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Additives to preservation solutions

Compléments aux solutions de conservation

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KEYWORDS
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Summary
As the impact of ischemia reperfusion injury on graft outcome is now well defined, efforts are made towards decreasing these lesions, typically through the improvement of preservation techniques.
The use of pharmacological supplements which could be compatible with any preservation solution used by the transplant center and target specific pathways of IR is an interesting strategy to improve graft quality. However, the extensive number of studies showing the benefits a molecule in an animal model of IR without thorough mechanistic determination of the effects of this agent make it difficult to opt for specific pharmaceutical intervention. Herein we expose studies which demonstrate the benefits of several molecules relying on a thorough mechanical analysis of the events occurring during preservation, both at the cellular and the systemic levels. We believe this approach is the most appropriate to truly understand the potential benefits of a molecule and particularly to design a comprehensive pharmaceutical regiment, with several agents acting synergistically against IR, to improve organ preservation and graft outcome.

MOTS CLÉS
Ischémie-reperfusion ;
Solution
de préservation ;
Supplements ;
Transplantation rénale

Résumé
L'impact de l'ischémie reperfusion sur les résultats de la transplantation rénale étant maintenant bien défini, les efforts se concentrent maintenant sur les moyens de diminuer ces lésions, en particulier par l'amélioration des techniques de préservations.
L'utilisation de suppléments pharmacologiques, compatible avec n'importe quelle solution de préservation utilisé par le centre de transplantation et ciblant les voies spécifiques de l'IR est une stratégie intéressante pour améliorer la qualité de la transplant. Cependant, le nombre important d'études montrant les avantages de telle ou telle molécule dans les modèles animaux d'IR sans détermination du mécanisme des effets de cet agent rend

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difficile le choix définitif pour une intervention pharmaceutique spécifique.
Dans cette article, les études qui démontrent les avantages de plusieurs molécules en s'appuyant sur l'analyse des mécanisme impliquées dans les événements survenus pendant la phase de préservation, tant au niveau cellulaire que systémiques sont passées en revue. A notre sens, cette approche est la plus appropriée pour comprendre les avantages potentiels d'une molécule et en particulier de concevoir un régime pharmacologique global, avec plusieurs agents agissant en synergie contre l'Ischémie-reperfusion, pour améliorer la conservation des greffons et les résultats de la greffe transplantation

Introduction

As the impact of ischemia reperfusion injury on graft outcome is now well defined, efforts are made towards decreasing these lesions, typically through the improvement of preservation techniques. Although advances are made in the design of preservation solutions, the lack of properly designed clinical trials to discriminate between them makes the choice for the right solution difficult [1]. This leads research teams to shift their focus from solution design, a very multifactorial issue, to the investigation of pharmacological supplements which could be compatible with any preservation solution used by the transplant center and target specific pathways of IR to improve graft quality. This approach, relying on a thorough mechanical analysis of the events occurring during preservation, both at the cellular and the systemic levels, presents the advantage of versatility, since it can be used in any solution and since agents can be combined to address multiple levels of the lesion.

The major hurdle to address in order to design a comprehensive supplementation agent-based strategy is choosing which compound to use. Indeed, a large number of agents are tested against ischemia reperfusion every year [2], using multiple models and hypotheses, with sometimes a lack of strong mechanism, confusing the issue and making any choice of compound difficult. In the present review, we attempted to provide a clearer view of the array of compounds available, focusing our presentation on agents and pathways which have strong bibliographic evidence of playing important parts in the development of ischemia reperfusion injury. We subdivided these into agents acting at the cellular level and compounds with larger areas of effects, keeping in mind that within a complex system such as an organ, the division will not be as strict.

Cell level

Oxygen

With the exception of the lung, ischemia of an organ is synonym of hypoxia. Several approaches have been attempted to face this key component of the injury mechanisms:

– oxygenation: direct delivery of oxygen to the organ through the use of artificial transporters such as perfluorocarbons [3] or gaseous oxygenation by retrograde persufflation [4] have shown some benefits in preclinical models, however it is still difficult to devise a safe and logistically efficient mean to bring these methods to the clinic. Machine perfusion appears to offer the possibility of oxygenation; however this will be discussed in another chapter. However, our team recently reported the use of a naturally occurring respiratory pigment in static preservation, which when used at a dose of 5g/L in UW or Custodiol improved graft quality and outcome in a large animal preclinical model [5]. Thus, although mechanistic analysis remains to be performed to understand its benefits, such molecule could be valuable in the future.

– oxygen dependent pathways: most cells are actually equipped to resist hypoxia, through the induction of specific pathways. These mechanisms are for instance described in hibernating animals, or during slow setting hypoxia. However, the suddenness and length of current organ preservation techniques do not allow for proper activation of these resistance pathways. Although proper use of preconditioning regiments have shown that preparing the organ for hypoxic stress was possible [6,7], the logistics of organ collection do not always allow for these complex steps to take place. However, recent research into the mechanical intricacies of preconditioning has shown that pharmacological mimicking was possible: a-the well described hypoxia inducible factor (HIF) pathway for instance, which is activated in case of hypoxia and induces the synthesis of pro-survival proteins such as erythropoietin and vascular endothelium growth factor, can be activated using inhibitors of propyl hydrolases which are normally in charge of HIF degradation [8, 9]. Such inhibition at the donor level was shown to offer a significant level of protection against transplantation-related IR; b-another pathway, working in close relationship with HIF, is the spingosine 1 phosphate (S1P) pathway, which is activated during IR in the kidney, particularly within tubular epithelium cells [10]. Interaction of S1P with its receptors commands the fate of the cell in sometimes opposing directions, S1PR1 inhibiting apoptosis in a MEK/EKR and PI3Kinase/Akt dependent manner [11], while S1PR2 promotes cell death and modulation of receptor expression, particularly S1P(2)R [12]. Hence, modulation of receptor expression as well as the use of specific agonists can improve resistance against IR.

Mitochondria

In the context of IRI, the mitochondria is the double edged sword which on one hand produces energy for the cell and on the other is the site of reactive oxygen species (ROS) production at reperfusion, which accumulation leads to cell death. The mitochondria also plays a key role in ionic

homeostasis regulation during IR, and can be led to release cytochrome c in the cytosol and thus induce apoptosis through the secondary pathway in case the mitochondrial membrane polarity disruption leads to the opening of the mitochondrial transition pore (mPTP).

It is thus clear that protecting the mitochondria is a key pillar in the design of an anti-IRI strategy. Protecting the mitochondria during preservation is possible, for instance with the use of dedicated molecules which adapt the mitochondrial metabolism to the stresses of IR, such as trimetazidine (TMZ). This molecule has the dual effect of favoring ATP synthesis through glysolysis and deprotonate the cytosol in case of ionic imbalance, reducing the risk of mitochondrial membrane depolarization. Use of TMZ in UW was beneficial in pigs, against a high level of IR stress by preserving kidneys in UW solution for 48-hour preservation period [13,14].

Another avenue to protect the mitochondria is through the regulation of the translocator protein (TSPO) pathway. Indeed, although the polymeric version of this protein is essentially involved in cholesterol transport, the monomeric form is beneficial against IR when overexpressed in cells. TSPO expression in the tubules after reperfusion is also a marker of good organ quality [15]. In animal model, regulation of TSPO with specific markers improved recovery by reducing mitochondrial damage and mPTP opening [16].

Maintaining mitonchondrial integrity has also been accomplished through reduction of ROS generation. Numerous studies show the benefits of antioxidants against IRI, but few refined the molecule to the point of specifically targeting the mitochondria. Such research produced molecules which readily enter the cell and are taken up by the mitochondria, allowing their antioxidative proterties to take place at the side of superoxyde anion production [17]. This approach is interesting, as the use of a targeting system allows for lower doses of agents to be used, as well as protecting the remainder of the cell from potential side effects of the molecule.

Medical gases against oxidative stress

The use of medical gases in the context of preservation has been regaining popularity in recent years [18]. Among their many advantages, we can highlight their availability and relatively cheap prices, to which are added the benefits of a small molecule which can easily enter the cell. However, the danger of using a sometimes toxic or explosive gas in a clinical setting needs to be carefully considered.

Hydrogen has recently been studied for its anti-oxidative properties in several setting, particularly in dissolved form. Interestingly, hydrogen rich saline is stable and safe [19], and its use for injection in animal models of IR has proven beneficial [20, 21]. However, the incompatibility of saline solution for organ preservation was limiting its potential use in the clinic. However, a recently published elegant method to saturate UW solution with hydrogen was designed by immersing UW containers in hydrogen rich saline, the small molecule of dihydrogen is able to enter the container while maintaining sterility, allowing the use of the hydrogen-saturated UW solution for organ preservation and thus improving organ quality in a rat transplant model [22].

Hydrogen sulfide also presents interesting properties in the context of IR. In addition to its oxidized radical scavenging properties, it induces hypometabolism of the cell, mimicking thus the benefits of hibernation [23]. Moreover, recent mechanistic studies have shown that hydrogen sulfide had effects on several signaling pathways, for instance inhibiting Na^+/H^+ exchanger-1 (NHE-1) in a PI3K/Akt/PKG-dependent mechanism, hence preventing Ca^{2+} overload during IR [24], or through sulfur hydration of proteins, regulating their activity towards pro-survival roles [25]. Treatment with H_2S demonstrated beneficial effects against warm ischemia injury [26, 27], however the toxicity of this gas renders it difficult to transition to the clinic. Nonetheless, recent description of hydrogen sulfide releasing molecule [28] or of activators of H_2S production in the cell [29] could circumvent this problem and permit its safe use in the clinic.

Carbon monoxide was also studied for the prevention of IRI. Carbon Monoxyde is a product of Heme Oxygenase 1, a major antioxidative pathway, and within the cells CO has anti-apoptotic and vasodilatation properties, in addition to the ability to induce antioxidant genes, reduce superoxydee anion levels and increase glutathione (GSH) production. Supplementation of preservation solution with gaseous CO has been tested in several models, showing improvement of graft outcome [30,31], however here also its use in a clinical setting is difficult due to its toxicity. This later issue could be solved with the use of CO-releasing molecules (CORMs), which have shown promising results in several models of IR [32].

Gene therapy

Use of oligonucleotides or siRNAs represents one of the best approaches to specifically affect a signalling pathway. Several studies have shown that this strategy could improve outcome [33], when targeting caspase 3 [34], endothelin A receptor [35] or p53 [36,37] in animals models of IRI. Although targeting is an issue when used systematically, in the context of transplantation the organ preservation time represents an optimal treatment window allowing perfect targeting of the therapy to the organ of interest. In this context, use of a cocktail against C3, TNFα and Fas proved beneficial in the heart [38]. Another approach for efficient targeting is the use of nanoparticles specifically engineered to release the siRNA to the site of injury [39] or which can be triggered by finely targeted ultrasounds [40]. Other gene therapies can also be beneficial against IR, such as the overexpression of antioxidative proteins [41] and the use of micro-RNAs based therapies [42].

Endothelium lumen level

Coagulation

The coagulation pathway is intricately associated with inflammation development and the ‘no reflow’phenomenon in IRI. Preconditionning the organ during preservation with specific anti-coagulants has shown, in our own studies, that

it could improve cell survival and decrease the expression of proinflammatory factors at reperfusion, improving organ quality and impacting positively on graft outcome in a preclinical pig model of kidney transplantation [43-45].

Complement

The complement pathway is an integral element of the response to injury, associated with the development of inflammation [46]. Recent work has highlighted the importance of complement activation in IR [47,48], with links to the innate immune system and toll like receptor 2 signaling [49], making complement an valuable therapeutic target against IR. Indeed, several anti-complement approaches have been shown to be beneficial against IR in different models, ranging from pharmaceutical molecules to gene therapy tool, including a chimeric molecule inhibiting C1 in a biomedical pig model [50].

Proinflammatory pathways inhibition

Cells subjected to IRI release pro-inflammatory cytokines, inducing the immune response. Among the signalling pathway leading to this production, NFκB is a key component and its activation is well described in IRI. Reduction of NFκB signaling through inhibition of upstream proteins can be accomplished, for instance through antagonising TNFα signalling [51] or tool like receptors [52], and reduce IR associated damage.

p38MAPK is another well described actor in inflammation, apoptosis, differentiation as well as proliferation signalling, and its activation in the context of IRI is well documented. The importance of this pathway was confirmed in a preclinical pig model of kidney transplantation in which our team demonstrated that a specific inhibitor of p38MAPK, when used in the peritransplant period and during organ preservation, improved graft quality [53] and could be used in conjunction with other anti-IRI molecules [54].

Invading cell adhesion

Although situated far downstream from the source of IRI, the adhesion of immune competent cells to the endothelial wall represents a turning point in the injury, as these cells enhance local oxidative stress, mediate cellular death as well as signaling for adaptative immune system activation. Decreased adhesion can be obtained by gene therapy directed at intercellular adhesion molecule-1 (ICAM-1) either during preservation [55] or after reperfusion [56]. However, clinical trials of this strategy (renamed ISIS 2302) did not show extensive benefits [57]. Another strategy is to block the receptor using a protein sequence mimicking its ligand, for instance using Bß15-42, a breakdown product of fibrin VE-cadherin binding sequence which lacks the leukocyte binding site, effectively antagonizing the anchoring og the cell to the endothelial wall, hence reducing significantly the damage following IR [58].

Conclusion

In this review, we highlight that the regulation of key pathways involved in the response to IR can have important benefits in terms of organ quality and graft outcome. Although investigations into the mechanistic implications of these intervention need to be completed, it is now clear that supplementation of the preservation solution with dedicated molecule is possible and has the potential to greatly improve graft quality, and major advantage in the current situation of decreasing donor organ quality. Importantly, these strategies can be adapted to most preservation protocols used today, usually requiring only the addition of the compound to solution containers already in use in the transplantation center, and more importantly there has been several investigation detailing the use of combination of compounds, each directed against a specific pathway of the injury, demonstrated additivity of the approaches. Hence, the design of a multi-agent regiment to increase graft quality is possible, and in the future can be combined with the advances in pre-transplant organ evaluation to obtain customized regiment adapted to the quality of the organ to be transplanted. However, such design will rely on strong knowledge of the true effect of the molecule at the cellular level, which can only be obtained through properly designed mechanistic investigation. It is thus of paramount importance to encourage this research, insisting in particular on the proper mechanistic evaluation of each intervention.

Disclosure of interest

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

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