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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