Progrès en urologie (2014) 24, S4-S12

Disponible en ligne sur
SciVerse ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Ischemia-reperfusion: From cell biology to acute kidney injury

Ischémie-reperfusion : de la biologie cellulaire à la lésion rénale

N. Chatauret[a,b], L. Badet[a], B. Barrou[a], T. Hauet[a,b,c,*]

[a]INSERM, U1087, Ischémie-reperfusion en transplantation d'organe : mécanismes et innovations thérapeutiques, Poitiers ; université de Poitiers, faculté de Médecine et de Pharmacie, 86021 Poitiers, France
[b]CHU de Poitiers, Laboratoire de biochimie, 86021 Poitiers, France
[c]IBISA, Domaine expérimental du Magneraud, 17700 Surgères, France

KEYWORDS
Acute Kidney Injury;
Chronic allograft nephropathy;
Innate Immune Response;
Ischemia-reperfusion injury;
Reactive oxygen species

Summary
Ischemia reperfusion injury occurs in the kidney when blood supply is interrupted in clinical settings such as kidney transplantation or nephron sparing surgery for renal tumors. These lesions lead to acute kidney injury (AKI) a detrimental situation associated with impaired short-term allograft function (delayed graft function or primary non function) but also long-term transplant survival through the onset of chronic allograft nephropathy.
The present review details the cellular and molecular consequences of ischemia reperfusion in a native kidney as well as in a kidney graft after cold ischemia time, giving a comprehensive description of biological pathways involved during the phase of ischemia and during the reperfusion period where the rapid return to normoxia leads to a large burst of reactive oxygen species along with a dramatic reduction in antioxidant defenses. This work also focuses on the distinct susceptibilities of kidney cells to ischemia (endothelial vs epithelial) and the outcome of acute kidney injury.

*Corresponding author.
E-mail adress: t.hauet@chu-poitiers.fr (T. Hauet).

MOTS CLÉS
Immunité innée ;
Ischémie-reperfusion ;
Nécrose tubulaire aigue ;
Néphropathie chronique ;
Radicaux libres ;
Stress oxydatif

Résumé
Les lesions d'ischémie-reperfusion rénales surviennent lorsque le flux sanguin rénal est interrompu, dans des situations cliniques comme la transplantation rénale ou la chirurgie conservatrice pour le traitement des tumeurs rénales. Ces lésions conduisent à une atteinte rénale aigue compromettant la fonction rénale à court terme (reprise retardée de fonction ou non-fonction primaire en transplantation rénale) mais aussi à long terme par le développement de lésions de néphropathie chronique d'allogreffe ou de fibrose rénale.
Cette revue détaille les mécanismes moléculaires et cellulaires impliqués lors de la phase d'ischémie rénale mais aussi lors de la période de reperfusion, lorsque le retour rapide à des conditions normoxiques entraine un relargage massif des dérivés de radicaux libres contemporain d'une diminution drastique des mécanismes de défense contre le stress oxydant. Ce travail décrit aussi les différences de sensibilité entre les cellules endothéliales et épithéliales et les conséquences globales des lésions rénales aigues post-ischémiques.

Introduction

Ischemia reperfusion (IR) injury occurs when blood supply to part or the whole of an organ is interrupted or drastically reduced. For the kidney, IR is either due to cardiac arrest (systemic hypoperfusion), shock, surgical interventions leading to local renal hypoperfusion such as aortic cross-clamping, partial nephrectomy as well as transplantation. The duration of ischemia at either body temperature for the organs *in situ* or at 4 °C for grafts will determine the extent of tissue injury ranging from no visible symptoms to acute kidney injury (AKI). AKI has been traditionally defined as a rapid (ranging from hours to weeks) decrease in kidney function measured by increases in serum creatinine levels [1]. AKI is independently associated with increased morbidity and mortality as well as increased length of hospital stays [2]. It is commonly accepted that AKI may have chronic consequences. Indeed, AKI is associated with a high risk of developing a chronic kidney disease (CKD) or exacerbates a CKD, leading more rapidly to end-stage renal disease [3]. In kidney transplantation, ischemia-reperfusion injury can be associated with a form of AKI recognized as delayed graft function (DGF) (requirement for at least one dialysis session during the first week post-transplantation) [4], slow graft function (SGF) (defined as a reduction in serum creatinine from immediately after transplant to day 7 by less than 70%) [5] or PNF (primary non function) define as no reduction in serum creatinine level due to irreversible cellular lesion. DGF and SGF are associated with higher risks of chronic allograft nephropathy and fibrosis [6]. Ischemia-reperfusion-induced AKI for native kidneys or DGF for transplanted kidneys share similar cellular and molecular pathophysiological changes linked to both blood flow cessation and restoration. In addition, the IR lesions in kidney transplantation are associated with hypothermic injuries sustained during cold storage of the graft. This review will detail the cellular and molecular consequences of ischemia reperfusion in a native kidney as well as in a kidney graft.

Consequences of ischemia reperfusion at the cellular level

In any organs, a drastic blood flow reduction will lead to decreases, at the cell level, in oxygen and nutrients deliveries as well as waste product removal.

During ischemia

Depending on the importance and duration of ischemia, the organ will either completely recover or will sustain cellular injuries once a critical ischemia duration is exceeded. In humans, the critical ischemia duration, at body temperature, depends on the organ, ranging a few minutes for brain to 30 minutes for the kidney [7]. Longer exposure to hypoxia will invariably lead to changes in cellular metabolism with deleterious consequences after reperfusion (Fig. 1).

The first change induced by ischemia is associated to the decreased oxygen delivery. Decreased O_2 levels will induce a switch from aerobic (generation of 36 molecules of ATP from 1 molecule of glucose *via* the tricarboxylic acid cycle) to anaerobic glucose metabolism (generation of 2 molecules of ATP from 1 molecule of glucose by lactate synthesis) [8]. This anaerobic metabolism is insufficient to meet the demands of aerobic tissues [8] and the lack of oxygen will further enhance ATP consumption in the mitochondria by reversal of the F1F0 ATP synthase (hydrolyzing ATP instead of synthesizing it) in order to maintain the mitochondrial membrane potential compromised by the inhibition of the electron transfer chain [9]. Therefore, intracellular ATP levels will rapidly fall and this fall will be directly linked to the duration of ischemia. In addition, the lactate-dependent ATP production causes intracellular acidosis by accumulation of lactic acid in the cells as well as in the interstitium as it is no longer removed by blood flow. Lowering of both the intracellular pH and ATP levels will: i) destabilize the lysosome membrane which will leak various hydrolases leading to disruption of

the cell structure [10]; ii) inhibit the ionic pumps and in particular the Na^+ /K^+ ATPases [11,12], thereby disrupting the electrolytes homeostasis involving a massive entrance of Na^+ ions and water, producing edema [8] (Fig. 1). Intracellular sodium levels are further increased by the action of the Na^+ / H^+ exchanger which will pump protons out of and Na^+ ions in the cell in an attempt to correct the intracellular pH [13] (Fig. 1). As the Na^+ ions accumulate within the cell, the Na^+ /Ca^{2+} antiporter stops pumping Ca^{2+} out of the cell and starts working in the reverse direction [8,14]. Intracellular Ca^{2+} levels are further increased by the inhibition of Ca^{2+} reuptake into the endoplasmic reticulum due to the ATP depletion [15]. Altogether, these phenomena produce a calcium overload "priming" the activation of calcium-dependent proteases such as calpains which are inhibited by the low intracellular pH present during the ischemic phase but will become activated upon pH normalization at reperfusion [14].

The increased intracellular Na^+ and Ca^{2+} levels will cause the mitochondria to retain Ca^{2+} in the mitochondrial matrix leading to a calcium overload. Mitochondrial calcium levels at the end of ischemia have been linked to the extent of IR injury in cardiomyocytes [16]. Mitochondrial calcium overload is directly involved in Reactive Oxygen Species (ROS) generation during ischemia by enhancing cytochrome c dislocation from the mitochondrial inner membrane, the first step of the 2-step cytochrome c releasing process during mitochondrial transition pore (mPTP) opening [17]. At physiological pH, excess mitochondrial calcium is linked to opening of the mPTP, an event linked with cell death and apoptosis [18]. During ischemia, Ca^{2+} -induced mPTP opening is prevented by the low intracellular pH but will occur when pH values return to normal upon reperfusion (see next paragraph) [18]. Ischemia and Ca^{2+} overload sensitize mPTP to opening [19] (Fig.1).

During hypoxia, relatively small quantities of reactive oxygen species (ROS) are generated in comparison after reperfusion. During hypoxia, ROS are generated following: (i) redox-reduction of the cytochromes allowing them to directly transfer ("leak") electrons to the oxygen [20]; Nitric Oxide (NO) synthases uncoupling which normally reduce arginine to produce NO in the presence of tetrahydrobiopterine and oxygen [21]; Xanthine oxidase and NADPH oxidase activations [22] . Oxidative stress is also enhanced by the hypoxia-related decrease in activity of anti-oxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase [22,23]. Anion superoxide ($O^{2\cdot -}$) will react with free NO (derived from the nitric oxide synthases or from the xanthine oxidase through reduction of nitrite or nitrate) [7] to form peroxynitrite (ONOO-): a potent oxidant modifying the protein conformation by nitrotyrosylation. In addition, hypoxia inhibits the expression of the complex IV cytochrome oxidase subunits (the final electron acceptor) leading to further ROS production upon reperfusion [22] (Fig. 1). Despite all this, there is very little cell loss during ischemia in comparison to the cell loss observed after reperfusion (4% and 17% of cardiomyocyte lost viability respectively after 1h and 4h of simulated ischemia *in vitro* in comparison to 73% of viability loss after 3h of reperfusion following a 1h of simulated ischemia)[24].

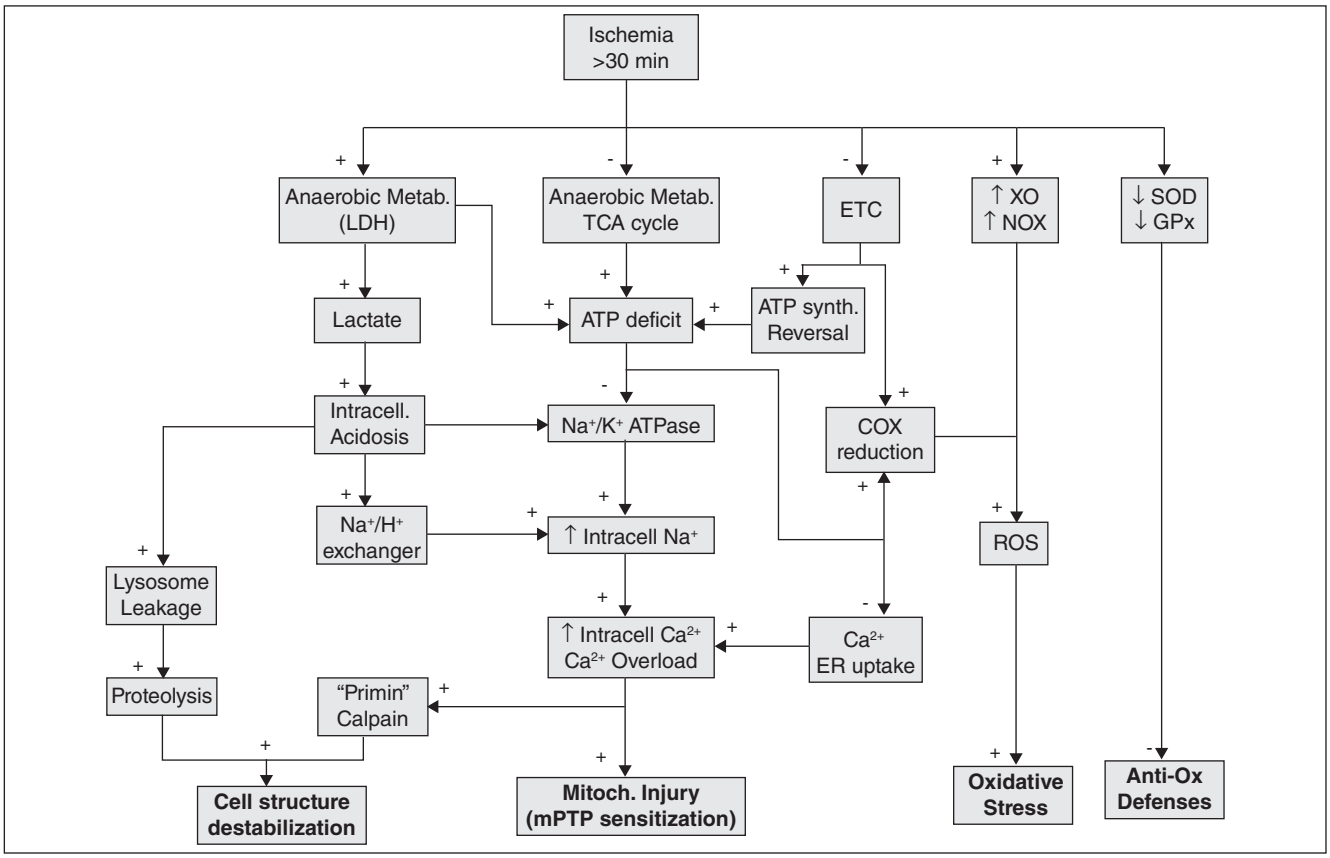

Figure 1. Consequences of ischemia.

After reperfusion

Upon restoration of blood flow, oxygen levels rapidly increase and extracellular pH rapidly normalizes by extracellular wash out. Paradoxically, these rapid returns to "normality" are deleterious for the cells having undergone ischemia. As mentioned above, the cells at the end of ischemia have a low intracellular pH, a calcium-induced mitochondrial injury (mPTP sensitization), a downregulation of antioxidant defenses and an inhibition of the cytochrome c complex IV of the electron transport chain (Fig. 2). When the organ is reperfused the prompt return of the extracellular pH to physiological values will instantly create an extreme H^+ gradient across the plasma membrane that triggers Na^+/H^+ exchange and a massive Na^+ influx [15]. This additional increase in intracellular sodium content will reverse the Na^+/Ca^{2+} exchanger leading to furthering of the cytoplasmic and mitochondrial calcium overloads that had already primed the opening of the mPTP and the activation of the calpains during ischemia. The reperfusion-related normalization of the intracellular pH will activate the calpains and will participate in the opening of the mPTP (see below). Once activated, the calpains hydrolyzes target proteins leading to structural impairment, mitochrondrial dysfunction and altered calcium handling [14]. Ultimately, calpains activation leads to cell death.

Rapid return to normoxia will lead to a large burst of ROS associated with a loss of ATP-inhibition of the complex IV [25] and a reduction in antioxidant defenses [22,23] which occurred during ischemia. ROS will damage macromolecules such as membrane, lipids and DNA [7]. Together, the ROS burst and the high mitochondrial calcium content will trigger mPTP opening creating a pore in the inner mitochondrial membranes [7]. This pore allows water and solute (<1.5 kDa) to enter the mitochondrial matrix causing swelling that will induce rupture of the outer membrane [18]. With this rupture, the cytochrome C is released and permeates to the cytosol where it activates the pro-apoptotic caspase 3 [8]. mPTP opening equilibrates Na^+ concentrations on both side of the inner membrane abolishing ATP-synthase driving force [19]. Once opened, mPTP leads to rapid cell death through a variety of independent and redundant mechanisms (apoptosis, necrosis and autophagy). Apoptosis, or programmed cell death, requires ATP and leads to complete cellular elimination without induction of inflammation whereas necrosis is mediated by cell swelling and plasma membrane disruption and leakage of intracellular components leading to inflammation [26]. Autophagy is a mechanism of bulk removal of intracellular aggregates and organelles and provides energy-generating substrates under conditions of nutrient limitations [27]. It seems that activation of autophagy during ischemia protects the heart whereas it is detrimental after

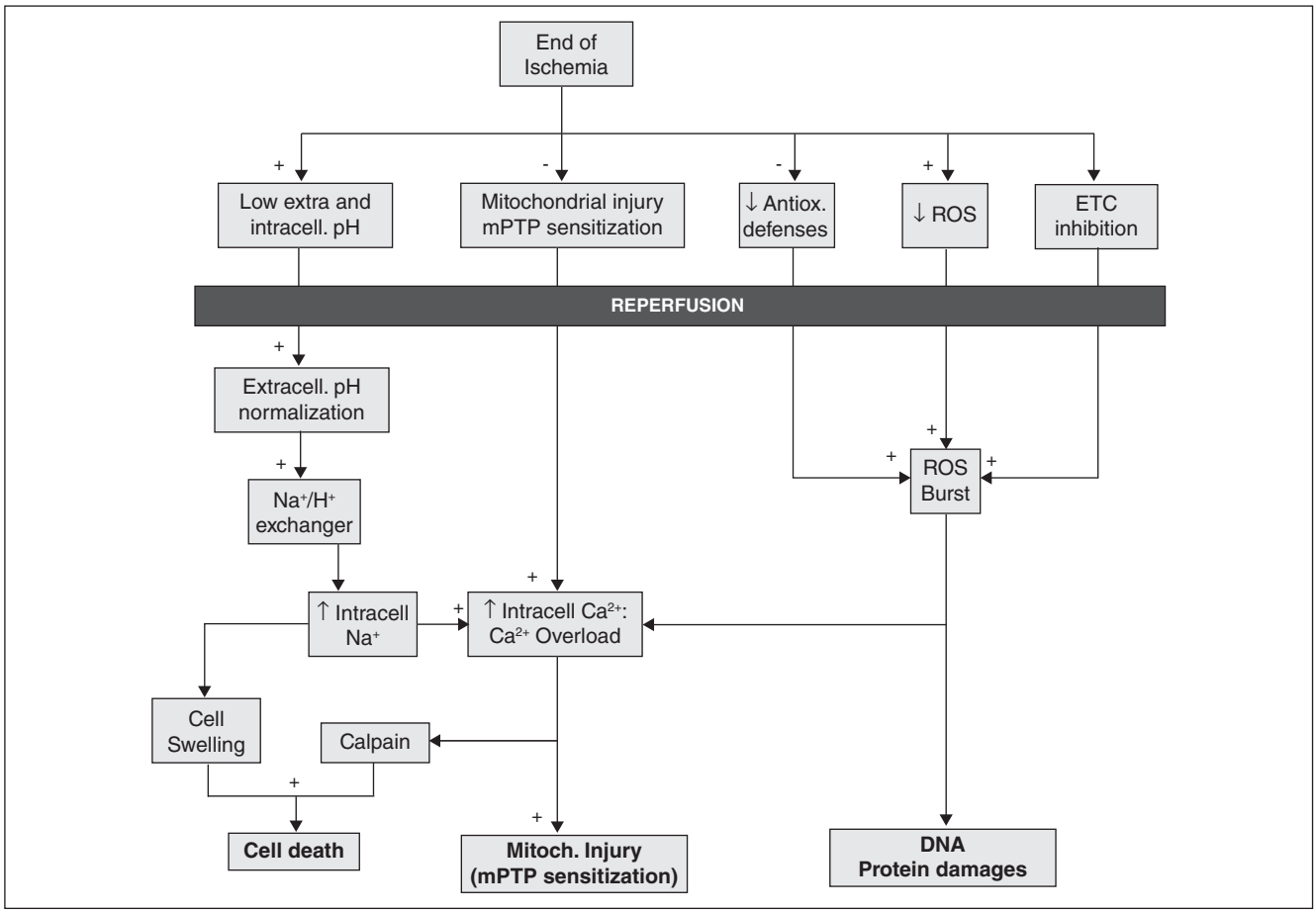

Figure 2. Consequences of reperfusion.

reperfusion [28]. The incidence of apoptosis is lower than necrosis after IR [7] and the cell death pathway taken by post-ischemic cells seems to depend on their post-reperfusion energy state [29].

Transplantation-specific ischemia reperfusion injuries: the cold ischemia

As illustrated above, it is clear that organs or cells cannot endure long period of ischemia at physiological temperature. This is a problem in organ transplantation from cadaveric donors as the *ex vivo* ischemic phase has to be of several hours (more than 24 hours for the kidney) in order to have time to locate an appropriate recipient and transport the organ. The solution adopted to prolong the storage time of the grafts has been to preserve them at very low temperatures (4 °C) with the rational that according to the Van't Hoff rule, cooling from 37 °C to 0 °C slows the cell metabolism 12 to 13 times and therefore oxygen requirement decreases [30]. Nevertheless, at 4 °C, there is still 10-12% cellular metabolic activity. Therefore, the deleterious effects of ischemia still occur in cold-stored grafts. Cold itself is detrimental to tissue. It can cause changes similar to those observed in warm ischemia even in normoxia (i.e: mitochondrial swelling, extra- and intra-cellular edema, disturbances of ion homeostasis including calcium ion influx) [31,32]. Cooling and rewarming without ischemia can induce apoptosis in liver cells [33]. Currently, the field of organ preservation is trying to improve the balance between the cold-induced injuries and the cold-induced reduction in IR injuries by modifying the preservation solutions and modes (see part III of this monograph).

Distinct susceptibilities of kidney cells to ischemia

All the cells respond to hypoxic conditions as described above, however they are not all equally sensitive to the lack of oxygen. Therefore, there is an organ-specific susceptibility to IR (for review see Kalogeris et al) [7]. This is also true within the same organ. Some cells are more hypoxia tolerant than others, in particular in the kidney. The kidney is composed of more than 26 different cell types such as multiple types of tubular epithelial cells, glomerular cells, and interstitial cells [34]. This number is underestimated as it does not include the different subtypes of endothelial cells. The major renal cell types involved in IR injury are the endothelial cells and the tubular epithelial cells.

Endothelial cells

Endothelial cells are very sensitive to warm and cold ischemia both inducing apoptosis [35]. Cold itself can induce endothelial cell apoptosis [33]. Therefore, endothelial cells are the first cell type to suffer damage during whole organ ischemia and reperfusion, leading to partial denudation as demonstrated in the liver [36] or in the lung [37]. In addition, IR induced a wide range of endothelium-dependent effects such as vasoconstriction as well as the expression of vasoactive genes regulated by hypoxia [38]. Modifications in the expression of these genes will directly impact the organ recovery and outcome after IR.

Epithelial cells

Renal parenchymal oxygenation is graded with the highest oxygen levels noted in the cortex, medium levels in the outer medulla, and the lowest levels in the papillae [39]. As a consequence, epithelial cells in each kidney region are adapted to function optimally at the oxygenation levels in their respective microenvironments [40]. Lactate synthesis capacity of renal epithelial cells is not homogenous in the rat nephron with a lactate production only in distal segments and not in the proximal tubules [41]. Cortical epithelial cells mainly use O_2-dependent metabolism of short- and long-chain fatty acids, lactate, ketones and amino acids. Cells in the outer medulla metabolize succinate and, when O_2 levels decrease, these cells can shift to O_2 independent lactate and glucose metabolism. The inner medulla predominantly uses glucose to generate ATP *via* anaerobic glycolysis. Therefore, the sensitivity to ischemia of renal epithelial cells will depend on their location within the kidney [40]. The outer cortex has a high O_2 reserve and, thus, cells in this region are relatively protected if the ischemia duration is short. Outer medullary epithelial cells are most susceptible to hypoxia as they operate on the verge of anoxia in the normal kidney and they have a high metabolic rate to fulfill their reabsorption functions [42]. Papillary epithelial cells reside in a constitutively hypoxic environment and they can survive on anaerobic metabolism during short periods of ischemia. With prolonged warm ischemia ultimately all kidney regions are affected.

Consequences of ischemia reperfusion at the organ level

As developed above, it is clear that prolonged ischemia followed by reperfusion will lead to cell loss of all kidney cell types by apoptosis and/or necrosis. These cell losses represent the initial IR injuries. If ischemia is too severe, the organ will not recover from the initial injury. However, if ischemia is sublethal, the initial cell loss participates to the establishment of AKI but several cellular events occurring in the hours to days after IR will extend the first IR insult conditioning the severity of AKI and the long term outcome. Ischemic AKI is associated with acute tubular necrosis, decreased glomerular filtration rate, increased serum creatinine or cystatin C levels or oliguria [43]. This is accompanied by a dissipation of glomerular filtration pressure associated with an increased basal renal vascular tone, a loss of autoregulatory ability of the renal vasculature, an aberrant renal vascular reactivity, and tubular obstruction [44]. Total renal blood flow is decreased by about 30–70% following the initial ischemic insult [45]. The underlying cellular mechanisms leading to these dysfunctions are reviewed below.

Vascular injury

Vascular injuries play a major role in the hemodynamic consequences of IR. In addition to induce apoptosis and necrosis, IR leads to endothelial cell swelling (reducing capillary lumen), loss of glycocalyx, disruption of actin cytoskeleton, alterations of endothelial cell-cell contacts and breakdown of the perivascular matrix leading to increased microvascular permeability and fluid loss in the interstitium [46]. Furthermore, IR also induces modifications in the expression levels of various endothelial-derived proteins in the surviving cells [38]. In particular, IR will promote vasoconstriction by inducing the endothelial production of vasoconstrictor substances (platelet-derived growth factor-B and Endothelin-1) [38]. Vasoconstriction is amplified by a reduced NO production at reperfusion associated with a downregulation of eNOS protein and with other vasodilatory substances produced by the damaged endothelium [44]. Furthermore, arterioles can exhibit increased reactivity to endogenous vasoconstrictors after ischemia including Angiotensin II, Thromboxane A2, prostanglandin H2, leukotrienes C4 and D4 and adenosine [1,47]. IR and the decreased endothelial NO production will "activate" endothelial cells by inducing the expression of adhesion molecules (such as Intercellular adhesion molecule-1 (ICAM-1), Vascular Adhesion molecule-1 (VCAM-1) as well as P- and E-Selectins) on the endothelial plasma membranes [48]. Endothelial activation increases the adherence of platelets and polymorphonuclear neutrophils promoting capillary congestion and the no-reflow phenomenon [47]. These vasomotor disturbances are responsible for the reduced total renal blood flow and glomerular filtration rate as well as for the extension of the duration of hypoxia in some region of the kidney potentiating the epithelial cell injuries.

Epithelial injury

Renal IR results in a rapid loss of cytoskeletal integrity and epithelial cell polarity with shedding of the proximal tubule brush border, mislocalization of adhesion molecules (integrins) and other membrane proteins such as Na^+/K^+ ATPase, apoptosis and necrosis [49]. These changes promote epithelial cell desquamation (exposing the basal membrane) [49] and the appearance of casts (aggregates of cellular debris in the tubule), obstructing the lumen and increasing the intratubular pressure [1]. Both phenomena lead to backleakage of the filtrate and impaired ion reabsorption. The tubular obstruction will also be involved in the reduction of GFR upon reperfusion. Also, injured proximal tubules will not reabsorb sodium correctly causing the macula densa to sense elevated solute levels in the distal nephron and trigger the tubulo-glomerular feedback [50]. This feedback is likely contributing to a pre-glomerular arterial constriction further reducing the GFR.

Inflammation/immune system

Sterile inflammation, both innate and adaptative immune systems and complement activation are involved in IR injury [51]. Their respective role will be reviewed in detail by Tullius et al in this monography. Briefly, vascular and epithelial injuries will trigger inflammation upon release of intracellular factors after cell necrosis [52]. Vascular injury also involves endothelial cell activation and leukocytes recruitment whereas epithelial injury involves epithelial cell release of pro-inflammatory and chemotactic cytokines (TNFα, IL1β, IL6, IL8...) activating the innate immune system [52]. Activation of the innate immune system is responsible for the early responses to IR injury in a non-antigen-specific fashion [1]. Indeed, the neutrophils, monocytes/macrophages, dendritic cells and T cells are important contributors to ischemic AKI and repair. Neutrophils attached to the endothelium will produce proteases, myeloperoxidase, ROS and cytokines which will lead to increased vascular permeability and reduced tubular epithelial and endothelial cell integrity aggravating kidney injury [53].

Coagulation

Endothelial cell activation promote platelet aggregation and activation leading to the activation of the coagulation cascade and to inflammation [35]. Coagulation cascade is tightly linked to inflammatory processes. In particular, abnormal tissue factor (TF) expression by the vascular territory damaged during ischemia is responsible for the generation of active thrombin (Factor IIa). In addition to its role in the coagulation cascade, thrombin has direct action on cellular processes. Activated thrombin modulates calcium homeostasis as well as the expression of pro-fibrotic factors on glomerular epithelial cells [54]. Thrombin will also promote retention of inflammatory cells in the parenchyma by increasing vascular permeability and by promoting activation of monocytes/macrophages, endothelial cells and neutrophils. Thrombin, Xa and VIIa factors are activators of the protease-activated receptors (PAR) inducing synthesis of pro-inflammatory and pro-fibrotic factors [55,56]. PAR activation has been linked to vasconstriction and reduction in glomerular filtration rate [57]. Inhibition of the coagulation cascade has been reported to be beneficial after ischemia reperfusion in the heart [58,59], lungs [60] or in the kidney [61,62].

AKI outcome

The recovery of kidney from IR injury will depend on the extent of repair as this organ unlike the heart or brain has the capacity to replace the lost epithelial cells, if the insult was sub-lethal. Cell proliferation is behind the repair of injured kidney [63]. There is a controversy about which cell type is proliferating in response to IR injury. Endogenous surviving epithelial cells, bone marrow stromal cells, intrarenal progenitor cells and intrarenal interstitial cells have been proposed to be responsible for repair after AKI. Evidences in favor of the involvement of all these cells have been found in the past [1], but recent genetic fate-mapping techniques in transgenic mice have demonstrated that the surviving tubular cells are responsible for replenishment of the tubular epithelium after ischemia [64]. After IR, the remaining epithelial cells dedifferentiate (losses of cell polarity and brush border), migrate to the site of injury and proliferate

to restore the cell number. Then, the new cells differentiate into functional polarized epithelial cells [65].

If the IR injury is mild, function recovery will be complete. However, if the injury is extensive the repair process will be abnormal leading to tubular atrophy and fibrosis responsible for chronic kidney disease. Ischemic AKI can lead to incomplete tubular repair, chronic inflammation and hypoxia leading to proliferation of fibroblasts and excessive extracellular matrix deposition: two characteristics of tissue fibrosis. Ischemia-associated kidney fibrosis is most prominent in kidney transplantation probably because in this paradigm, kidneys sustain both warm and cold ischemia injuries associated with a reduction in the nephronic mass, once the graft is implanted into the recipient [66]. Renal fibrogenesis follows the initial repairing processes consisting in kidney resident cell activation with production of proinflammatory cytokines. These cytokines attract inflammatory monocytes/macrophages and T cell to the injured sites where they become activated and produce ROS, fibrogenic (Transforming growth factor β) and inflammatory cytokines. Then these cytokines will stimulate mesangial cells, fibroblasts and TEC to undergo phenotypic activation or epithelial-to-mesenchymal transition (EMT) upon which these cells produce large amounts of extracellular matrix (ECM) components. The role of EMT in matrix deposition is still controversial. In favor of tubular epithelial cell EMT, a recent study demonstrated that TGF β leads to the loss of expression of PTEN (Phosphate and tension homolog: an antagonist of PI3K signaling) in the tubule and that these PTEN negative tubule failed to differentiate and started to express vimentin (an EMT marker) [67]. In contrast, genetic fate mapping experiments revealed that kidney fibrogenesis was not associated with EMT but rather with pericytes/perivascular fibroblasts as the source of myofibroblast progenitor [64]

Independently of the origin of the cell type producing the ECM components, the ECM material will accumulate and form the fibrous scars impairing kidney function [68]. It is still not clear what tips the balance in favor of fibrogenesis instead of repair but chronic hypoxia linked to capillary dysfunction and rarefaction [69] as well as chronic macrophages activation [70] have been demonstrated as being directly involved. The threshold of injury between full recovery and kidney fibrosis is not known and may depend on the presence of a pre-existing kidney disease before IR [71]. So far, there is no rigorous prospective study allowing to answer the question of whether AKI is responsible for the development of CKD on the long term [72] but animal studies and clinical meta-analysis suggest that the answer to this question is yes [73].

Conclusion

In conclusion, ischemia reperfusion has a large panel of cellular consequences all contributing to the development of acute kidney injury. Even if the pathophysiology of warm or cold ischemic AKI is well characterized, there is still a lack of efficient therapy to prevent or abolish IR injury. In particular, a lot of work remains to be performed to reduce the consequences of cold ischemia in the transplantation setting.

Disclosure of interest

The authors have no conflicts of interest to declare in relation to this review.

References

[1] Bonventre JV, Yang L. Cellular pathophysiology of ischemic acute kidney injury. J. Clin. Invest 2011 nov;121(11):4210-21.
[2] Munshi R, Hsu C, Himmelfarb J. Advances in understanding ischemic acute kidney injury. BMC Med 2011;9:11.
[3] Coca SG, Yusuf B, Shlipak MG, Garg AX, Parikh CR. Long-term risk of mortality and other adverse outcomes after acute kidney injury: a systematic review and meta-analysis. Am. J. Kidney Dis 2009 juin;53(6):961-73.
[4] Yarlagadda SG, Coca SG, Garg AX, Doshi M, Poggio E, Marcus RJ, et al. Marked variation in the definition and diagnosis of delayed graft function: a systematic review. Nephrol. Dial. Transplant 2008 sept;23(9):2995-3003.
[5] Hall IE, Doshi MD, Poggio ED, Parikh CR. A comparison of alternative serum biomarkers with creatinine for predicting allograft function after kidney transplantation. Transplantation 2011 janv 15;91(1):48-56.
[6] Perico N, Cattaneo D, Sayegh MH, Remuzzi G. Delayed graft function in kidney transplantation. Lancet 2004;364(9447):1814-27.
[7] Kalogeris T, Baines CP, Krenz M, Korthuis RJ. Cell biology of ischemia/reperfusion injury. Int Rev Cell Mol Biol 2012;298:229-317.
[8] Kosieradzki M, Rowinski W. Ischemia/reperfusion injury in kidney transplantation: mechanisms and prevention. Transplantation proceedings 2008;40(10):3279-88.
[9] Di Lisa F, Canton M, Menabò R, Kaludercic N, Bernardi P. Mitochondria and cardioprotection. Heart Fail Rev 2007 déc;12(3-4):249-60.
[10] Sugiyama S, Hanaki Y, Ogawa T, Hieda N, Taki K, Ozawa T. The effects of SUN 1165, a novel sodium channel blocker, on ischemia-induced mitochondrial dysfunction and leakage of lysosomal enzymes in canine hearts. Biochem. Biophys. Res. Commun 1988 déc 15;157(2):433-9.
[11] Kako K, Kato M, Matsuoka T, Mustapha A. Depression of membrane-bound Na+ -K+ -ATPase activity induced by free radicals and by ischemia of kidney. Am. J. Physiol 1988 févr;254(2 Pt 1):C330-337.
[12] Kato M, Kako KJ. Effects of N-(2-mercaptopropionyl)glycine on ischemic-reperfused dog kidney in vivo and membrane preparation in vitro. Mol. Cell. Biochem 1987 déc;78(2):151-9.
[13] Roberts BN, Christini DJ. NHE inhibition does not improve Na(+) or Ca(2+) overload during reperfusion: using modeling to illuminate the mechanisms underlying a therapeutic failure. PLoS Comput Biol 2011 oct;7(10):e1002241.
[14] Inserte J, Hernando V, Garcia-Dorado D. Contribution of calpains to myocardial ischemia/reperfusion injury. Cardiovascular research [Internet] 2012 juill 10 [cité 2012 août 22]; Available de: http: //www.ncbi.nlm.nih.gov/pubmed/22787134
[15] Sanada S, Komuro I, Kitakaze M. Pathophysiology of Myocardial Reperfusion Injury: Preconditioning, Postconditioning and Translational Aspects of Protective Measures. American Journal of Physiology. Heart and Circulatory Physiology [Internet] 2011 août 19 [cité 2011 oct 13]; Available de: http: //www.ncbi.nlm.nih.gov/pubmed/21856909
[16] Miyata H, Lakatta EG, Stern MD, Silverman HS. Relation of mitochondrial and cytosolic free calcium to cardiac myocyte recovery after exposure to anoxia. Circ. Res 1992 sept;71(3):605-13.
[17] Peng T-I, Jou M-J. Oxidative stress caused by mitochondrial calcium overload. Ann. N. Y. Acad. Sci 2010 juill;1201:183-8.

[18] Javadov S, Hunter JC, Barreto-Torres G, Parodi-Rullan R. Targeting the mitochondrial permeability transition: cardiac ischemia-reperfusion versus carcinogenesis. Cell. Physiol. Biochem 2011;27(3-4):179-90.
[19] Gustafsson AB, Gottlieb RA. Heart mitochondria: gates of life and death. Cardiovasc. Res 2008 janv 15;77(2):334-43.
[20] Becker LB. New concepts in reactive oxygen species and cardiovascular reperfusion physiology. Cardiovasc. Res 2004 févr 15;61(3):461-70.
[21] Alkaitis MS, Crabtree MJ. Recoupling the cardiac nitric oxide synthases: tetrahydrobiopterin synthesis and recycling. Curr Heart Fail Rep 2012 sept;9(3):200-10.
[22] Li C, Jackson RM. Reactive species mechanisms of cellular hypoxia-reoxygenation injury. Am. J. Physiol., Cell Physiol 2002 févr;282(2):C227-241.
[23] Bayrak O, Bavbek N, Karatas OF, Bayrak R, Catal F, Cimentepe E, et al. Nigella sativa protects against ischaemia/reperfusion injury in rat kidneys. Nephrol. Dial. Transplant 2008 juill;23(7):2206-12.
[24] Vanden Hoek TL, Shao Z, Li C, Zak R, Schumacker PT, Becker LB. Reperfusion injury on cardiac myocytes after simulated ischemia. Am. J. Physiol 1996 avr;270(4 Pt 2):H1334-1341.
[25] Kadenbach B, Ramzan R, Moosdorf R, Vogt S. The role of mitochondrial membrane potential in ischemic heart failure. Mitochondrion 2011 sept;11(5):700-6.
[26] Kanduc D, Mittelman A, Serpico R, Sinigaglia E, Sinha AA, Natale C, et al. Cell death: apoptosis versus necrosis (review). Int. J. Oncol 2002 juill;21(1):165-70.
[27] Gottlieb RA. Cell death pathways in acute ischemia/reperfusion injury. J. Cardiovasc Pharmacol Ther 2011 déc;16(3-4):233-8.
[28] Baines CP. How and when do myocytes die during ischemia and reperfusion: the late phase. J. Cardiovasc Pharmacol Ther 2011 déc;16(3-4):239-43.
[29] Saikumar P, Dong Z, Weinberg JM, Venkatachalam MA. Mechanisms of cell death in hypoxia/reoxygenation injury. Oncogene 1998 déc 24;17(25):3341-9.
[30] Belzer FO, Southard JH. Principles of solid-organ preservation by cold storage. Transplantation 1988 avr;45(4):673-6.
[31] Tveita T, Johansen K, Lien AH, Myklebust R, Lindal S. Morphologic changes in tubular cells from in situ kidneys following experimental hypothermia and rewarming. APMIS 2005 janv;113(1):13-20.
[32] Hochachka PW. Defense strategies against hypoxia and hypothermia. Science 1986 janv 17;231(4735):234-41.
[33] Rauen U, Polzar B, Stephan H, Mannherz HG, de Groot H. Cold-induced apoptosis in cultured hepatocytes and liver endothelial cells: mediation by reactive oxygen species. FASEB J 1999 janv;13(1):155-68.
[34] Al-Awqati Q, Oliver JA. Stem cells in the kidney. Kidney international 2002;61(2):387-95.
[35] Koo DD, Welsh KI, West NE, Channon KM, Penington AJ, Roake JA, et al. Endothelial cell protection against ischemia/reperfusion injury by lecithinized superoxide dismutase. Kidney Int 2001 août;60(2):786-96.
[36] Stolz DB, Ross MA, Ikeda A, Tomiyama K, Kaizu T, Geller DA, et al. Sinusoidal endothelial cell repopulation following ischemia/reperfusion injury in rat liver transplantation. Hepatology 2007 nov;46(5):1464-75.
[37] White LE, Cui Y, Shelak CMF, Lie ML, Hassoun HT. Lung endothelial cell apoptosis during ischemic acute kidney injury. Shock 2012 août;38(3):320-7.
[38] Faller DV. Endothelial cell responses to hypoxic stress. Clin Exp Pharmacol. Physiol 1999 janv;26(1):74-84.
[39] Brezis M, Rosen S. Hypoxia of the renal medulla--its implications for disease. N. Engl. J. Med. 1995 mars 9; 332(10): 647-55.
[40] Silva P. Energy and fuel substrate metabolism in the kidney. Semin Nephrol 1990 sept;10(5):432-44.
[41] Bagnasco S, Good D, Balaban R, Burg M. Lactate production in isolated segments of the rat nephron. Am J Physiol 1985 avr; 248(4 Pt 2): F522-526.
[42] Brezis M, Rosen S, Silva P, Epstein FH. Renal ischemia: a new perspective. Kidney Int 1984 oct;26(4):375-83.
[43] Lameire N, Van Biesen W, Vanholder R. Acute kidney injury. Lancet 2008 nov 29;372(9653):1863-5.
[44] Kwon O, Hong S-M, Ramesh G. Diminished NO generation by injured endothelium and loss of macula densa nNOS may contribute to sustained acute kidney injury after ischemia-reperfusion. Am J Physiol Renal Physiol 2009 janv;296(1):F25-33.
[45] Molitoris BA, Sandoval R, Sutton TA. Endothelial injury and dysfunction in ischemic acute renal failure. Critical care medicine 2002;30(5 Suppl):S235-40.
[46] Basile DP, Friedrich JL, Spahic J, Knipe NL, Mang HE, Leonard EC, et al. Impaired endothelial proliferation and mesenchymal transition contribute to vascular rarefaction following acute kidney injury. American journal of physiology [Internet]. Available de: file: //C: \article\21123492.pdf
[47] Legrand M, Mik EG, Johannes T, Payen D, Ince C. Renal hypoxia and dysoxia after reperfusion of the ischemic kidney. Molecular medicine (Cambridge Mass.) 2008;14(7-8):502-16.
[48] Molitoris BA, Sutton TA. Endothelial injury and dysfunction: role in the extension phase of acute renal failure. Kidney international 2004;66(2):496-9.
[49] Lameire N, Van Biesen W, Vanholder R. Acute renal failure. Lancet 2005 févr 29;365(9457):417-30.
[50] Blantz RC, Deng A, Miracle CM, Thomson SC. Regulation of kidney function and metabolism: a question of supply and demand. Trans Am Clin Climatol Assoc 2007;118:23-43.
[51] Eltzschig HK, Eckle T. Ischemia and reperfusion--from mechanism to translation. Nat Med 2011;17(11):1391-401.
[52] Thurman JM. Triggers of inflammation after renal ischemia/reperfusion. Clin Immunol 2007 avr; 123(1):7-13.
[53] Jang HR, Ko GJ, Wasowska BA, Rabb H. The interaction between ischemia-reperfusion and immune responses in the kidney. Journal of molecular medicine (Berlin, Germany) [Internet]. 2009; Available de: file: //C: \article\19562316.pdf
[54] He CJ, Peraldi MN, Adida C, Rebibou JM, Meulders Q, Sraer JD, et al. Thrombin signal transduction mechanisms in human glomerular epithelial cells. J Cell Physiol 1992 mars;150(3):475-83.
[55] Chambers RC, Laurent GJ. Coagulation cascade proteases and tissue fibrosis. Biochem Soc Trans 2002 avr;30(2):194-200.
[56] Grandaliano G, Monno R, Ranieri E, Gesualdo L, Schena FP, Martino C, et al. Regenerative and proinflammatory effects of thrombin on human proximal tubular cells. J Am Soc Nephrol 2000 juin;11(6):1016-25.
[57] Gui Y, Loutzenhiser R, Hollenberg MD. Bidirectional regulation of renal hemodynamics by activation of PAR1 and PAR2 in isolated perfused rat kidney. Am J Physiol Renal Physiol 2003 juill;285(1):F95-104.
[58] Erlich JH, Boyle EM, Labriola J, Kovacich JC, Santucci RA, Fearns C, et al. Inhibition of the tissue factor-thrombin pathway limits infarct size after myocardial ischemia-reperfusion injury by reducing inflammation. Am J Pathol 2000 déc;157(6):1849-62.
[59] Hölschermann H, Bohle RM, Schmidt H, Zeller H, Fink L, Stahl U, et al. Hirudin reduces tissue factor expression and attenuates graft arteriosclerosis in rat cardiac allografts. Circulation 2000 juill 18;102(3):357-63.
[60] Farivar AS, Delgado MF, McCourtie AS, Barnes AD, Verrier ED, Mulligan MS. Crosstalk between thrombosis and inflammation in lung reperfusion injury. Ann Thorac Surg 2006 mars;81(3):1061-7.
[61] Favreau F, Thuillier R, Cau J, Milin S, Manguy E, Mauco G, et al. Anti-thrombin therapy during warm ischemia and cold preservation prevents chronic kidney graft fibrosis in a DCD model. Am J Transplant 2009;10(1):30-9.

[62] Giraud S, Thuillier R, Belliard A, Hebrard W, Nadeau C, Milin S, et al. Direct thrombin inhibitor prevents delayed graft function in a porcine model of renal transplantation. Transplantation 2009;87(11):1636-44.
[63] Benigni A, Morigi M, Remuzzi G. Kidney regeneration. Lancet 2010 avr 10;375(9722):1310-7.
[64] Duffield JS, Humphreys BD. Origin of new cells in the adult kidney: results from genetic labeling techniques. Kidney Int 2011 mars;79(5):494-501.
[65] Thadhani R, Pascual M, Bonventre JV. Acute renal failure. N. Engl J Med 1996 mai 30;334(22):1448-60.
[66] Jayle C, Faure JP, Thuillier R, Goujon JM, Richer JP, Hauet T. Influence of nephron mass and a phosphorylated 38 mitogen-activated protein kinase inhibitor on the development of early and long-term injury after renal warm ischaemia. Br J Surg 2009 juill;96(7):799-808.
[67] Lan R, Geng H, Polichnowski AJ, Singha PK, Saikumar P, McEwen DG, et al. PTEN loss defines a TGF-β-induced tubule phenotype of failed differentiation and JNK signaling during renal fibrosis. Am J Physiol Renal Physiol 2012 mai;302(9):F1210-1223.
[68] Liu Y. Renal fibrosis: new insights into the pathogenesis and therapeutics. Kidney international 2006;69(2):213-7.
[69] Fine LG, Norman JT. Chronic hypoxia as a mechanism of progression of chronic kidney diseases: from hypothesis to novel therapeutics. Kidney Int 2008 oct;74(7):867-72.
[70] Ko GJ, Boo C-S, Jo S-K, Cho WY, Kim HK. Macrophages contribute to the development of renal fibrosis following ischaemia/reperfusion-induced acute kidney injury. Nephrol Dial Transplant 2008 mars;23(3):842-52.
[71] Hertig A, Verine J, Mougenot B, Jouanneau C, Ouali N, Sebe P, et al. Risk factors for early epithelial to mesenchymal transition in renal grafts. Am J Transplant 2006 déc;6(12):2937-46.
[72] Rifkin DE, Coca SG, Kalantar-Zadeh K. Does AKI truly lead to CKD? J Am Soc Nephrol 2012 juin;23(6):979-84.
[73] Hsu C. Yes, AKI truly leads to CKD. J Am Soc Nephrol 2012 juin;23(6):967-9.