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Innate and adaptive immune responses subsequent to ischemia-reperfusion injury in the kidney

Impact des lésions d'ischémie-reperfusion sur la réponse immunitaire innée et acquise

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Summary
Understanding innate immune responses and their correlation to alloimmunity after solid organ transplantation is key to optimizing long term graft outcome. While Ischemia/Reperfusion injury (IRI) has been well studied, new insight into central mechanisms of innate immune activation, i.e. chemokine mediated cell trafficking and the role of Toll-like receptors have evolved recently. The mechanistic implications of Neutrophils, Macrophages/Monocytes, NK-cells, Dendritic cells in renal IRI has been proven by selective depletion of these cell types, thereby offering novel therapeutic interventions. At the same time, the multi-faceted role of different T-cell subsets in IRI has gained interest, highlighting the dichotomous effects of differentiated T-cells and suggesting more selective therapeutic approaches. Targeting innate immune cells and their activation and migration pathways, respectively, has been promising in experimental models holding translational potential. This review will summarize the effects of innate immune activation and potential strategies to interfere with the immunological cascade following renal IRI.

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MOTS CLÉS
Immunité adapatative ;
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Lymphocytes T ;
Récepteurs Toll-like ;
Reperfusion

Résumé
La compréhension des relations entre immunité innée et adaptative est essentielle pour optimiser les résultats de la transplantation d'organe.
En parallèle des mécanismes -déjà explorés – des lésions d'ischémie-reperfusion, le rôle de l'activation l'immunité innée et de ses effecteurs (récepteurs toll-like, cytokines,etc.) est un concept plus récent. Ainsi, de nombreux modèles expérimentaux de déplétion de types cellulaires ont prouvé l'implication des polynucléaires neutrophiles, des monocytes-macrophages, des cellules NK ou encore des cellules dendritiques dans le développement des lésions d'ischémie-reperfusion, suggérant de nouvelles perspectives thérapeutiques sélectives: cibler l'activation et la migration des effecteurs de l'immunité innée semble être une méthode prometteuse.
Notre travail fait le point sur les effets de l'activation de l'immunité innée en transplantation rénale et les différentes stratégies possibles visant à interférer avec la cascade immunitaire déclenchée par l'ischémie-reperfusion.

Introduction

In the past years, transplantation research has emphasized on understanding the mechanisms of innate immune activation and their initiation of alloimmune responses in organ transplantation. While mechanisms of acute rejections (AR) have been well elucidated and treatment has been effective, innate immune activation early after transplantation has not been targeted successfully, yet. Thus, understanding the consequences of IRI on innate and adaptive immune activation appears critical for an early interference with with the activated immune cascade.

The innate immunity acts as the first line of defense against foreign tissue by detecting so called damage-associated or pathogen – associated molecular patterns (DAMP's, PAMP's) which bind to pattern recognition receptors (PRR) on APC's and other innate immune cells. Mechanical, thermal and pathogen induced cell damage cause a non-specific inflammatory response including TLR activation and proinflammatory cytokine release, thus starting a cascade of neutrophil, DC and T-cell activation [1]. Indeed, surgery itself, brain death and ischemia have all been shown to activate innate immune responses [1-3]. Thus, IRI serves as a non-specific inflammatory injury which elicits a coordinated alloimmune specific response against the graft.

Ischemia Reperfusion injury

IRI is characterized by ATP depletion, lack of glycogen and oxygen supply, all resulting into metabolic changes. As a consequence, renal tubular epitihelial cells are injured, tissue resident leukocytes are activated and endothelial cell function is impaired leading to vascular leakage and interstitial edema. Following the upregulation of adhesion molecules (ICAM-1, P-Selectin and others), endo- and epithelial damage is furthermore accelerated by complement activation with subsequent increased cytokine levels resulting into the adhesion of leukocytes to the endothelium capturing red blood cells and platelets in turn [4-6]. Tubular epithelial cells, on the other hand, upregulate TLR-2 and TLR-4 and internalize the complement inhibitory factor Crry which, in turn, causes deposition of complement, production of chemokines and recrution of polymorph nuclear leukocytes (PMN's) [7,8].

Besides, reactive oxygen species (ROS) such as superoxide, peroxynitrite or H_2O_2 derived hydroxyl radicals facilitate further DNA damage and activate an ADP polymerase (PARP-1) causing considerable tissue injury. Various inflammatory cells express NADPH oxidases and act as a source of ROS, neutrophils being the most abundant [9]. Arandomized clinical trial in kidney transplant patients demonstrated a beneficial effect of the free radical scavenger superoxide dismutase [10]. Amelioration of endothelial cell damage caused by free oxygen radicals lead to significantly improved long-term graft survival and reduced rates of acute rejection (AR) suggesting a causal relation between innate immune injury and chronic immune stimulation.

Furthermore, cell death programs such as apoptosis, autophagy-associated cell death and necrosis are initiated subsequent to IRI [11]. While necrosis causes further immune stimulation, apoptosis is supposed to cause less inflammation. Yet, there are recent reports of an apoptosis associated stimulation of monocytes and macrophages presumably also leading to innate immune activation [12].

Activation of innate immune cells

The innate immune response as a first line response is carried out by neutrophils, macrophages, Dendritic Cells (DC), NK and NKT-cells and T-cells. Following reperfusion, neutrophils adhere to the endothelium and migrate into the tissue. Neutrophils react immediately to unspecific injury, infiltrate the tissue and release proteases, oxygen-free radicals through degranulation and start producing pro-inflammatory cytokines such as IL-4, IL-6, IFNγ, TNFα [13]. In line with those findings, neutrophil depletion protected mice from IRI [14].

Similarly, macrophages exhibiting an activated phenotype and producing proinflammatory cytokines (IL-1_a, IL-6 IL-12, TNFα) can be found at very early stages of IRI [15,16]. Migration of monocytes/macrophages is mediated by various