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A Spatial Distribution of Two Isoforms of Matrix Metalloproteinase-2 In Murine Diabetic Kidney according to the Time of Diabetic Milieu

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Objectives : To date, MMP-2 consists of the conventional secreted, full length MMP-2 isoform (FL-MMP-2) and a novel intracellular N-Terminal Truncated isoform (NTT-MMP-2) generated by oxidative stress-mediated activation of an alternate promoter in the MMP-2 first intron. We recently reported on the enhanced expression of two isoforms of matrix metalloproteinase-2 (MMP-2) in diabetic stress including in vitro, murine model and human kidney via oxidative stress related NF-kB. Based on our prior studies with renal tubule-specific transgenic expression of the FL-MMP-2 isoform, we suggest that the final pathologic phenotype of diabetic nephropathy is induced by the combined actions of the FL-MMP-2 isoform on the tubular basement membrane and on the induction of tubular cell necrosis and inflammation by the NTT-MMP-2 isoform. This study aimed to evaluate a distinct spatial distribution of two isoforms of MMP-2 within the kidney according to the time of diabetic milieu in the diabetic murine models.

Methods : Diabetic murine models were low dose streptozotocin-induced diabetic mice (STZ mice) and db/db mice. We quantified the abundance of the FL-MMP-2 and NTT-MMP-2 transcripts by qPCR in the whole kidneys of both diabetic murine models. Also, a spatial distribution of two isoforms of MMP-2 was analyzed semi-quantitatively according to the time of diabetic milieu (STZ mice: control, 4 weeks, 8 weeks, 12 weeks, 24 weeks; db/db mice: db/m, 10weeks, 16 weeks). The anatomical areas within the kidney were divided into two groups (cortex vs. medulla).

Results : Both isoforms of MMP-2 in STZ mice and db/db mice were upregulated in whole kidney. In the case of FL-MMP-2, the transcripts by quantitative PCR statistically increased at 12 weeks and 24 weeks in STZ mice and 16 weeks in db/db mice, respectively. The expression of FL-MMP-2 protein gradually increased both in the cortex and outer medulla of STZ and db/db mice according to the time of diabetic milieu. In the case of NTT-MMP-2,

the transcripts by quantitative PCR statistically increased earlier at 4 weeks in STZ mice and 10 weeks in db/db mice as compared with FL-MMP-2. The expression of NTT-MMP-2 protein gradually increased mainly in the cortex of STZ and db/db mice according to the time of diabetic milieu consistent with FL-MMP-2. In the medulla, the expression of NTT-MMP-2 was not prominent as compared with FL-MMP-2 in both diabetic models.

Conclusions : Although two isoforms of MMP-2 is consistently highly inducible in different diabetic murine model, the expression patterns of FL-MMP-2 and NTT-MMP-2 were somewhat different according to the anatomical location and the time of diabetic milieu. So, the further investigation including individual genetic inhibition is needed to uncover the respective pathobiological roles of two isoforms of MMP-2 in diabetic nephropathy.

Keywords : diabetes mellitus, hyperglycemia, matrix metalloproteinase-2, oxidative stress