Circulating matrix metalloproteinase-2 is associated with cystatin C level, posttransplant duration, and diabetes mellitus in kidney transplant recipients

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Studies have indicated that matrix metalloproteinase-2 (MMP-2) is vital for the patient's condition after renal transplantation. Although the allograft survival rate has been improved, the relationships between various clinical parameters in stable graft function and serum MMP-2 still need to be clarified. In this study, gelatin zymography and enzyme-linked immunosorbent assay were employed to measure MMP-2 level in the plasma of 152 kidney transplant recipients, 41 chronic kidney disease patients, and 50 healthy control subjects. The creatinine and the MMP-2 levels in the transplant recipients were significantly greater ($P < 0.001$) than those of control subjects. Univariate and stepwise regression analysis demonstrated the MMP-2 level was associated with cystatin C level ($P < 0.001$), creatinine level ($P = 0.036$), proteinuria ($P = 0.043$), posttransplant days ($P = 0.025$), and posttransplant diabetes mellitus ($P = 0.03$). We conclude that circulating MMP-2 is associated with cystatin C, posttransplant duration, and diabetes mellitus in kidney transplant recipients and suggest that MMP-2 may be critical for graft survival. (Translational Research 2008;151:217–223)

Abbreviations: CAN = chronic allograft nephropathy; CCr = creatinine clearance; CKD = chronic kidney disease; CsA = cyclosporine-A; ECM = extracellular matrix; ELISA = enzyme-linked immunosorbent assay; GOT = glutamyl oxaloacetic transaminase; GPT = glutamyl pyruvic transaminase; MMP = matrix metalloproteinase; MT-MMP = membrane-type matrix metalloproteinases; SCr = serum creatinine; TAC = tacrolimus; TIMP = tissue inhibitor of metalloproteinase; WBC = white blood cell

Kidney transplantation is the treatment of choice for patients with end-stage renal disease. Kidney transplantation not only improves the quality of life but also prolongs life. Over the last decade, the short-term allograft survival rate has been improved dramatically.[1] However, chronic allograft dysfunction is the main cause of graft failure in stable graft. Differential diagnoses of chronic allograft dysfunction include ureteric obstruction, renal artery stenosis, glomerulonephritis, infection, nephrotoxic agents, late or recurrent acute rejection, and chronic allograft nephropathy (CAN).[2] Renal-transplant glomerulosclerosis represents the final and irreversible destruction of functioning nephrons and could be observed as occurring in 2 phases.[3] Glomerulosclerosis is a time-dependent response to glomerular injury from early ischemia,

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AT A GLANCE COMMENTARY

Background

Serum matrix metalloproteinase-2 (MMP-2) has been reported to be greater in patients with chronic transplant nephropathy than in patients with acute rejection, stable graft function, and healthy donors. However, additional clarification of the relationships between serum MMP-2 and various clinical parameters is needed.

Translational Significance

We found that MMP-2 level was associated with cystatin C level ($P < 0.001$), creatinine level ($P = 0.036$), proteinuria ($P = 0.043$), posttransplant days ($P = 0.025$), and posttransplant diabetes mellitus ($P = 0.03$). We conclude that circulating MMP-2 is associated with cystatin C, posttransplant duration, and diabetes mellitus in kidney transplant recipients and suggest that MMP-2 may be critical for graft survival.

immune-mediated tubular loss, and late calcineurin nephrotoxicity.[4] It is well known that extracellular matrix (ECM) turnover plays a critical role in the process of glomerulosclerosis, and remodeling of ECM is an important physiologic feature of normal growth and development. Many diseases, including CAN, have been associated with an imbalance between ECM synthesis and degradation, which may result in an accumulation of ECM molecules.[5] The major regulators of ECM degradation in the glomerulus are matrix metalloproteinases (MMPs). Thus, changes in MMPs expression or activity may directly alter ECM turnover, which may lead to glomerular scarring and a decline in allograft function.[5]

MMPs are a large family of zinc-requiring enzymes, which include interstitial collagenases, stromelysins, gelatinases, elastases, and membrane-type MMPs (MT-MMPs).[6] They synergistically degrade ECM components, and as such, are involved in embryonic development and a variety of pathophysiologic tissue remodeling processes (which includes angiogenesis, invasive cell behavior, inflammation, wound healing, and fibrosis).

The gelatinases (MMP-2 and MMP-9) are a subfamily of MMPs that share the ability to degrade basement membrane types IV and V collagens, aggrecan, elastin, and gelatins.[6] Their involvement in the pathogenesis of chronic kidney disease was suggested. Various studies have shown that MMP-2 plays a role in both normal renal development and glomerular diseases.[4,7] In the developing kidney, MMP-2 mRNA expression is limited to the mesenchyme. However, MMP-2 protein has been found in immature nephron structures that undergo epithelial differentiation.[8,9] Accumulating evidence has established that MMPs play a role in the development of glomerulosclerosis,[4,9] glomerulonephritis,[10,11] and interstitial renal fibrosis.[12,13] A recent development is the production of a transgenic model in which renal proximal tubular cells overexpress MMP-2. These mice recapitulate human CKD, which includes tubular atrophy, glomerulosclerosis, and tubulointerstitial fibrosis, providing compelling evidence for a role of MMP-2 in CKD.[14] Regarding diabetes mellitus, a marked decrease in MMP-2 mRNA expression was detected in glomeruli of diabetic patients.[15]

A rat model of CAN showed intense expression of MMP-2 mRNA in the tubular epithelial cells and interstitium; MMP-2 and MMP-9 were upregulated, and the inhibitory effect of tissue inhibitor of metalloproteinase-3 (TIMP-3) was downregulated in the kidney allografts.[16] In this model, MMP-2 expression preceded the development of fibrosis, and MMP-2 levels ultimately correlated with increased net collagen volumes. BAY 12–956, which is a relatively selective MMP-2 inhibitor, attenuated CAN in a rat model when administered early (first 10 days after transplantation); however, disease progression was exacerbated if administered late (in weeks 12–20).[17] In CAN patients, serum proMMP-2 and −3 are increased;[18] however, in biopsies of CAN patients, MMP-2 was decreased.[19]

Currently, cystatin C, which is a member of the cystatin family and a very potent inhibitor of lysosomal cysteine proteinases, has been clinically applied as a sensitive marker of glomerular filtration rate and as an early indicator of impaired renal function to replace the determination of serum creatinine (SCr). In addition, it is less sensitive to changes in body mass.[20] Based on changes in MMPs, expression or activity may directly alter ECM turnover, which may lead to glomerular scarring and a decline in allograft function.[4,5] The aim of this study was to investigate the relationships between circulating MMP-2 plasma levels and various clinical parameters in stable graft function of kidney transplant recipients.

MATERIALS AND METHODS

Subjects and specimen collection. Patients were excluded if they were with acute rejection; infected with viral hepatitis B, C, or B + C[21]; or had abnormal liver function,[22] malignancy, hepatocellular carcinoma, lung cancer, adrenal tumor,[23,24] active infection, cytomegalovirus infection, herpes zoster,[25] subclinical leukocytosis defined as white blood cell count greater than 11,000/mm^3 without clinical symptoms, combination therapy with sirolimus, and calcineurin