

DELAYED PROGRESSION OF RENAL FIBROSIS IN C57BL6/J MICE IS ASSOCIATED WITH ROBUST MMP ACTIVITY

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BACKGROUND

C57Bl6/J (B6) mice are less susceptible to experimental renal fibrosis induced by subtotal nephrectomy or unilateral ureter obstruction (UO). However, the cause of this relative resistance is still poorly understood. Here we investigated the strain dependent development of renal fibrosis and matrix metalloproteinase-9 (MMP-9) activity following UO at early (1 day) and late (7 days) stages.

METHODS

Animal model:

The left ureter of 8-week-old male C57Bl6/J (B6) and CBA/J (CBA) mice was proximally ligated (unilateral ureter obstruction, UO) under anesthesia.

Contralateral kidneys served as controls (CTL). Kidneys were analyzed 24 hours (early stage) and 7 days (late stage) after surgery.

Experimental groups analyzed:

- 1) B6 UO 1 day (n=4)
- 2) CBA UO 1 day (n=4)
- 3) B6 UO 7 day (n=6)
- 4) CBA UO 7 day (n=6)



Performed analyses:

- Renal histology
- Gelatinase zymography
- mRNA expression of TIMP-1 and collagen-1

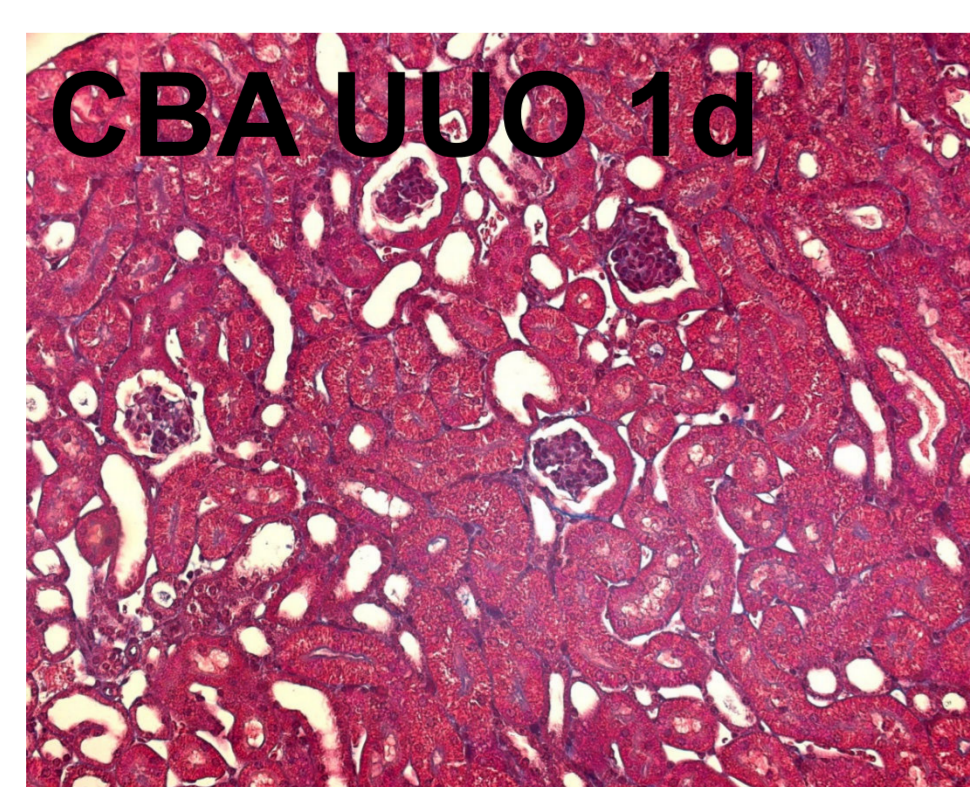
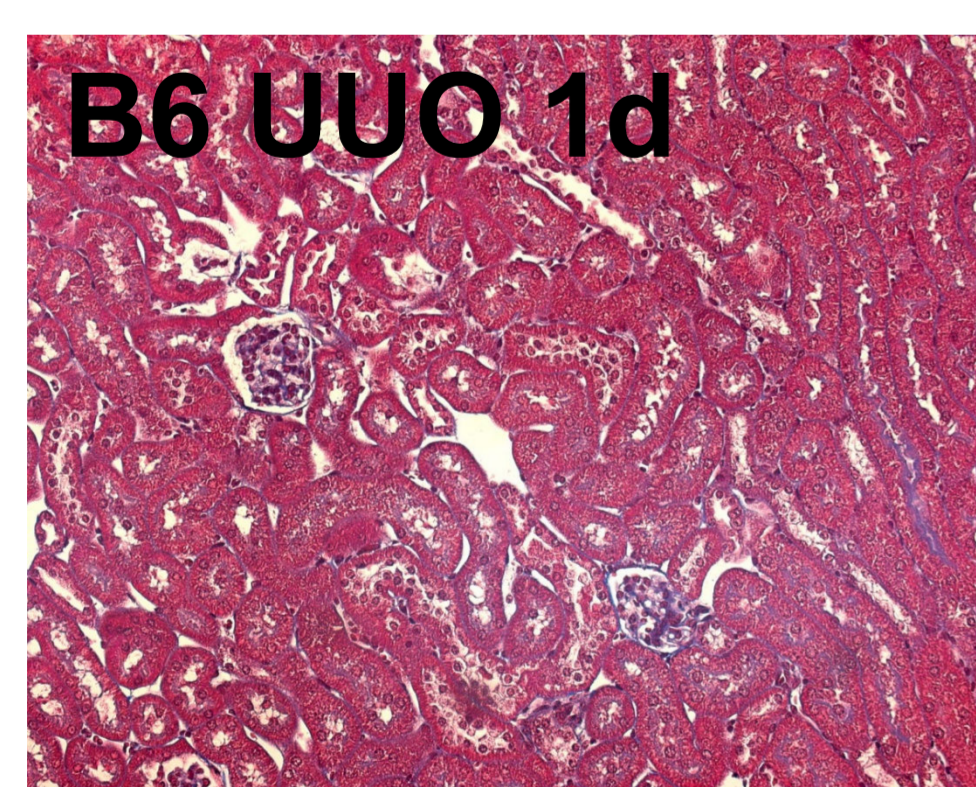
Statistics:

Data were normalized to a control (1 day) sample. All data are presented as mean±SD. Statistical analysis was performed using Mann-Whitney test (SPSS 10).

RESULTS

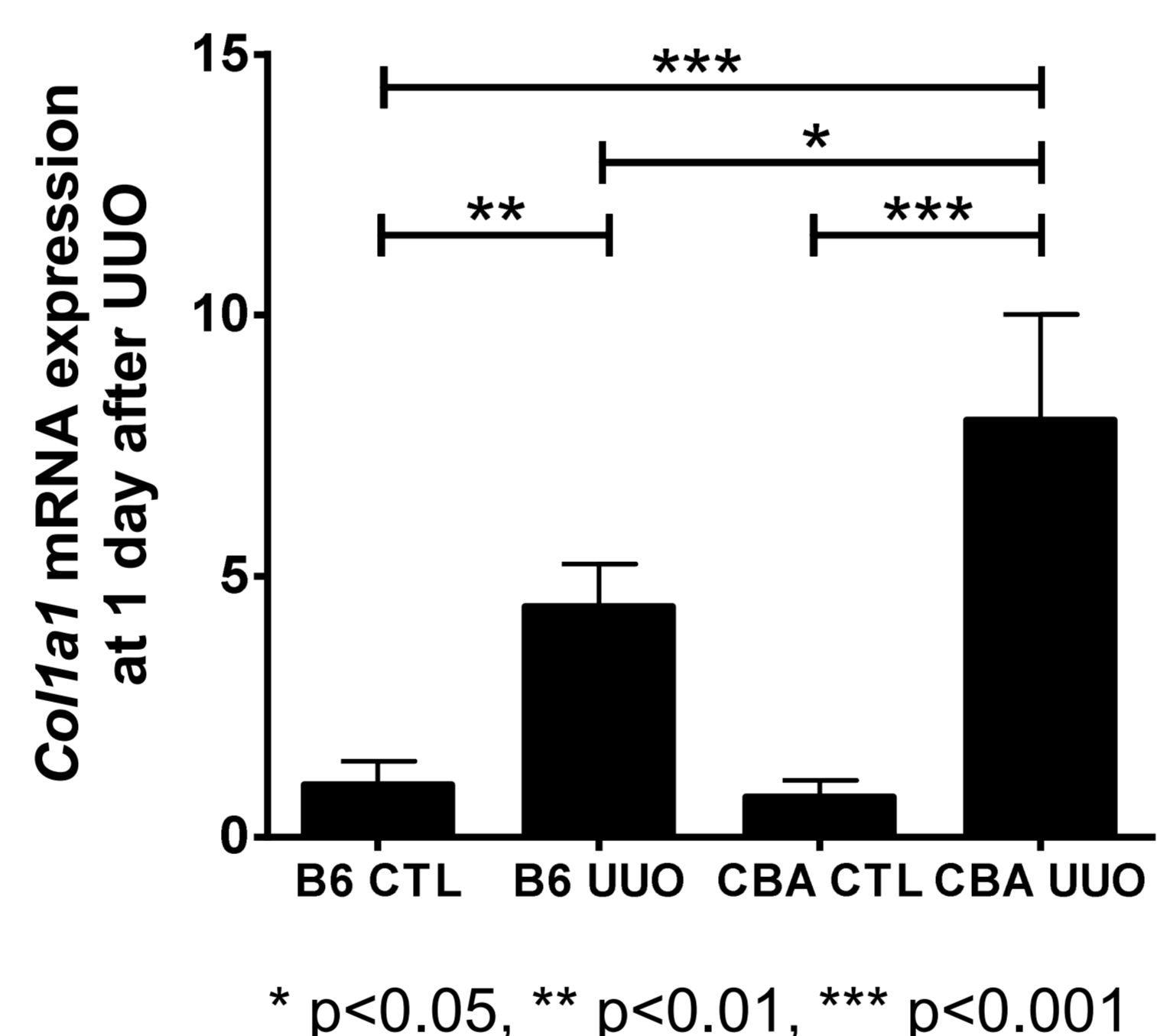
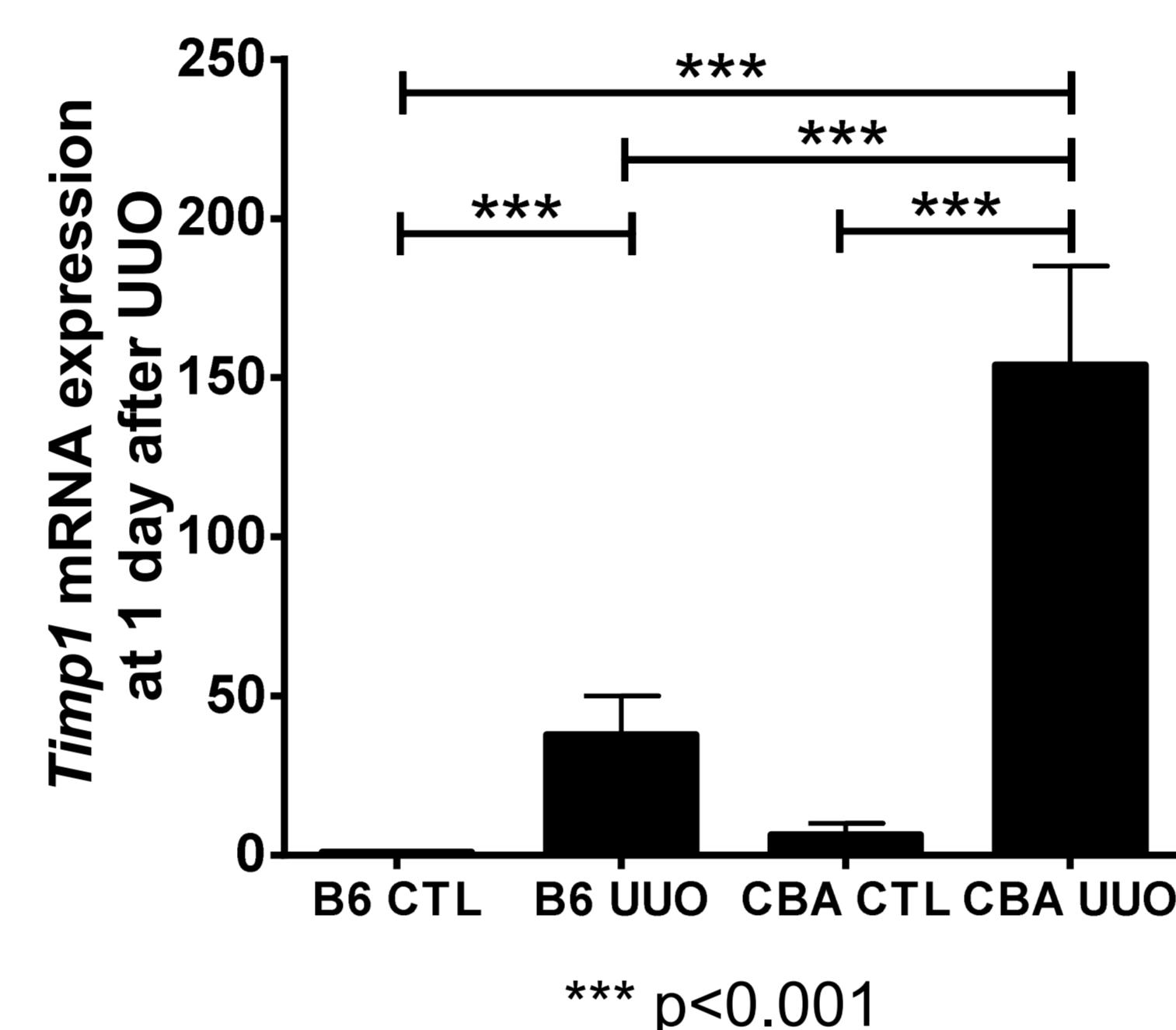
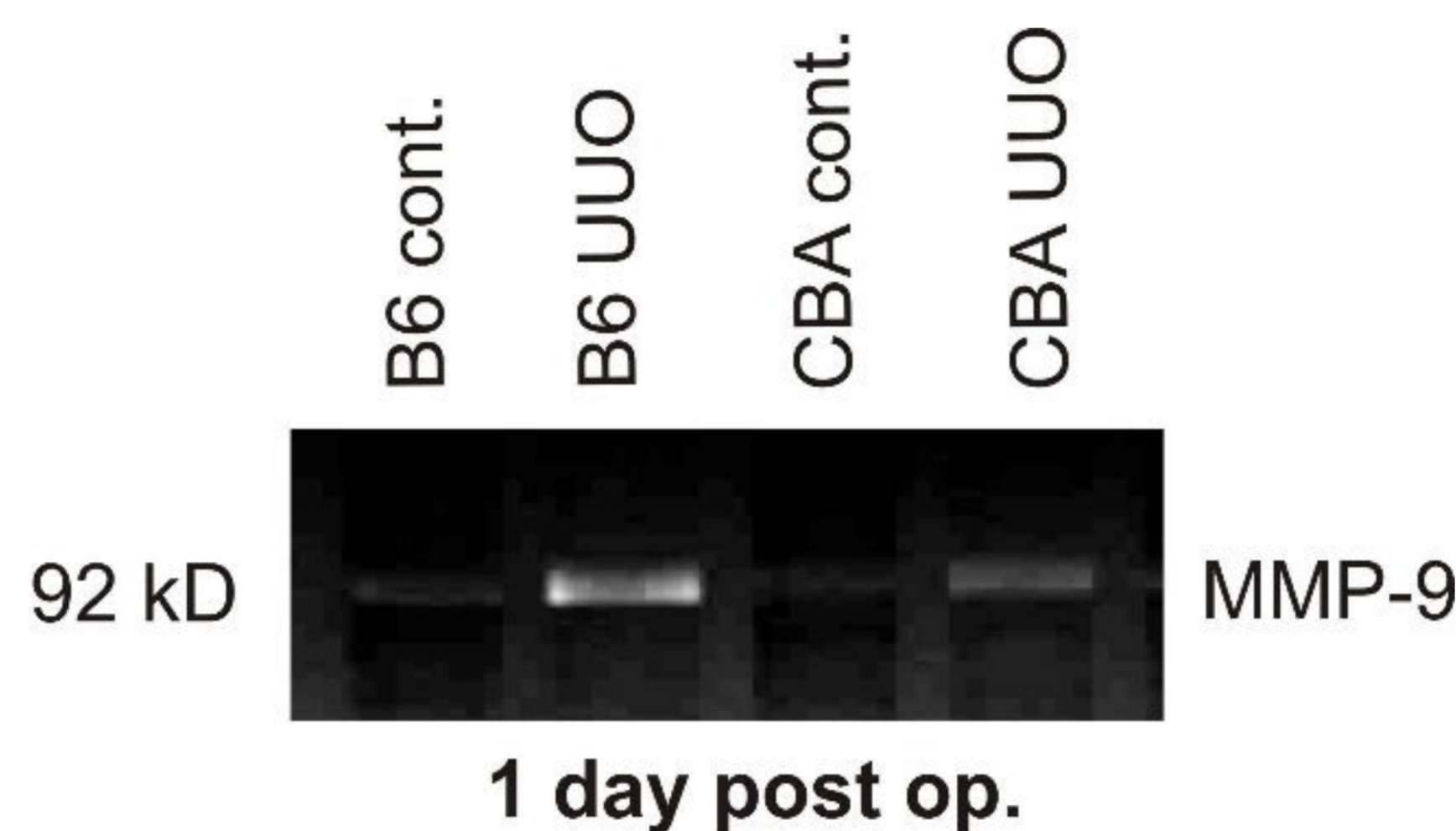
Early stage kidney pathology

Kidney histology of UO kidneys at 1 day showed only a few dilated tubules, otherwise normal structure and no signs of matrix accumulation.



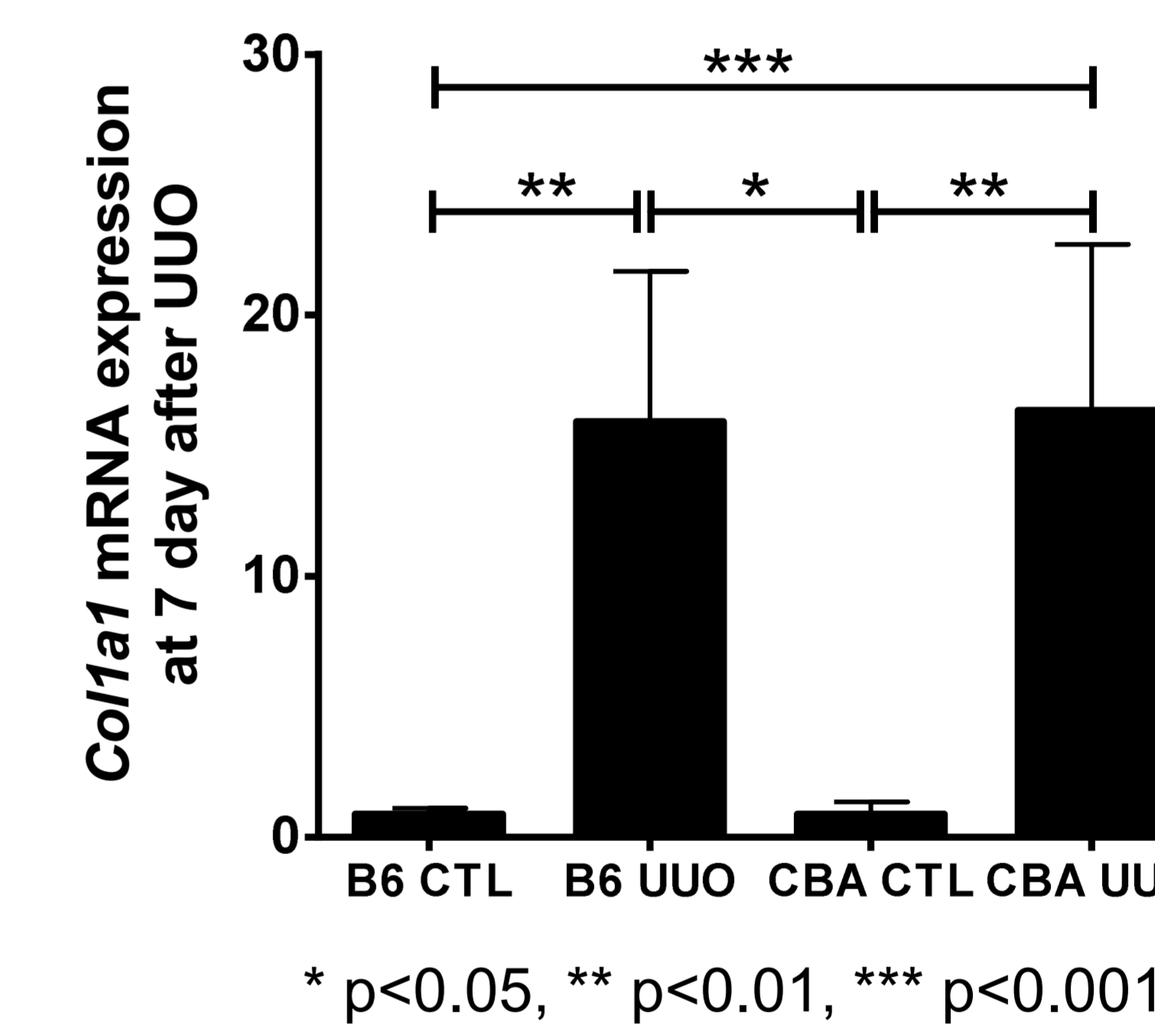
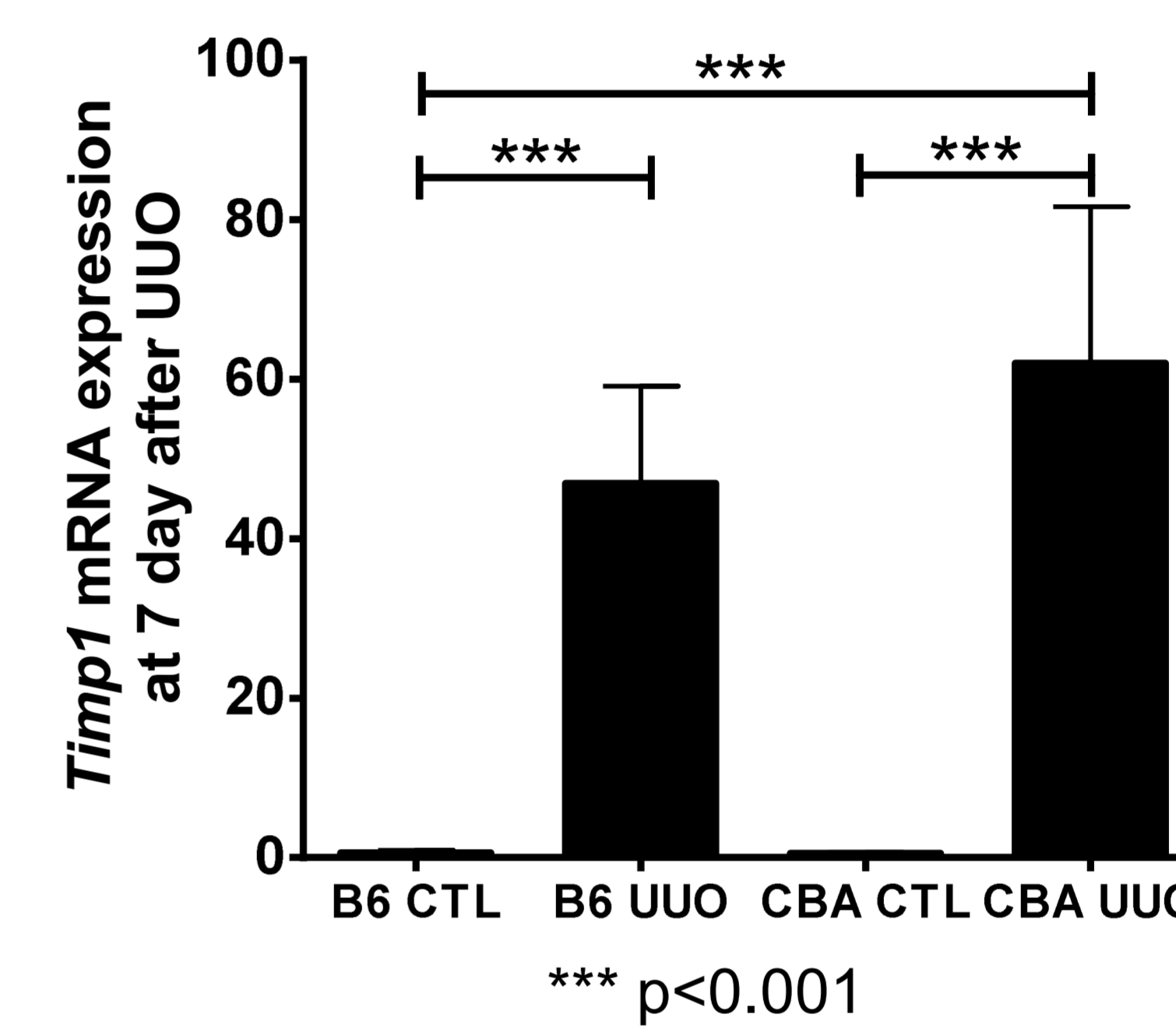
Early stage MMP activity and gene expression

We observed an early increase of 92 kD gelatinase activity in B6 vs CBA accompanied by marked overexpression of TIMP-1 and collagen-1.



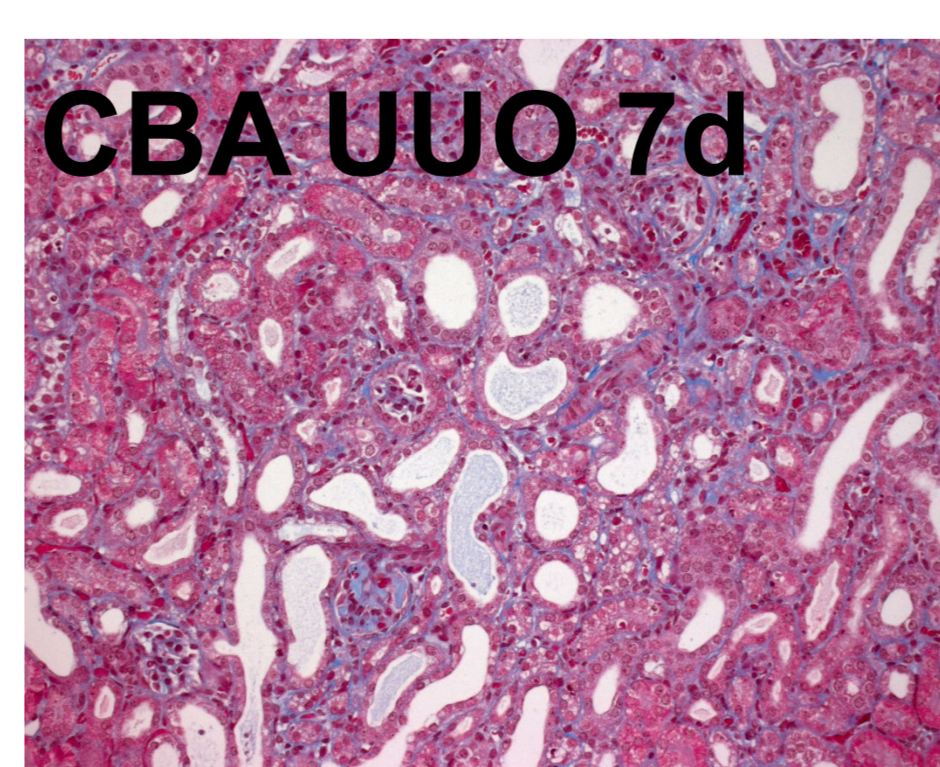
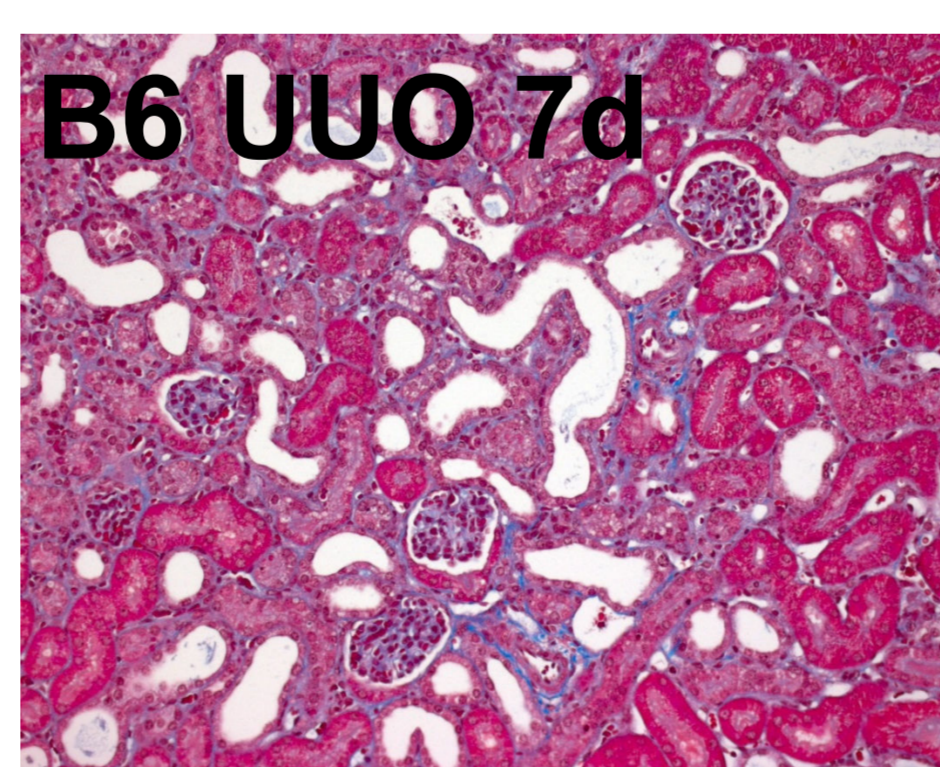
Late stage MMP activity and gene expression

On the 7. day, the 92 kD gelatinase activity was barely detectable in CBA UO kidneys vs B6, although TIMP-1 and collagen-1 mRNA expressions were similar in both strains.



Late stage kidney pathology

UO kidneys on the 7th day depicted massive tubular dilatation in both strains, but more severe tubular damage and interstitial matrix accumulation in CBA mice.



CONCLUSION

We conclude that the delayed progression of renal extracellular matrix accumulation after UO in C57Bl6/J mice might be an effect of the more robust renal MMP-9 activity accompanied by reduced TIMP-1 response and delayed collagen production.

REFERENCES

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2. Takemoto et al. Am J Pathol. 2002 Sep; 161(3): 799-805.

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Masson's trichrome stain, 200x magnification
(blue: connective tissue)

