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ROLE OF LEUKOCYTES AND LEUKOCYTE ADHESION MOLECULES IN RENAL ISCHEMIC-REPERFUSION INJURY

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1. ABSTRACT

Renal ischemic-reperfusion injury (IRI) occurs frequently in transplanted as well as native kidneys. Effective treatment for this process is still elusive. Leukocytes and their products may be important in the pathogenesis of renal IRI, however their role is still controversial. Recently, adhesion receptors on leukocytes and their corresponding ligands have been identified. In the heart, considerable evidence supports the role of CD11/CD18, ICAM-1, and the selectin receptors in IRI. However, based on experimental studies in animal models, even though renal IRI appears to be ICAM-1 mediated, the role of the CD11/CD18 pathway appears to be minimal. In addition, the available evidence does not support the concept that L-selectin has significant involvement in renal IRI. In this review, the data and controversies regarding the role of leukocytes and leukocyte adhesion molecules in renal IRI are discussed.

2. INTRODUCTION

Renal transplantation is the preferred treatment for end-stage renal disease. From the time of procurement of the kidney from the donor until the time that vascular anastomosis has been established in the recipient, the blood flow to the kidney is interrupted. The incidence of the postischemic allograft injury during the first post-operative week is about 30-40% (1). Such injury contributes to delayed graft dysfunction as well (1).

Native kidneys also undergo ischemic acute renal failure which is associated with a mortality rate of upto 50% (2). Despite the development of dialysis this mortality rate has not improved in the last 30 years (2). This poor clinical outcome has given impetus to investigate mechanisms of post-ischemic renal failure and to develop novel strategies for its therapy.

Ischemia to the kidney triggers complex pathophysiologic responses so that restoration of normal renal blood flow soon after an ischemic insult may not prevent the development of processes that perpetuate tissue damage (3). Redistribution of renal blood flow, tubular lumen obstruction, tubular cell swelling, and most recently, apoptosis, are some of the processes thought to perpetuate the postischemic renal damage (2,3). The production of reactive oxygen species (ROS) has also been implicated in renal ischemic reperfusion injury (IRI), however the sources of these ROS have not been fully defined thus far (4). Possible sources of ROS include infiltrating neutrophils, mitochondria and peroxisomes, while enzymes that generate ROS include xanthine oxidase and prostaglandin synthetase (4). In addition to the production of ROS, leukocytes can produce arachidonic acid metabolites, proteases, and other deleterious agents (5). In this manuscript the role of leukocytes and leukocyte-endothelial adhesion molecules in the pathogenesis of renal IRI is reviewed.

3. LEUKOCYTES AND RENAL REPERFUSION INJURY

There is a considerable body of evidence that leukocytes are involved in the process of renal IRI. In postischemic human and rat kidneys, an increase in the number of leukocytes was noted in the ascending vasa recta in the outer and inner medulla (6,7). Willinger *et*

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al. quantified polymorphonuclear cells (PMNs) in the post-ischemic rat kidney and found a greater than 9-fold increase in the total number of PMN 2 hours after a 45 minute clamping of the renal artery (8). At this time point, increased neutrophils were seen in the renal cortex, outer medulla and also the inner medulla using a modified Leder stain. In a seperate study, an increase in the number of rat peritubular neutrophils was observed 24 hours after the renal artery was clamped for 60 min (9). In mice, a greater than 10-fold increase in the number of peritubular PMNs was observed 24 hours after the renal pedicle was clamped for 30 minutes (10). Using a myeloperoxidase assay as a measure for the neutrophil influx, Kelly *et al.* found a significant increase in the renal tissue myeloperoxidase activity as early as 4 hours after renal ischemia (11). This activity peaked at 24 hours after the ischemic episode (11). Thus, one may need special stains or biochemical assays to adequately quantify the increased PMNs in the postischemic kidney.

The increase in PMNs in the postischemic organ may be involved in the healing process or may potentially contribute to the tissue damage. Consistent with the latter possibility, neutrophil depletion reduced the postischemic injury to heart, liver, and gut (12-15). Thus PMNs may have a pathophysiologic role in renal IRI. Depletion of rat neutrophils by a rabbit antiserum to neutrophils afforded marked protection in ischemia-induced renal dysfunction and tubular necrosis 24 hours after the renal pedicle was clamped for 45 minutes (5). In addition, the neutropenia was associated with less increase in the amount of renal vein leukotriene B4 and thromboxane B2 after ischemia. Hellberg and Kallskog demonstrated that the post-ischemic tubular leakage in rat kidneys can in part be limited by depletion of neutrophils (16). In a series of studies by Linus *et al.* using isolated perfused rat kidneys there has been further demonstration that neutrophils have an adverse effect on renal IRI. PMNs can lead to a more severe compromise in GFR and tubular sodium reabsorption postischemia (17). The contribution of neutrophils was shown to be dependent on the duration of renal ischemia and the state of PMN activation (18). More recently, these investigators have found that IRI leads to neutrophil retention, thereby further compromising kidney function (19). It should be noted that these studies by Linus *et al.* evaluated the effects of human neutrophils on the isolated rat kidneys.

Despite this strong evidence supporting the adverse role of leukocytes in renal IRI, this issue is not settled yet. Morphologic examination of the post-ischemic human kidney as well as reports from animal models of experimental ischemic acute renal failure have only infrequently reported an increase in the number of neutrophils (19,20). In addition, it is well recognized in clinical practice that neutropenic patients can develop acute renal failure. Forty minutes of renal artery occlusion produced similar worsening of renal function in rats depleted of neutrophils and in control rats (4). Nevertheless induction of neutropenia with nitrogen mustard, was associated with a higher inulin clearance after IRI (4). In another study, anti-neutrophil serum did not confer functional or morphologic protection after either 29 minutes or 37 minutes of renal artery occlusion (21). These findings cast doubt whether neutrophils play a major role in the pathogenesis of renal injury after ischemia.

4. THE ROLE OF LEUKOCYTE ADHESION MOLECULES IN RENAL REPERFUSION INJURY

Over the last decade there has been an explosion of information regarding the biological basis of leukocyte interaction with other cells as well as with matrix. Developments in this field of leukocyte adhesion have led to a resurgence of interest in studying the role of leukocytes in mediating tissue injury, particularly due to the development of specific blocking antibodies and other reagents directed to these adhesion molecules. There are many excellent reviews on the basic biology of the three main leukocyte adhesion molecule families: integrins (22,23), immunoglobulin superfamily members (24), and selectins (25). Thus, only the some of the most relevant aspects of these molecules will be reviewed here. This will be followed by a section discussing the role of these molecules in renal IRI.

4.1 Integrins:

The integrins which appear most important in leukocyte-endothelial adhesion, particularly in terms of clinical relevance in the kidney, are the beta-1 integrin VLA-4 (very late antigen-4) and the beta-2 integrins, CD11/CD18 (26,27). The VLA-4 molecule is found on lymphocytes, basophils, and eosinophils, but not neutrophils. This protein binds to endothelial cells through an inducible ligand, vascular cell adhesion molecule-1 (VCAM-1) (28). CD11/CD18 integrins are expressed solely on leukocytes, and there are 3 known members of this family, all with a distinct alpha subunit and a common beta subunit. CD11/CD18 deficiency disease (leukocyte adhesion deficiency) is a rare childhood immunodeficiency that initially shed light on the key physiologic role of CD11/CD18 (29). Subsequently, the molecular basis for complete and partial CD11/CD18 deficiency has been largely worked out (30-33). The major ligand for CD11a/CD18 is intercellular adhesion molecule-1 (ICAM-1), though other ligands such as ICAM-2 and ICAM-3 exist (34-37). CD11b/CD18, in addition to binding to ICAM-1, also binds to complement fragment iC3b, factor X and fibrinogen (38). CD11c has not been studied as extensively. CD11/CD18 functions are tightly regulated, in part by key amino acid residues on the CD18 cytoplasmic domain (39).

4.2 Immunoglobulin super family members:

Immunoglobulin (Ig) - like adhesion receptors are single-chain transmembrane proteins that contain

one or more immunoglobulin domains (24). Among the many members of this family are ICAM-1, VCAM-1, CD4, CD8 and carcinoembryonic antigen (24). ICAM-1 is expressed on endothelial, epithelial and fibroblast cells as well as on leukocytes (24). Various cytokines (eg. interferon, tumor necrosis factor-alpha, and interleukin-1) can induce ICAM-1 expression. VCAM-1 is one of the major ligands for VLA-4 (28). VCAM-1 is expressed on many different tissues, including vascular endothelium, epithelial cells, bone marrow cells, and some macrophages (40). Like ICAM-1, VCAM-1 is also cytokine-inducible, but may have differential regulators (41).

4.3 Selectins:

The selectin family consists of 3 different single chain transmembrane receptors: E, P, and L-selectin. These receptors have an N-terminal lectin domain, an epidermal growth factor domain, complement regulatory repeats, and a transmembrane and short cytoplasmic domain (25). E-selectin is expressed on cytokine (eg. IL-1, TNF-alpha, endotoxin) stimulated endothelium but usually not on non-activated endothelium (42). L-selectin is constitutively expressed on lymphocytes, neutrophils, monocytes and other myeloid cells (43). L-selectin on lymphocytes mediates adhesion to high endothelial venules in peripheral lymph nodes, as well as neutrophil recruitment to the inflammatory sites (25). P-selectin is expressed in platelets and activated endothelial cells, and appears to have different inducers than E-selectin (eg. hydrogen peroxide, thrombin) (25). The selectins bind to sialylated and fucosylated structures related to the Lewis-X blood group antigen (44,45). Like CD11/CD18 deficiency disease, some children have been identified that suffer from a defect in the selectin pathway (46). Children lacking SLe^x, a selectin ligand, are predisposed to infections. It is currently felt that selectins are important in initiating leukocyte rolling on vascular endothelium. This binding is a pre-requisite for firmer adherence via integrins before leukocyte emigration from blood vessels into the target tissues (47).

4.4 Do leukocyte adhesion molecules mediate renal reperfusion injury?

With evidence implicating leukocytes and oxygen free-radicals in renal reperfusion injury, there has been recent interest in delineating the role of leukocyte adhesion molecules in these processes. In animal experiments administration of monoclonal antibodies to leukocyte adhesion molecules has attenuated reperfusion damage in many organs, including heart, liver and skeletal muscle (14, 48).

As compared to control rats, administration of blocking monoclonal antibodies to the CD11a & CD11b subunits prior to 60 min of renal artery occlusion was associated with a 25% lower serum creatinine and less evidence of pathologic damage 24 hours later (9). Although the increase in renal neutrophils was slightly lower in the treatment group, it was not statistically significant (9). These same antibodies virtually abolished neutrophil migration to LPS-stimulated dermis (9), but caused little change in airway leukocytes while significantly attenuated allergic airway hyperresponsiveness to antigen (49). These studies suggested that CD11/CD18 may play a role in renal IRI, but the neutrophil's dependance on this pathway for tissue migration is stimulus- and organ- specific. ICAM-1 blockade by monoclonal antibody IA29 in rats afforded more protection against renal ischemia (50). This treatment was associated with better preservation of structure and function (by nearly 50%), and attenuated the rise in the renal tissue neutrophils after induction of ischemia (50). It is important to note that neither CD11a/CD11b, ICAM-1 or control antibodies caused leukopenia. It is likely that the renal protection from anti CD11 or ICAM-1 antibodies was due to blockade in neutrophil migration, however other protective effects of the antibodies such as alteration of signal transduction or even apoptosis may have played a role (9,50).

In a different set of studies, monoclonal antibody blockade of CD11a had a small effect and blockade of ICAM-1 had a pronounced effect in affording protection against post-ischemic renal injury which occured after 30 min of renal pedicle clamping (11). Consistent with ICAM-1's role in neutrophil migration, ICAM-1 blockade significantly attenuated the rise in postischemic renal myeloperoxidase activity, (11). The functional protection that was observed by Kelly *et al.* with the IA29 antibody to ICAM-1 was more pronounced than our study with the same antibody (50). We suspect that this may in part be because our model consisted of 60 min of renal artery clamping, thus producing a more severe tissue injury by ICAM-1 independant mechanisms. Consistent with a role of ICAM-1 in renal IRI, Kelly *et al.* have also demonstrated that ICAM-1 deficient mice were protected from renal IRI (51). Further evidence supporting the role of ICAM-1 in renal IRI is provided by the isolated kidney perfusion model in which ICAM-1 has been shown to play a role in neutrophil retention in post-ischemic kidney (19). Taken together, these findings support the concept that leukocyte adhesion molecules may play a role in the pathogenesis of renal IRI.

Protection of renal function by anti-CD18 or ICAM-1 antibodies however, has not been universal. In a study in a rabbit model of IRI neither renal structure nor function was protected by the monoclonal 60.3 against CD18 (21). In this study, both 38 and 50 minutes of renal artery occlusion were tested (21). Also in rabbits, neither mAb R15.7 to CD18 nor R6.5 to ICAM-1 was found to protect kidney from IRI (Neuringer J & Brady HR, unpublished observations).

Selectins are felt to be required to set the stage for the CD11/CD18 - ICAM-1 interactions (47). Recent work in skeletal muscle, ear and myocardium have demonstrated that selectin blockade affords protection against postischemic damage (52-54). We evaluated

renal IRI in L-selectin deficient mice generated by homologous recombination. These mice, except for small lymph nodes and thymus, are grossly normal in appearance and survive well under sterile conditions (55). Using flow cytometry, we confirmed that L-selectin on leukocytes was deficient from the batches of mice we used. Chemical peritonitis was significantly reduced in the L-selectin deficient mice, with a 47% reduction in peritoneal neutrophils 4 hours after thioglycollate injection (10). Using 30 min of bilateral renal pedicle clamping, there was more than 10-fold increase in the number of peritubular neutrophils 24 hours after ischemia was induced in normal mice. However, as compared to normal mice after renal ischemia, the L-selectin deficiency did not lead to lower number of renal tissue neutrophils. In addition, renal function was similar in L-selectin mice and controls 24 and 48 hours postischemia. This study suggests that neutrophil migration to postischemic kidney can be L-selectin independent, and that L-selectin does not mediate renal IRI. However, one must interpret results in knockout mice with caution, as aberrant adaptive mechanisms may be occurring which may not normally take place. For example other selectins may be substituting the function which is normally exerted by L-selectin. Evaluation of the role of other selectin knockouts in renal IRI is being performed. These studies and studies that block all three selectin pathways or use of glycomimetic ligand analogs may clarify the precise role of selectins in renal IRI.

5. SUMMARY

Leukocytes and leukocyte adhesion molecules such as CD18 and particularly ICAM-1 may be implicated in IRI. However the role of infiltrating leukocytes in renal IRI may not be as important as it is in other organs such as heart and gut. The results summarized in this manuscript raise questions as to what role different leukocyte adhesion molecules play in renal IRI. It is likely that the role of these molecules may be independent of their role in cell migration, and may be virtue of mediating cell activation and signalling. The development of improved blocking modalities such as humanized antibodies (56), peptides (57) and antisense oligonucleotides (58), plus the results from ongoing clinical human trials, should clarify the role(s) and the degree of importance of these pathways in renal IRI.

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