective effect translated into a long-term improvement in allograft function and prolonged graft-dependent survival in recipient animals (chronic model, 24 weeks).

We know empirically that early graft dysfunction has a significant impact on long-term graft survival, and obviously a temporal insult to the graft at the moment of transplantation may decide its ultimate fate. While a recent meta-analysis calculated the cumulative incidence of CKD or ESKD after an episode of AKI, the authors could not calculate relative risks for the development of CKD because no study to date has included similar controls without AKI [9]. Nevertheless, previous experimental studies by Basile and colleagues showed that severe ischaemic injury results in a permanent alteration in renal capillary density, predisposing toward the development of renal fibrosis in the long term [10].

Immunological reactions play a crucial role in chronic injury of the donated organ. While accumulating evidence emphasizes immune regulation by HIF [11], it seems unlikely that long-term survival is achieved by immunological regulatory effects by temporary treatment of the donor; rather, the better long-term outcome of transplantation is more likely due to protection against ischaemia.

Bernhardt and colleagues also performed microarray analysis of whole kidney extracts and found that retinoic acid receptor responder 2 (Rarres 2) and lysyl oxidase (Lox) were the two genes most strongly up-regulated by the HIF stabilizer. The Rarres 2 gene encodes the novel adipokine chemerin, and while previous studies suggested the involvement of chemerin in adipocyte metabolism, it is also involved in angiogenesis [12]. Lox is also involved in the maintenance of normal endothelial functions [13]. HIF regulates a hundred adaptive genes against oxygen depletion, however, and although undoubtedly important, it may not be possible to distinguish which single factor among them was responsible for the protection of the transplanted kidney. Regarding the activation of HIF by PHD inhibition, moreover, the expression profile of HIF target genes may vary according to which of the three PHD isoforms (PHDs1–3) is inhibited, given recent studies using PHD knockout mice which suggest that they display distinct profiles in different organs and genetic backgrounds [14,15]. On this basis, use of PHD inhibitors with distinct properties may produce different effects. These speculations notwithstanding, Bernhardt and colleagues have presented here an example of the beautiful concept that HIF activation by PHD inhibition leads to the concerted activation of many protective genes, which may be superior to single gene induction.

Fig. 1. Ischaemic injury of the donated kidney is potentially problematic in the long term and may result in graft loss. Preconditioning with a HIF activator will induce a wide range of defensive mechanisms against ischaemia in a coordinated manner, making the donated organ intact at the moment of transplantation and leading to long-term graft survival.
Potential clinical implications

The essence of preconditioning in transplantation is its feasibility: in other diseases, preconditioning may not be realistic because one cannot predict the development of the disease, but this is not the case with transplantation. In addition, transient treatment avoids unnecessary risks with the reagent. While HIF activation has been the focus of intense research in a variety of hypoxia-related diseases, including CKD [16], a potential impact on tumours may be of concern, on the basis that HIF activation may encourage angiogenesis in tumours. Experimentally, HIF-2 in a von Hippel Lindau gene (VHL)-deficient tumour cell line was responsible for a more aggressive phenotype [17]. These warnings aside, however, temporary administration of an HIF activator should not be of concern, and preconditioning to activate HIF is in perfect accord with current transplantation practice.

HIF activation might also be implicated in a wide variety of other fields in nephrology. Amelioration of AKI and CKD by HIF activation has been repeatedly demonstrated using various animal models [18]. Clinical trials of HIF-activating therapies are on-going, with targets of renal anaemia and arteriosclerosis obliterners. We eagerly await the day when HIF-based therapy will be available to patients with AKI, CKD and ESKD.

Take-home message

Preconditioning of the donated kidney by HIF activation can improve long-term survival of the graft via the coordinated activation of various protective genes and protection against the initial injury.

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References


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