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Pathophysiological Contributions of Fucosyltransferases in Renal Ischemia Reperfusion Injury[1]

Melissa J. Burne and Hamid Rabb[2]

Ischemia reperfusion injury (IRI) is a major cause of delayed graft function. Recent studies have shown that selectins play an important role in IRI. Selectins bind to sialylated and fucosylated sLe^x receptors, and two enzymes, fucosyltransferase IV (FucT-IV) and VII (FucT-VII), are important in the function of these receptors. We hypothesized that fucosyltransferase (FucT) enzymes were important pathophysiologic mediators of renal IRI. We therefore evaluated renal IRI in mice deficient in FucT-IV, FucT-VII, and both FucT-IV and FucT-VII and compared their renal function, tubular injury, selectin ligand expression, and neutrophil infiltration to those in wild-type control mice. Bilateral 30-min renal IRI was performed, and the results demonstrated that mice deficient in both FucT-IV/FucT-VII were significantly protected from renal IRI at 24 and 48 h compared with wild-type control mice. FucT-IV-deficient mice showed only modest protection from renal injury at 24 h. However, FucT-VII-deficient mice had similar injury as wild-type mice. Histological analysis of kidney tissue postischemia revealed that mice deficient in both FucT-IV and FucT-VII had significantly reduced tubular injury compared with wild-type mice. Selectin ligand expression increased post-ischemia in wild-type, but not FucT-IV/FucT-VII-deficient, mice. Neutrophil infiltration in postischemic kidneys of FucT-IV/FucT-VII-deficient mice was also attenuated. These data demonstrate that fucosyltransferases are important in the pathogenesis of renal IRI and are potential therapeutic targets. ***The Journal of Immunology,*** **2002, 169: 2648–2652.**

Ischemia reperfusion injury (IRI)[3] is a common cause of acute renal failure in both native kidneys and allografts (1). Native kidney acute renal failure is associated with high morbidity and mortality that has not improved over 40 years despite the advent of dialysis (1). There are a number of potential mediators of renal IRI, including abnormal vascular reactivity, tubular obstruction, epithelial cell dysfunction, and apoptosis (2). Recently, there has been an increased awareness of the role of inflammation in the pathogenesis of renal IRI (3). Neutrophils, monocytes, and lymphocytes are recruited into the postischemic kidney in humans as well as in animal models (4, 5). Leukocyte recruitment initiates with leukocyte rolling on the inflamed endothelium.

Leukocyte rolling is mediated by a class of adhesion molecules known as selectins (6), and precedes subsequent firm adhesion mediated by CD11/CD18 and ICAM-1, and then leukocyte transmigration in acute and chronic inflammation. The selectin family consists of three different transmembrane receptors, E-, P-, and L-selectin (6, 7). Initial studies with P-selectin Ab have demonstrated a pathogenic role for P-selectin in renal IRI in rats (8). However, L-selectin-deficient mice subjected to IRI showed brisk neutrophil migration to the postischemic kidney as well as equivalent renal dysfunction compared with wild-type mice (5). More recently, protection has been observed in cold renal IRI in rats treated with a soluble form of P-selectin glycoprotein-1, a major ligand for P-selectin that can effectively block P-selectin-dependent leukocyte recruitment as well as E- and L-selectin-dependent recruitment to some degree (9). Blockade of selectin ligands using a small molecule approach has also been effective in a rat model of renal IRI (10). Blockade of E- and P-selectin in a murine model of renal IRI has been found to be protective (11, 12).

The selectins bind to sialylated and fucosylated counter-receptors. Regulated specific expression of the α(1,3)fucosyltransferases (FucTs) responsible for the α(1,3)fucosylation controls the expression of selectin counter-receptor activities. Two mammalian FucT loci, termed FucT-IV and FucT-VII, have been implicated in the control of leukocyte selectin ligand activities by virtue of their expression patterns, the structure of the fucosylated glycans they elaborate, and analysis of mice with induced null mutations in these loci (13–15). FucT-IV was the first leukocyte-associated enzyme linked to selectin-ligand synthesis (16, 17). FucT-IV, can synthesize the Le^x, Le^y, and sLe^x epitopes, although the activity for sLe^x synthesis is very weak. FucT-IV is also in various non-myeloid tissues. Subsequently, the gene encoding a distinct FucT, termed FucT-VII, was cloned (18, 19). FucT-VII has a more strict specificity for substrates, and only synthesizes the sLe^x epitope or its 6-*O*-sulfated variant. Tissue distribution of FucT-VII is restricted to leukocytes and their progenitors and to the specialized endothelial cells in high endothelial venules within lymph nodes. While much is known about the substrate specificities and expression patterns of these enzymes, their roles in health and disease in vivo are only now beginning to be explored. This is especially important in the development of novel therapeutics, as pharmacological inhibition of leukocyte-specific FucTs could lead to an anti-inflammatory outcome by interrupting the function of selectin ligands.

Based on the above data on the role of selectins in renal IRI and advances in FucTs, we sought to determine whether FucTs play an important role in renal injury following IRI. We initially explored

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[3] Abbreviations used in this paper: IRI, ischemia reperfusion injury; FucT, fucosyltransferase; PMN, neutrophil.

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selectin ligand expression in the murine kidney using an E-selectin/IgM chimera to identify FucT-dependent expression of selectin ligands (20). We then investigated the pathophysiologic role of FucTs in an established murine model of renal IRI (21). Renal function and structure were analyzed in mice deficient in FucT-IV, FucT-VII, and both enzymes, and these results were compared with those in wild-type mice. Neutrophil (PMN) infiltration in kidneys was also analyzed postischemia. We found that mice deficient in both FucT-IV and FucT-VII were markedly protected from renal dysfunction, structural damage, and neutrophil infiltration postischemia.

Materials and Methods

Knockout animals

C57BL/6 mice possessing a homozygous deletion of the FucT-IV gene, the FucT-VII gene, and both FucT-IV and FucT-VII genes were used and have previously been described in detail (20). Phenotypically these mice were healthy, fertile, and had no growth abnormality in appearance or body weight (14). C57BL/6 wild-type littermates served as controls.

E-selectin/IgM chimera staining

Kidneys were stained with an E-selectin/IgM chimera to examine up-regulation of selectin ligand expression in renal IRI. The construction of the E-selectin/IgM chimera has been previously described in detail (14). Briefly, the chimera was constructed from mouse E-selectin cDNAs. PCR-amplified fragments corresponding to their lectin, epidermal growth factor, and two complement repeat domains were linked to DNA sequence encoding the CH2, CH3, and CH4 domains of human IgM in a mammalian expression vector, as described for a mouse L-selectin-IgM chimera (22). Kidney sections at 0, 2, and 24 h were fixed in 1% paraformaldehyde and 0.1 M cacodylate (pH 7.1) for 20 min on ice and then washed with TBS (pH 7.4). The E-selectin/IgM chimera was applied to sections at a concentration of 60 μg/ml in blocking solution B (TBS (pH 7.4) containing 2% goat serum) supplemented with either 3 mM $CaCl_2$ or 5 mM EDTA and was allowed to incubate overnight at 7°C. EDTA was added to the chimeric protein in one group of slides to distinguish nonspecific binding. Selectins recognize their counter-receptors in a divalent cation-dependent manner, and EDTA prevents this specific recognition. The sections were washed and supplemented with 3 mM $CaCl_2$ and then incubated for 1 h at 7°C with a biotinylated goat anti-human IgM reagent (Sigma-Aldrich, St. Louis, MO) diluted 1/200 in blocking solution B and supplemented with 3 mM $CaCl_2$ or 5 mM EDTA. The sections were again washed, supplemented with 3 mM $CaCl_2$, and incubated for 1 h at 7°C with an FITC-conjugated streptavidin reagent (Vector Laboratories, Burlingame, CA) diluted 1/200 in blocking solution B supplemented with 3 mM $CaCl_2$. The slides were washed, then supplemented with 3 mM $CaCl_2$, mounted with Citifluor, and examined by immunofluorescence microscopy.

Renal ischemia reperfusion model

An established model of renal IRI in mice was used (21). Briefly, mice weighing 25–30 g were anesthetized with pentobarbital sodium (35–60 mg/kg) i.p. The abdominal region was shaved, and the animals were placed on a heating table to keep them at a constant temperature (37°C), which was monitored with a rectal thermometer. The abdomen was then soaked with Betadine, and sterile drapes were applied. An abdominal incision was made, and the kidneys were exposed. The renal pedicles were bluntly dissected and a nontraumatic vascular clamp (Roboz Surgical Instrument, Washington, D.C.) was applied across the pedicles for 30 min. After the clamps were released, the wounds were closed in two layers with 4-0 silk. The animals received 100 ml/kg warm saline instilled into the peritoneal cavity during the procedure and were then allowed to recover, with free access to food and water. All animal experimentation was conducted in accord with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Assessment of postischemic renal function

Blood samples were obtained from the tail vein at 0, 24, 48, and 72 h postischemia. Renal function was assessed by measurement of serum creatinine on a Cobas Fara automated system (Roche, Nutley, NJ) using a creatinine 557 kit (Sigma-Aldrich).

Pathological evaluation of postischemic kidneys

At 24 and/or 72 h postischemia, kidneys were dissected from mice and cut coronally. These sections were fixed in 10% formalin and processed for histology using standard techniques as previously described (21).

PMN infiltration analysis using immunohistochemistry

This method has been previously described in detail (21). Briefly, sections from frozen kidneys (5 μm) were fixed with ice-cold acetone and air-dried. Sections were blocked with a 1/100 dilution of normal rabbit serum in PBS containing avidin DH (Vector Laboratories). The primary Ab, Ly-6G (Gr-1), targeting neutrophils (BD PharMingen, San Diego, CA) was added, and sections were incubated at room temperature for 1 h. Background staining isotype controls consisted of rat IgG1 in place of the mAb.

Sections were then treated with 3% hydrogen peroxide in biotin (10 μg/l PBS), and slides were incubated in biotin-conjugated rabbit anti-rat IgG secondary Ab (Vector Laboratories) for 35 min at room temperature. Finally, slides were incubated for 45 min in Elite ABC (Vector Laboratories). Sections were developed with 3,3-diaminobenzidine (Vector Laboratories) and counterstained with hematoxylin. Tissue sections (n = 4/group/time point) were examined by counting positively stained cells in 10 randomly selected, high powered fields of the corticomedullary junction (magnification, ×400). Baseline (0 h) values were normalized to 100%, and increases in neutrophil infiltration at 24 and 72 h in each group were compared with their individual baseline values and represented as the percent increase from baseline.

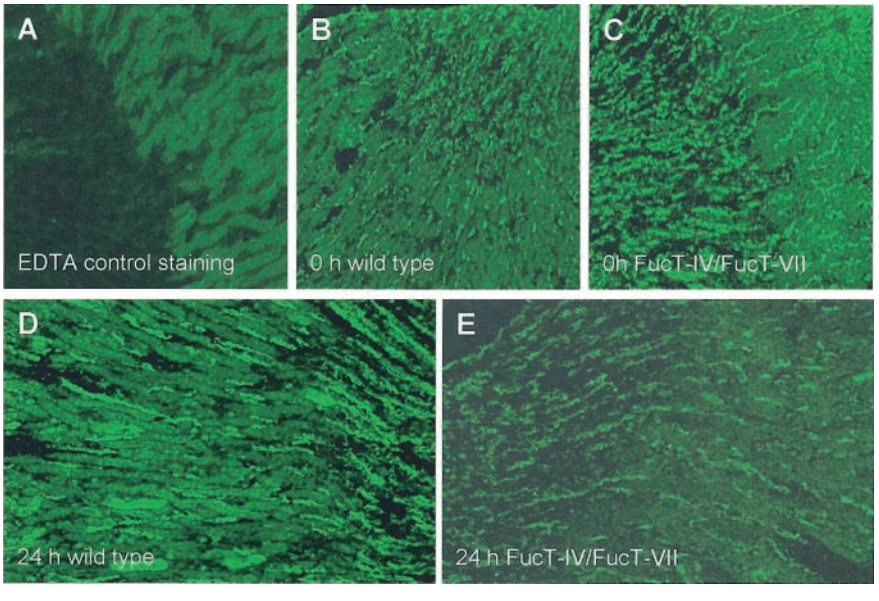

FIGURE 1. E-selectin/IgM chimera staining in the postischemic kidney. Representative slides from the outer medulla are shown. *A*, EDTA plus chimera control; *B*, 0 h wild-type kidney; *C*, FucT-IV/FucT-VII-deficient mice at 0 h; D, 24-h postischemia wild-type control; E, FucT-IV/FucT-VII-deficient mice at 24 h postischemia.

Statistical analysis

All values are presented as the mean ± SE. Statistical analysis comparing control and transgenic groups was performed by ANOVA (Dunnett's), and significance was set at $p < 0.05$.

Results

E-selectin/IgM chimera staining

Postischemic kidneys from each group of mice were stained with an E-selectin/IgM chimera to evaluate selectin ligand expression in the kidney. Representative slides from the outer medulla are shown in Fig. 1. EDTA control staining (Fig. 1*A*) showed background nonspecific staining. At 0 h there was a low level of specific staining in the tubular interstitial area in the wild-type control kidney (Fig. 1*B*). At 0 h in the FucT-IV/FucT-VII mice (Fig. 1*C*) there was increased E-selectin chimera staining compared with that in wild-type controls (Fig. 1*B*). At 24 h postischemia (Fig. 1*D*) there was a large increase in selectin ligand expression, mostly in the peritubular region in the wild-type control. However, in FucT-IV/FucT-VII-deficient mice at 24 h (Fig. 1*E*) there was decreased staining compared with that at 0 h. Kidney sections from mice deficient in FucT-IV alone or FucT-VII alone showed that selectin ligand expression was relatively unchanged from 0 to 24 h (data not shown).

FucT-IV/T-VII mice are protected from postischemic renal dysfunction

Serum creatinine levels were evaluated on animals at 0, 24, 48, and 72 h postischemia. At baseline all groups had serum creatinine levels ~0.5 mg/dl. FucT-IV/FucT-VII-deficient mice had a significantly reduced rise in serum creatinines at 24 and 48 h postischemia compared with their wild-type controls ($p < 0.05$; Fig. 2). FucT-IV mice also had a modest, but statistically significant, decrease in the rise in serum creatinine at 24 h postischemia; however, their 48 and 72 h serum creatinine levels were similar to those in wild-type control mice. FucT-VII mice showed no functional protection from renal injury, and at all time points their serum creatinine levels were similar to those in wild-type control mice.

FucT-IV/FucT-VII mice are protected from postischemic renal tubular necrosis

Tubular necrosis was absent in uninjured kidneys (Fig. 3*A*) but was pronounced in the postischemic kidney of a wild-type mouse (Fig. 3*B*). FucT-IV/FucT-VII mice had significantly reduced tubular injury (Figs. 3*C* and 4) compared with all other groups at 72 h postischemia. FucT-IV-deficient and FucT-VII-deficient mice did not demonstrate significant structural protection from ischemic damage and had similar injury as wild-type mice (Fig. 4).

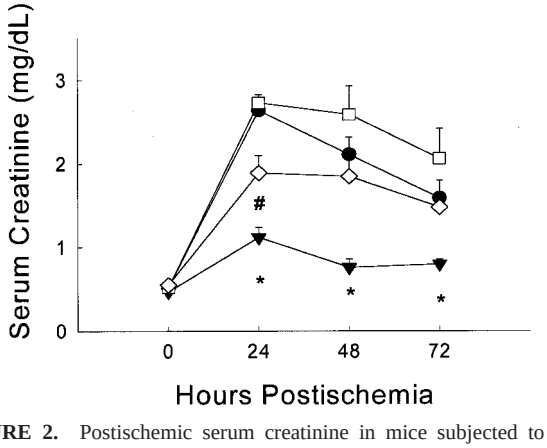

FIGURE 2. Postischemic serum creatinine in mice subjected to IRI: double FucT-IV/FucT-VII knockout mice (▼; *, $p < 0.05$, by ANOVA), FucT-IV knockout mice (◇; #, $p < 0.05$, by ANOVA), FucT-VII knockout mice (□), and wild-type C57BL/6 mice (●). $n = 5$ for each group.

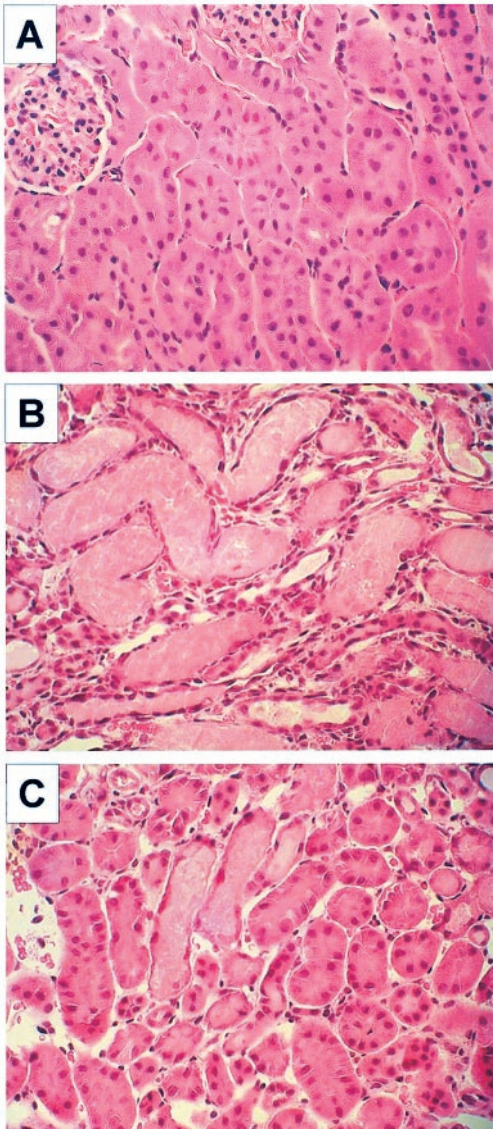

FIGURE 3. Renal tubular damage assessed by H&E staining at 72 h postischemia. *A*, Normal wild-type kidney. *B*, At 72 h postischemia, tubular injury is evident in wild-type control kidney, with tubular dilatation, tubular necrosis, and flattening of the tubular epithelial cells evident. *C*, FucT-IV/FucT-VII-deficient mouse kidney at 72 h postischemia displayed reduced injury compared with wild-type tissue. Tissue from FucT-IV-deficient and FucT-VII-deficient mice showed similar injury as wild-type controls at 72 h (see Fig. 4; representative photos not shown).

PMN infiltration postischemia

At baseline FucT-IV/FucT-VII-deficient mice exhibited a higher number of renal neutrophils than all other groups. This is consistent with the well-described increased numbers of intravascular neutrophils and extreme neutrophilia in these mice (20). Due to the baseline differences between groups at 0 h, we normalized the number of renal neutrophils at 0 h to 100% and then compared the postischemic increase in each group to the value obtained at 0 h. At 24 h postischemia there was a prominent increase in postischemic PMN infiltration in all groups, predominately in the outer

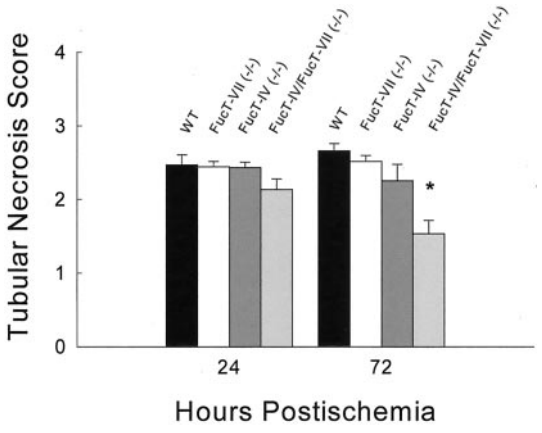

FIGURE 4. Quantitative assessment of postischemic tubular injury. Histologic examination was analyzed with a semiquantitative injury scale (see *Materials and Methods*) to assess tubular injury 24 and 72 h after ischemia.*, $p < 0.05$.

medulla (Fig. 5). FucT-IV/FucT-VII deficient mice had significantly less neutrophil infiltration at 24 and 72 h postischemia. At 72 h FucT-VII-deficient mice also had significantly reduced PMN infiltration compared with wild-type and FucT-IV deficient mice.

Discussion

These data demonstrate that members of the α(1,3)fucosyltransferase enzyme family represent important mediators of renal dysfunction and structural injury in renal IRI. More specifically, we observed that mice deficient in both FucT-IV and FucT-VII were significantly protected against renal dysfunction and tubular damage postischemia. In addition, FucT-IV/FucT-VII mice had a relative reduction in neutrophil infiltration into the postischemic kidney compared with wild-type mice.

We observed that wild-type postischemic kidneys stained with an E-selectin/IgM chimera had an increase in selectin ligand expression after IRI. In contrast, FucT-IV/FucT-VII-deficient mice showed a decrease in chimera binding with time after IRI. Selectin ligand expression in the FucT-IV-deficient and FucT-VII-deficient mice were unchanged following the ischemic period. The unchanged expression of selectin ligands found in the single FucT-deficient animals may have played a role in their relative lack of protection from renal IRI. In turn, the attenuated postischemic selectin ligand expression in the FucT-IV/FucT-VII-deficient mice may have played an important role in the protection seen in these mice. Many cytokines and other inflammatory mediators are known to be rapidly up-regulated following renal IRI, which could regulate selectin ligand expression postischemia (23). We cannot exclude the possibility that the E-selectin chimera, although very similar in structure to the L-selectin chimera, did not detect changes in some selectin ligands, and other important changes in selectin ligand expression could be occurring in wild-type and FucT-deficient mice.

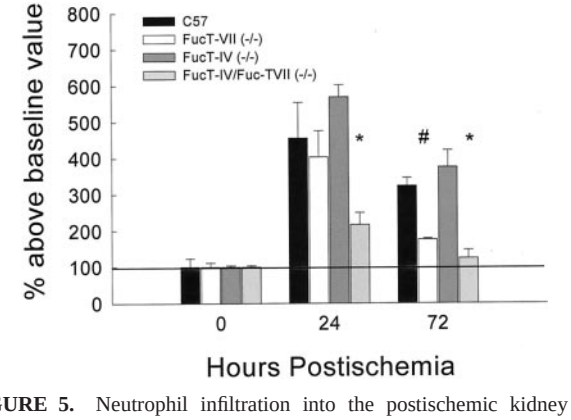

FIGURE 5. Neutrophil infiltration into the postischemic kidney assessed using immunohistochemistry (see *Materials and Methods*).

FucT-IV/FucT-VII-deficient mice demonstrated marked functional and structural protection from renal IRI. At baseline FucT-IV/FucT-VII-deficient mice showed a large number of renal neutrophils. This is due to the inherent defect in leukocyte extravasation from the circulation and neutrophilia in these mice (16). Despite increased numbers at baseline, relative increases in PMN counts postischemia were significantly decreased in FucT-IV/FucT-VII-deficient mice compared with wild-type mice. Thus, the high number of pre-IRI resident neutrophils is unlikely to play a role the injury response following renal IRI.

FucT-VII-deficient mice have been shown to display a marked defect in leukocyte recruitment following an acute inflammatory challenge (20) and therefore were predicted to show protection following ischemic injury. However, in the current study the FucT-VII-deficient mice did not show either functional or structural protection following IRI. Although FucT-VII has been shown to clearly provide a major contribution to the control of E-, P-, and L-selectin ligand activities in vivo (14), molecules responsible for selectin ligand activities retained in FucT-VII-deficient mice have not been defined. It is also possible that despite the reduced amount of neutrophils present at 72 h postischemia, those neutrophils would have residual amounts of selectin ligands associated with them, and perhaps the presence of these functional ligands is sufficient for an injury response. It is also possible that small numbers of neutrophils are sufficient for the full expression of injury after renal IRI. We have recently demonstrated that neutrophil infiltration to the kidney can also be dissociated from the effect of protective agent or knockout during renal IRI (24). We found that T cell-deficient mice were protected from renal injury; however, their neutrophil infiltration postischemia was comparable to that in wild-type controls.

Evidence for a role of FucT-IV regulation in selectin ligand synthesis remains unclear. This is because biochemical and genetic studies implicating this enzyme in selectin ligand synthesis have been conflicting (13). The fact that little, if any, structural protection was observed postischemia in the FucT-IV-deficient mice suggests that this enzyme by itself plays only a minimal role in the pathogenesis of renal IRI. It should be noted, however, that a common observation during human ischemic acute tubular necrosis is a dissociation between functional changes and structural evidence of tubular injury (2).

Redundancy probably exists in the functional roles of the individual FucT-IV and FucT-VII isoforms, such that blockade of both are required to effectively attenuate tissue dysfunction and injury postischemia. Although the mechanisms by which these enzymes mediate renal IRI remain to be fully elucidated, they represent a novel target for therapeutic intervention.

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