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Plasma matrix metalloproteinase-9 and diabetic microalbuminuria: Tip of the Iceberg?

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Related Article, p. 544

THE REPORT by Ebihara et al[1] currently establishes an elevated plasma level of matrix metalloproteinase-9 (MMP-9) as the earliest marker of diabetic renal disease. The authors prospectively followed 30 non–insulin-dependent diabetic subjects for 48 months while monitoring plasma levels of MMP-9, MMP-1, tissue inhibitor of metalloproteinase-1 (TIMP-1), and microalbuminuria, the well-established benchmark of early diabetic glomerulopathy and possibly other renal disorders. Their careful studies of eight patients who developed microalbuminuria demonstrated that plasma elevations of MMP-9 preceded the onset of microalbuminuria in all eight patients by at least 3 years. Intriguingly, in the microalbuminuric subset, conventional therapy with an angiotensin-converting enzyme (ACE) inhibitor for 6 months abolished the increments of MMP-9 and decreased, in parallel, the microalbuminuria. However, significant alterations of the plasma levels of MMP-1 and its principal inhibitor, TIMP, did not occur.

The matrix MMPs constitute a 15-member family of metalloendopeptidases engaged in the physiologic and pathologic turnover of the matrix proper and cell surface proteins.[2] These zinc-dependent, latently secreted enzymes remodel the extracellular matrix in the pericellular environment in conjunction with tissue serine proteinases (eg, thrombin, tissue plasminogen activator, urokinase, and plasmin), adamalysins, and bone morphogenetic proteins. Acting in concert, the MMPs have the capability to degrade all components of the extracellular matrix. MMPs are inhibited by TIMP-1 and TIMP-2. MMPs and TIMPs are regulated primarily at the transcriptional level either coordinately or reciprocally by a host of factors, including tumor promoters, retinoids, glucocorticoid steroids, cytokines, and the matrix itself.[3] Disruption of the balance between MMPs and TIMPs leads to either net matrix degradation or accrual. Normal functions of MMPs and TIMPs include regulation of cell migration, involution and apoptosis of the lactating mammary gland, morphogenesis in organismic development, and wound healing. Overzealous matrix degradation following overexpression of MMPs has been correlated with tumor metastasis, synovial degradation of rheumatoid pannus, and sinusoidal disintegration in the inflamed cirrhotic liver. Abrogation of such events by countervailing overexpression of TIMP in animal models has established the role of MMPs in these phenomena. Moreover, unrestrained overexpression of TIMPs has been documented in fibrogenic disorders. For example, exuberant expression of TIMP-1 by dermal fibroblasts occurs in progressive systemic sclerosis.[4] In the kidney, a defined role of MMPs and TIMPs in the pathogenesis of diabetic renal dysfunction is less clear.

MMPs and TIMPs are produced by a variety of cells housed within both glomerular and tubular compartments.[5] Diabetic glomerulosclerosis, readily verifiable at the time of kidney biopsy, is histologically evident as a primarily fibrotic lesion. Indeed, prognostic correlation is revealed by the degree of tubulointerstitial fibrosis. How then, could accelerated MMP-mediated proteolysis lead to a fibrogenic response? Following the paradigm of experimental hepatic inflammation invoked by carbon tetrachloride that eventuates in fibrotic cirrhosis, we can at least envision such a scenario.[6] In this model, there is first proteolytic destruction of the sinusoidal architecture. Healing by secondary intention, with scarring, follows repression or recession of MMP-3 activity and/or dominance of TIMP-mediated inhibitory capacity. Thus, acute perturbations of the normally balanced synthesis and degradation of matrix resulting from equivalent MMP and TIMP activities may result in loss of the scaffolding of an organ's cellular mass and its consequent replacement by scar tissue. Such a spatiotemporal evolution is mirrored in diabetic glomerulosclerosis in which mesangial cell expansion precedes, by years, the development of glomerular

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and interstitial fibrosis. That this thematic requires one or two decades to be completely manifest has forestalled our appreciation of it. A principal operative in this drama may be the mesangial cell, a multipotent pericyte that can secrete several MMPs and TIMP-1. The mesangial cell has been shown to participate in a proteolytic cascade in vitro with serine proteases such as plasmin, which can be activated at glomerular loci of inflammation.[5-7] Juxtaposed against endothelial cells within capillary loops, the products induced from these cells are naturally focused against their targets. In addition, the mesangial cell also becomes a target for soluble mediators of inflammation and fibrosis (eg, such as the chemokines, interleukin-1β, tumor necrosis factor-β, and transforming growth factor-β. Tumor necrosis factor-α has been shown to upregulate monocytic recruitment into early renal diabetic lesions while transforming growth factor-β provides a local microenvironmental fibrogenic stimulus for progressive glomerulosclerosis and which is also upregulated in the hyperglycemic milieu.[1] Nearly all of these factors influence net proteolytic activity via MMP/TIMP interactions that may, in turn, be regulated by changes in glomerular dynamics (ie, volume and stretch) as implied in the data reported by Cortes et al.[8] However, none of these mediators has been associated with an increased plasma level in diabetic nephropathy.

MMP-9, the 92-kd gelatinase B, is expressed by many cell types, including endothelial cells, immune cells, and parenchymal cells. Enhanced MMP-9 proteolytic activity by glomerular epithelial cells has been intimated as one mechanism underlying the pathophysiology of glomerular proteinuria that characterizes diabetic renal disease and other glomerular disorders.[9] However, renal tubular cells produce MMP-9. Proteolysis from this MMP might conceivably be of tubular origin rather than glomerular origin.[6,10] Because extensive glomerular-tubular or tubular-glomerular ''cross-talk'' might occur, this possibility is quite tenable, especially considering that the bulk of the kidney comprises cells within the tubulointerstitium. In addition, interactions among various MMPs and other proteases could lead to a proteolytic cascade that ultimately results in augmented MMP-9 activity. Activated MMP-3 can activate pro-MMP-9 and foster development of a wave of proteolysis.[3,6] With its broad substrate specificity, this MMP, which includes proteoglycans, collagens, and fibronectin, is produced by several indigenous renal cells, including tubular cells, mesangial cells, and cortical fibroblasts (unpublished observations). In fact, a recent report by Suzuki et al[5] demonstrated increased glomerular MMP-3 expression in kidney biopsy specimens from individuals afflicted with immunoglobulin A nephropathy and diabetes mellitus. Plasma and MMP-3 levels were not measured in the study. Had only plasma or urinary MMP-3 levels been elevated, however, these findings would not unequivocally establish that the source of the MMP-3 was of renal origin. Multiple sources exist to produce and secrete MMP-3. In addition, elevation of a urinary factor such as transforming growth factor-β in a crescentic model of glomerulonephritis does not equate to pathogenesis. It may, however, implicate a particular cytokine or other mediator as central to a renal disorder.[11]

The fact that MMP-9 is a product of the endothelium enhances the hypothesis that the vasculopathy of diabetes produces the findings reported by Ebihara et al.[1] However, there is no proof of this extant, and an inflammatory lesion involving the endothelium of glomerular capillary loops has not been described, as might be expected in an aggressive and active lesion that is overexpressing MMP-9. Perhaps, though, diabetic microalbuminuria represents ''the tip of the iceberg,'' reflecting the glomerular endovascular damage that precedes more widespread endothelial dysfunction elsewhere. The seminal data of Stehouwer et al[12] demonstrating elevated plasma von Willebrand factor levels in diabetic microalbuminuria support this construct.

Ebihara et al[1] treated microalbuminuric patients in conventional fashion with an ACE inhibitor, cilazapril. Although captopril has been shown to downregulate renal MMP-2 and -9 activities, possibly by interfering with the zinc-binding coordination sites of these enzymes, the repression of plasma MMP-9 toward control levels by the institution of ACE inhibition does not clarify whether the elevations of MMP derive from the kidney. This compound could be altering the balance of proteolysis elsewhere, particularly in the endothelium, which can remodel itself through altering its regulation of MMP activity.[13]

Despite the small number of patients and the conundrum regarding the origin of elevated plasma MMP-9 levels, the finding of Ebihara et al[1] (ie, that an almost indiscernible increment of proteolytic activity in the diabetic kidney spawns our earliest clinical manifestation of diabetic renal disease, microalbuminuria) represents a most fertile area for continued study. We await future studies that will localize the presence of MMP-9 in the diabetic human kidney, at the gene and protein levels, and those that determine the urinary levels of this powerful proteinase. If such studies demonstrate a clear-cut role of MMP-9 in the advent of diabetic nephropathy, then therapeutic targeted inhibition of this MMP, and possibly others, may amplify the salutary effects of ACE inhibition.

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