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## EDITORIAL

# Ischemia-reperfusion in the renal allograft: new clues in a cold-case

## *Ischémie-reperfusion en transplantation rénale : nouvelles avancées*

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**R**eperfusion of an ischemic organ is vital to prevent necrosis and definitive non-function but also leads to specific tissue injuries. The historical observation of myocardial necrosis by Jennings and al. [1] was based on coronary arterial occlusions in canine hearts when a temporary period of ischemia was followed by reperfusion.

The reperfusion lesions are directly related to the consequences of the “reflow”, and cannot be limited to the simple hastening of cell death that has been triggered by the ischemic insult. This known paradox has been widely investigated in the medical literature [2-6] and its mechanisms have been described through evolving theories accompanying the progressing knowledge of cellular pathways involved in ischemia and apoptosis. Focusing on the kidney in the setting of renal transplantation, this issue of “Progrès en Urologie” aims to review various aspects of renal ischemia-reperfusion.

After recalling the known mechanisms, authors describe the new players whose role have been recently exposed such as HIF signaling [7], VEGF and angiogenic response,

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**MOTS CLÉS**

Allogreffes ;  
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mammalian target of rapamycin signaling, endoplasmic reticulum stress and unfolded protein response [8]. It remains challenging to understand, not only the various mechanisms involved, but also the relationship between these miscellaneous pathways that appear to be intricate. For example, it is well known that renal ischemia leads to tubule-interstitial alteration and strong inflammatory response to the ischemic insult.[9] However, it has been also recently hypothesized that the interruption of the tubular flow promotes IL8 secretion and adhesion molecule expression by proximal tubule [10] in addition to the known relationship between flow cessation and endothelial dysfunction. [11] Which has the main role? Which actor is the leading one? Lack of oxygen or lack of flow? Which has the upmost relevance in the setting of renal transplantation [12]?

Similarly, how can we explain that potential inhibitors of angiogenesis such as endostatin, PAI-I, MMPs, ADAMTS1 and angiostatin, have been shown to be overexpressed in the setting of ischemia reperfusion [13,14] whereas other data strongly support the activation of HIF-dependent or -independent pro-angiogenic response [15,16] to the ischemic insult (VEGF secretion, etc.)? These controversial data highlight the difficulty to distinguish, at a mechanistic level, the insult from the protective pathway, the matter from the answer.

In addition, permanent re-evaluation of known hypothesis (a common concept in the field of biological sciences) has been particularly critical in solid organ transplantation basic sciences. For instance, the recent recognition of necroptosis - a programmed cell necrosis characterized by a loss of plasma membrane and extracellular release of damage-associated molecular pattern molecules - as a key player in ischemia-reperfusion injury [17-19] has dramatically opened new insights in the issue allograft innate and adaptive injuries. Lately, Linkermann et al. [20] showed that blocking necroptosis through the specific inhibition of receptor- interacting protein kinase 1 (RIPK1) by addition of necrostatin-1, led to reduction of organ damage and renal failure, suggesting that necroptosis may play a role in the pathogenesis of various kidney injuries including allograft rejection. Also, in a very elegant model of allogeneic (H-2b to H-2d) mice kidney transplantation, Lau et al. were recently able to demonstrate that RIPK3-mediated necroptosis in donor kidneys was promoting inflammatory injury; thus, inhibition of RIPK3 in kidney allografts prolonged long-term survival and improved renal function in allogeneic recipients [21].

Beside the mechanistic description of renal ischemia-reperfusion, this Special Issue of *Progrès en Urologie* review also recapitulates current therapeutic modalities as well as future perspectives. To our opinion, it is now mandatory to bring clinical insights regarding the matter of ischemia-reperfusion, focusing on acute injury and transplant outcome. For instance, numerous basic results obtained either in vitro or in small animal models (rodents), such as renal ischemic preconditioning [22,23], failed to demonstrate any significant relevance in porcine models or human clinical studies [24-26].

Thus, this special issue reviews major new therapeutic players proposed in ischemia-reperfusion kidney injury: additives to preservation solution [27], supplementation of preservation solution with gaseous carbon monoxide, [28] use of oligonucleotides or siRNAs targeting caspase 3[29], endothelin A receptor [30], or p53 [31]. The potential future role of normothermic kidney preservation with autologous oxygenated blood using extra corporeal membrane oxygenation or regional normothermic circulation is also reported [32,33].

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## Disclosure of interest

M.-O. Timsit: Clinical trials: as main (head) clinical or laboratory investigator, or study coordinator (MSD).

Clinical trials: as co-investigator or study contributor (Pfizer).

Occasional involvements: expert reports (Janssen-Cilag).

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