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Angiogenic response following renal ischemia reperfusion injury: new players

Réponse angiogénique après lésion d'ischémie-reperfusion : nouveaux acteurs

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Unfolded protein response

Summary
Ischemia-reperfusion (IR) injury can negatively influence the short- and long-term outcomes of kidney transplantation because it promotes acute tubular necrosis and tissue scarring and activates innate alloimmunity. The adaptive responses to IR are centrally involved in reducing tissue damage but can also be deleterious when they activate programmed cell death and inflammation. The HIF-1α-mediated angiogenic responses following IR at early and late stages are complex and poorly understood. The early stages of IR seem to be associated with an antiangiogenic response, whereas the hypoxia that follows IR at later stages may activate angiogenic factors such as vascular endothelial growth factor (VEGF) and may be beneficial by stabilizing the microvasculature and favoring local blood supply. In addition to HIF-1α, new players in angiogenesis, including mTOR and the unfolded protein response, may lead to innovative therapeutic strategies for treating patients with ischemia- and reperfusion-associated tissue inflammation and organ dysfunction.

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MOTS CLÉS
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lésions d'ischémie-reperfusion ;
Réponse aux protéines mal repliées ;
Transplantation rénale

Résumé
Les lésions d'ischémie-reperfusion peuvent altérer les résultats de la transplantation rénale à court et long terme par différents mécanismes liés à la survenue d'une nécrose tubulaire aigue, d'une fibrose tissulaire et à l'activation de l'immunité innée. La réponse immunitaire adaptative, qui vise essentiellement à restaurer l'intégrité tissulaire, peut en fait conduire à des effets délétères en activant la mort cellulaire programmée ou en déclenchant des cascades pro-inflammatoires.
La réponse angiogénique médiée par le facteur HIF-1 α est un mécanisme complexe et méconnu. Lors la phase ischémique aigue, cette voie conduit à l'activation d'agents angiogéniques (comme le VEGF) associés à une stabilisation de la micro vascularisation rénale contribuant à lutter contre l'hypoxie tissulaire. Parallèlement, des acteurs nouvellement identifiés comme la protéine mTOR ou les protéines mal conformées pourraient permettre de définir de nouvelles stratégies thérapeutiques contre les lésions d'ischémie-reperfusion en transplantation rénale.

Ischemia-Reperfusion Injury: definitions, controversies and approximations

The IR syndrome

Ischemia and reperfusion is a pathological condition characterized by an initial restriction of blood supply to an organ followed by the restoration of perfusion and concomitant reoxygenation. In its classic manifestation, an occlusion of the arterial blood supply results in a severe imbalance of metabolic supply and demand that causes tissue hypoxia. Perhaps surprisingly, the restoration of blood flow and reoxygenation is frequently associated with an exacerbation of tissue injury and a profound inflammatory response, which together are called "reperfusion injury" [1].

Ischemia-reperfusion (IR) is a cause of kidney structural deterioration that is omnipresent in kidney transplantation and contributes to acute and chronic kidney injury, loss of function, innate and adaptive immunity stimulation, and graft loss. Delayed Graft Function (DGF) is a clinical consequence of IR and is mostly often defined as the need for dialysis during the first week after transplantation [2]. Ischemic DGF is pathologically reflected by ischemic acute tubular necrosis, and its prevalence varies greatly depending on its definitions; however, recent comprehensive surveys indicate a prevalence of approximately 20% [3,4]. The limited oxygen availability (hypoxia) that occurs during the ischemic period is associated with impaired endothelial cell barrier function and a concomitant increase in vascular permeability and leakage. In addition, ischemia and reperfusion leads to the activation of cell death programs, including apoptosis, autophagy-associated cell death and necrosis [1]. Despite the restoration of its vascular supply, an ischemic organ may not immediately reperfuse (this is called the "no reflow phenomenon"). Moreover, reperfusion injury is characterized by immune responses that include natural antibody recognition of neoantigens and subsequent activation of the complement system. Innate and adaptive immune responses contribute to injury, including the activation of pattern recognition receptors such as Toll-like receptors (TLR) and inflammatory cell trafficking into the diseased organ (i.e., innate and adaptive immune activation).

IR, DGF and kidney allograft outcomes

Recent works have challenged the impact of ischemic DGF on long-term allograft outcomes [5,6]. Whereas the duration of cold ischemic time (CIT), i.e., the period of time from kidney removal until arterial declamping, is significantly associated with DGF, CIT does not influence long-term graft outcomes. This does not mean that DGF does not influence outcomes, but rather that the ischemic tubular necrosis that occurs following cold ischemia that contributes to DGF may be totally reversible without scar. One implication of one of these studies [5], which was performed with 9082 paired deceased-donor kidneys and 18164 recipients registered in the national Scientific Registry of Transplant Recipients and may explain why CIT is widely accepted as a factor that negatively influences graft outcomes, is that minimizing the deleterious impact of cold ischemia is dependent on the proper storage of kidneys, which, according to some authors [7], is not correctly performed in many centers. When placed directly into a cold bath and flushed with cold solution, vasoconstriction occurs, and blood remained trapped in vessels. Ideally, the kidney should be flushed at room temperature with warm solution.

These considerations of the clinical impact of IR are important because the medical and economic consequences of the therapeutic options that must be developed to avoid them need to be evaluated. Furthermore, the data regarding the effect of ischemic DGF on graft outcomes should be more than anecdotal. This observation also fuels discussions based on clinical and experimental evidence that acute (ischemic) tubular necrosis is not reliably followed by a regeneration ad integrum of the tubular epithelium and thus scarring may occur. Clinically, acute kidney injury is widely accepted as a factor that negatively influences long-term kidney function, especially if these episodes are severe, frequent and occur in already-altered kidney parenchyma [8]. The biological mechanisms that convert an acute kidney injury into a chronic injury are beyond the scope of this review; however, ischemia and hypoxia are centrally implicated in this process. Ischemic stress generates the conditions necessary for the establishment of a permanent state of tissue ischemia, and acute ischemia may thereby promote lesions (e.g., capillary