Decorin Deficient Diabetic Mouse Model of Diabetic Nephropathy

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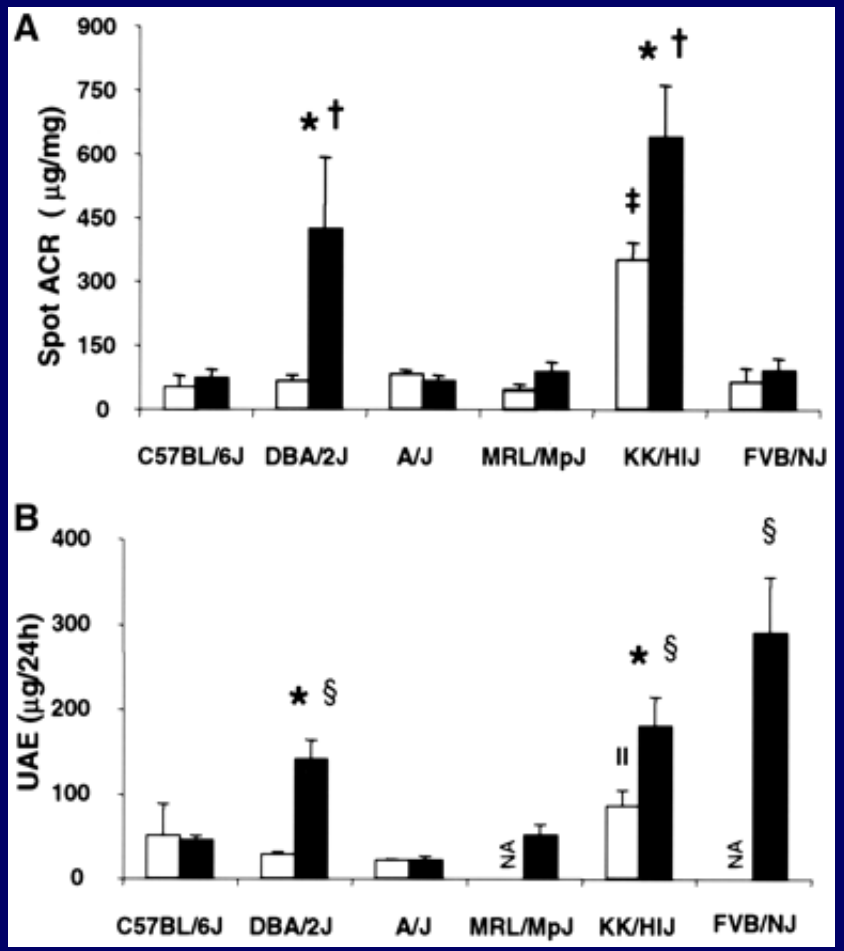
Genotype-Phenotype Unit

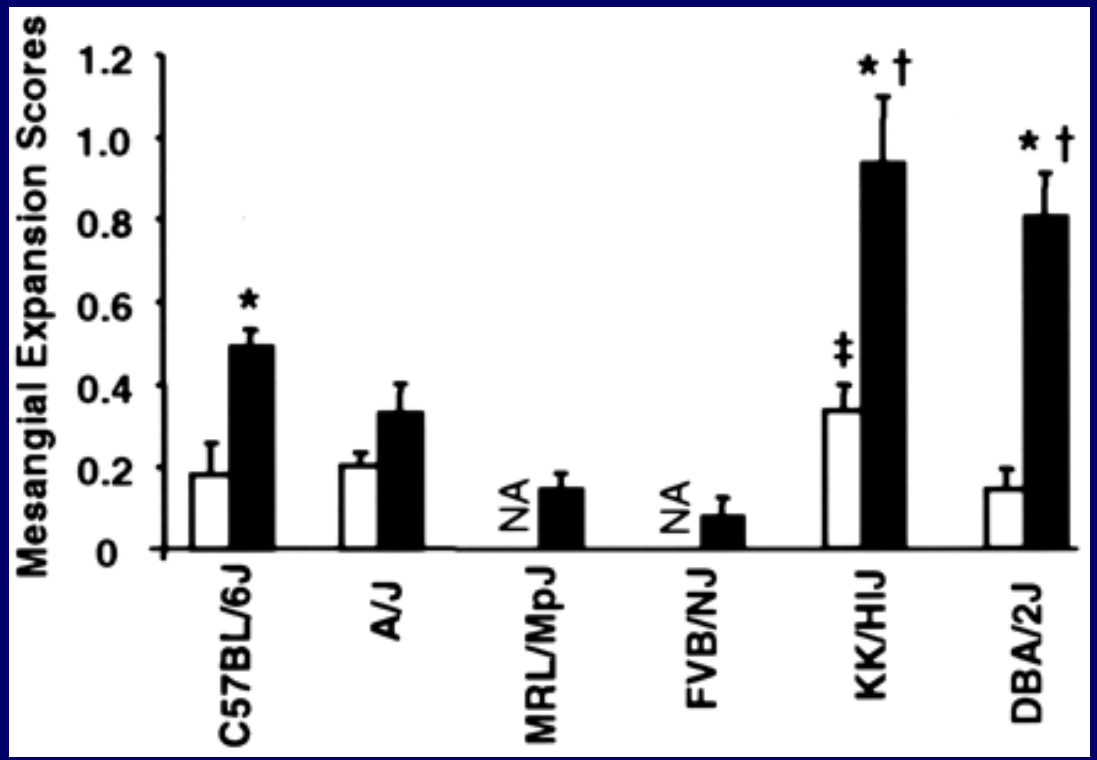
Albuminuria in Different Strains of Low Dose Strep-Diabetic Mice

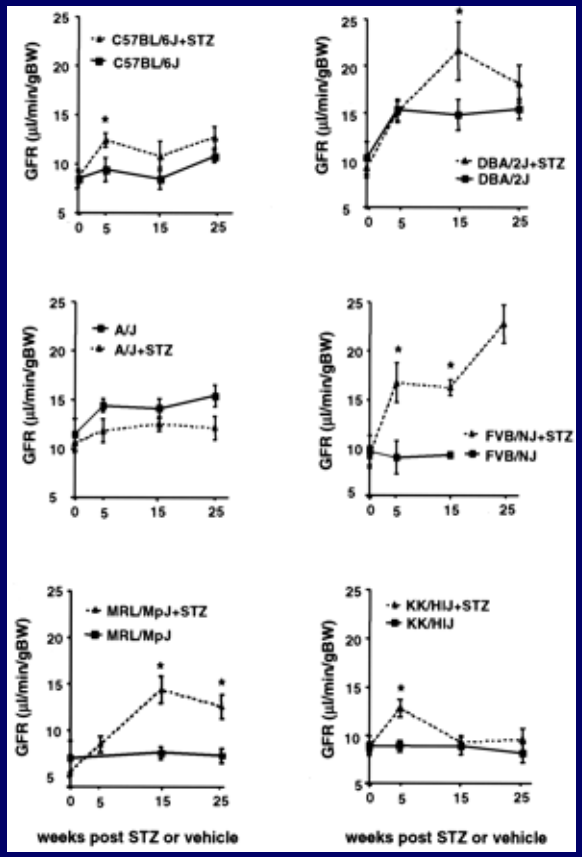


Qi et al, Diabetes

54:2628, 2005

Mesangial Matrix and GFR in Different Strains of Diabetic Mice



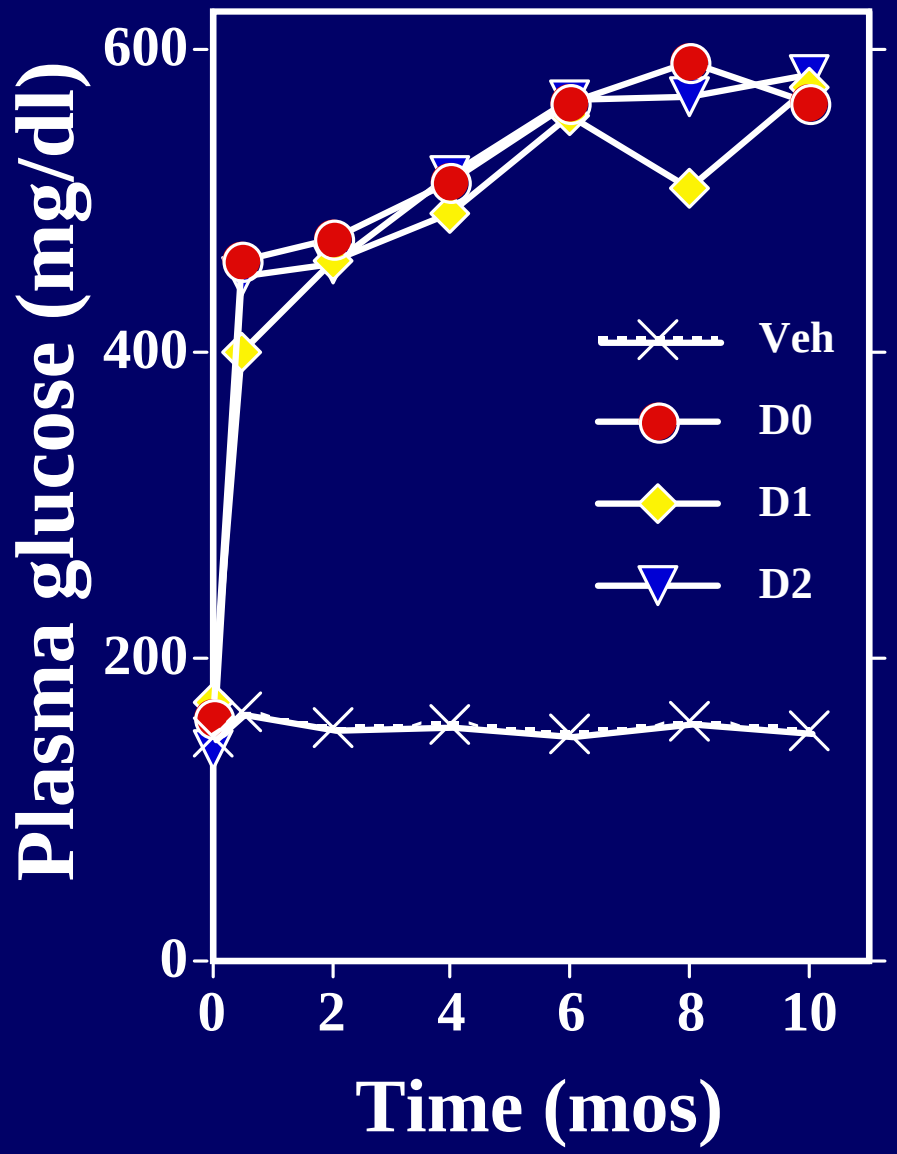


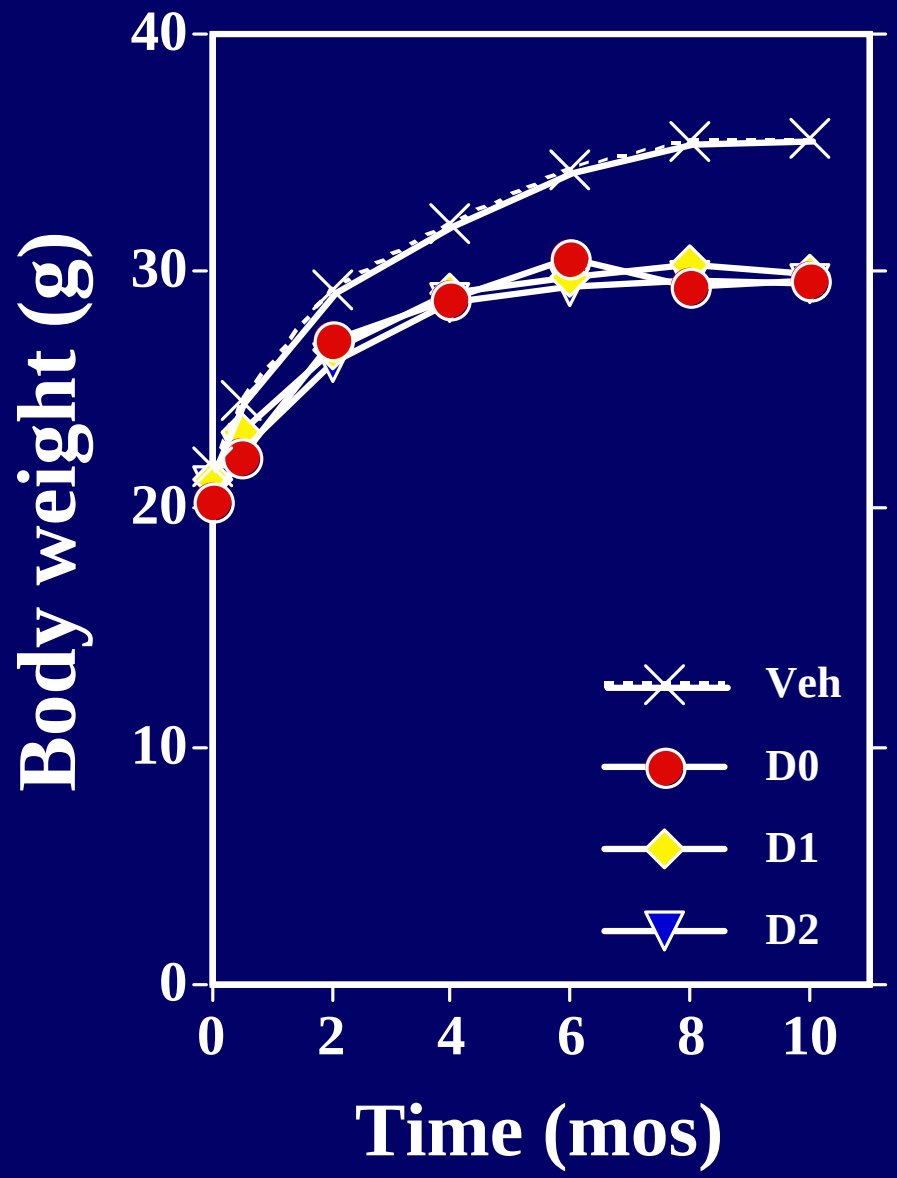
Qi et al, Diabetes, 54:2628, 2005

Decorin and Diabetic Nephropathy

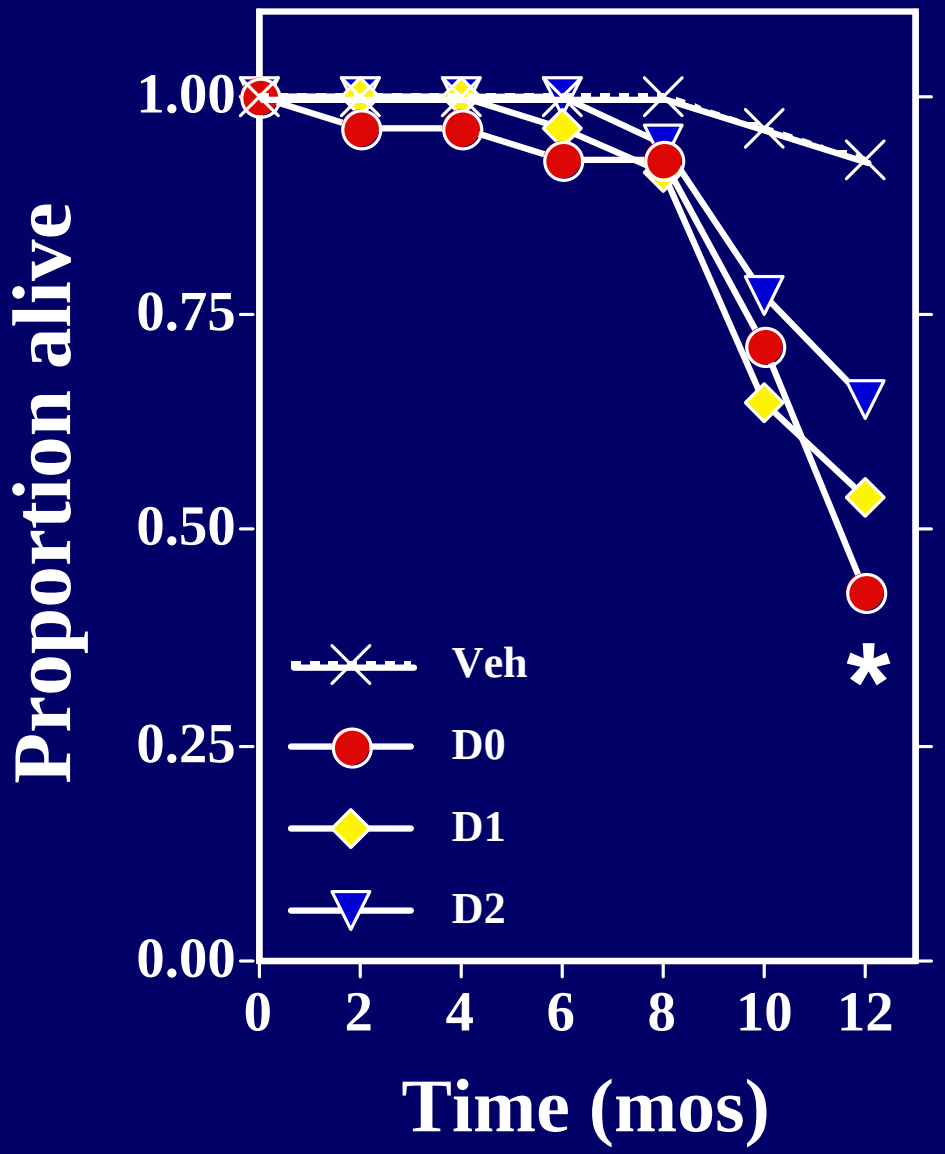
- Background: Decorin is a small proteoglycan that inhibits TGF-β via direct binding to active TGF-β. Decorin is stimulated in human mesangial cells by high glucose and stimulated in several mouse models of diabetic kidney disease.
- Hypothesis: Decorin protects against diabetic kidney disease.
- Back-cross *Dcn* KO allele onto the C57BL/6J background; induce STZ diabetes in male littermates with different *Dcn* gene doses
  - Albuminuria
  - Plasma creatinine by HPLC
  - Histologic parameters of diabetic nephropathy
  - EM analysis of GBM and TBM

Decorin gene dose and diabetic severity





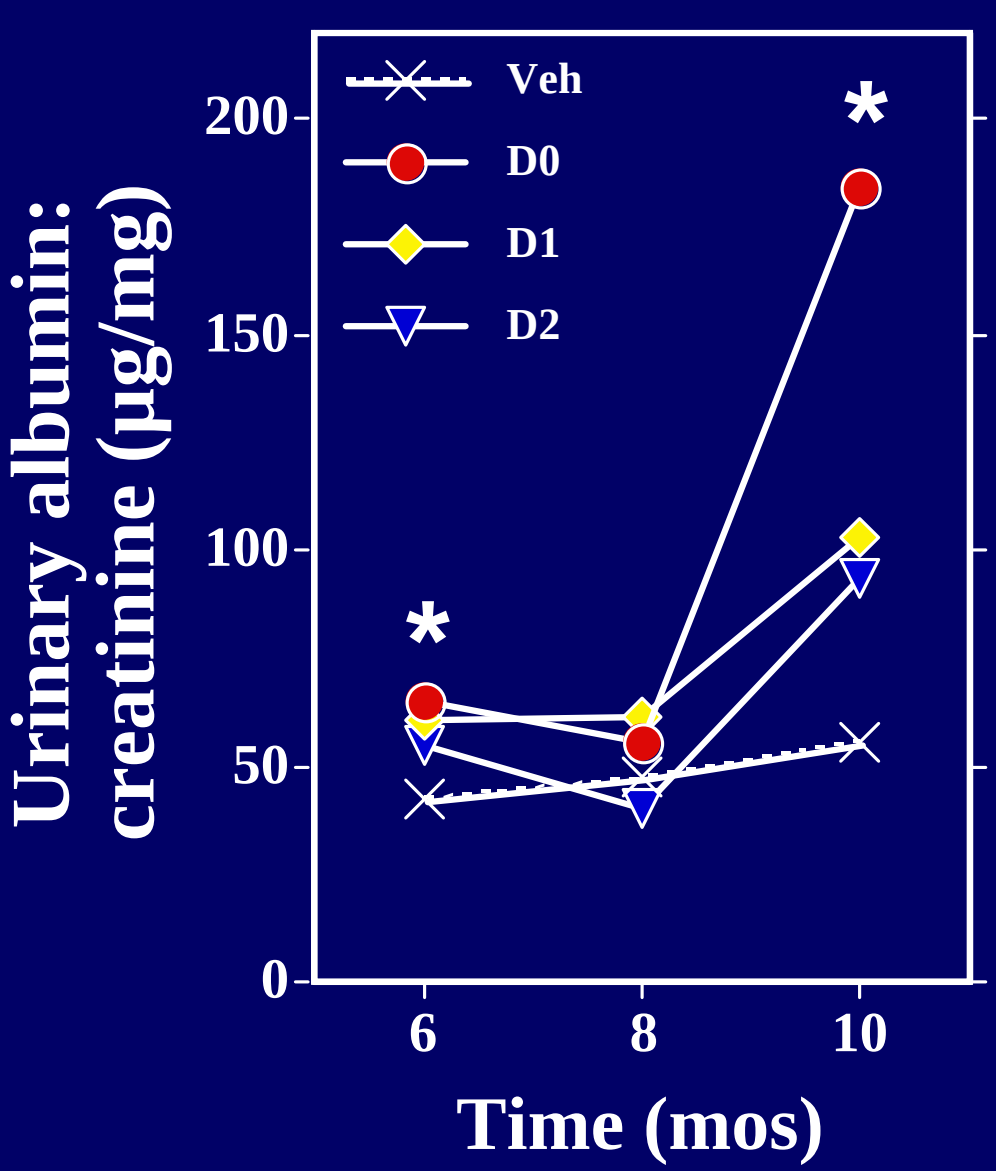
Decorin deficiency makes diabetes lethal

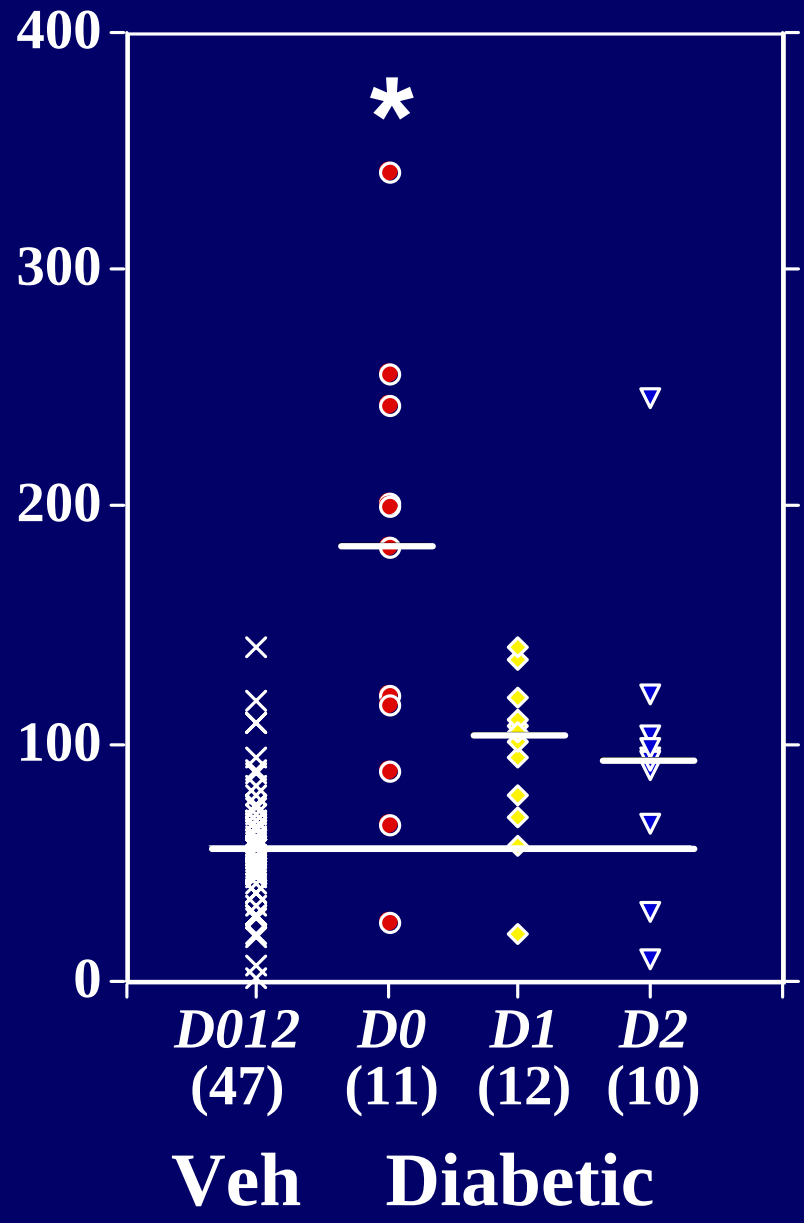


Clinical Parameters of Diabetic Mice that Died Spontaneously

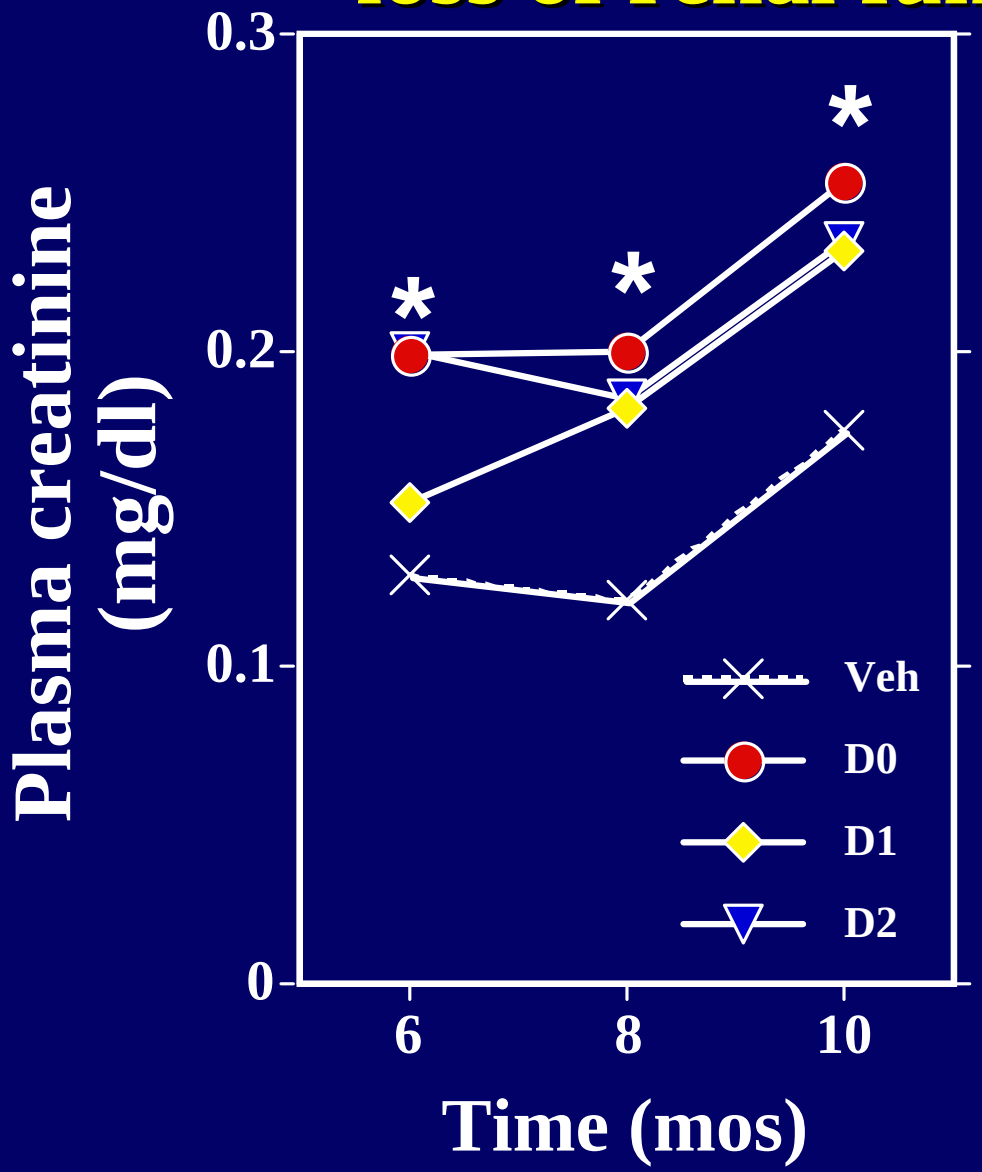
	Diabetic Mice (survived, n=30)	Diabetic Mice (died <12 m, n=21)
Body wt (g)	29.17 ± 0.65	29.96 ± 0.57
Blood gluc (mg/dl)	499 ±32.3	553.85 ±17.0
STZ dose (mg)	333 ±24.6	314 ±24.7
Urine alb/creat	98.8 ±11.7	115.52 ±21
Plasma Creat (mg/dl)	0.22 ±0.01	0.27 ±0.02*

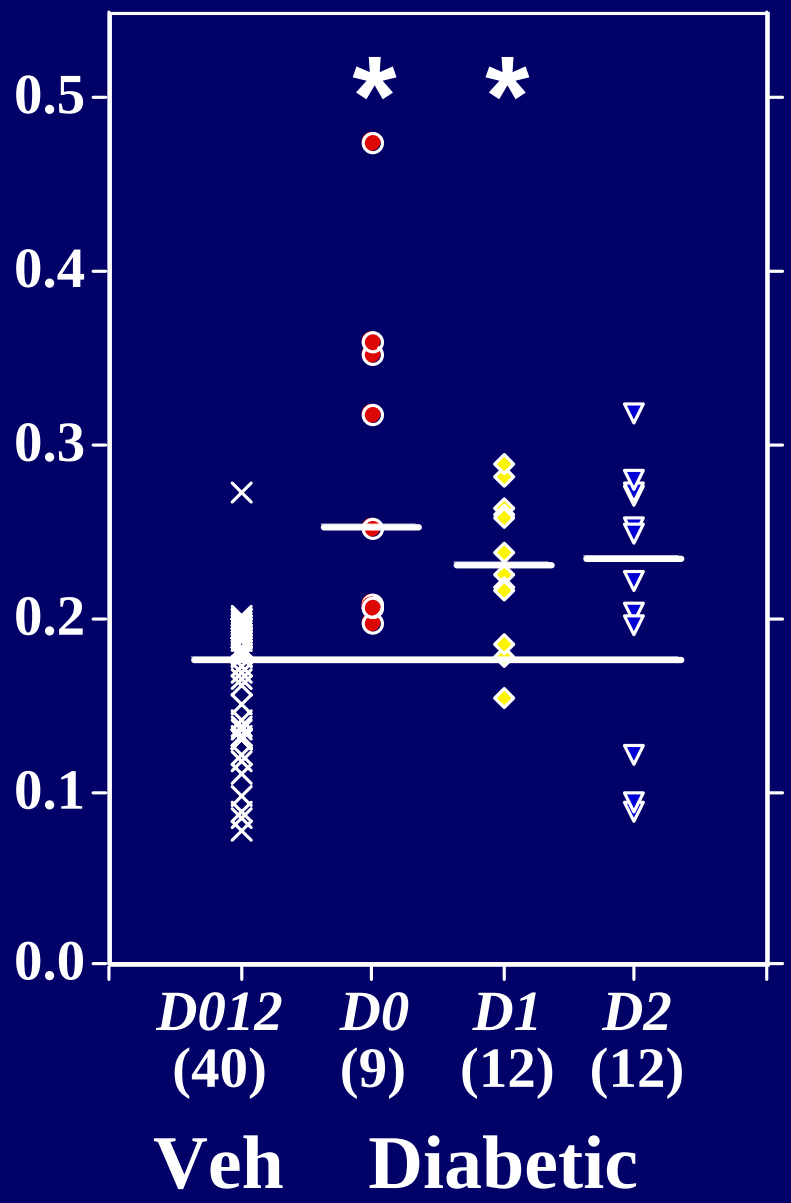
Decorin deficiency accelerates diabetic albuminuria



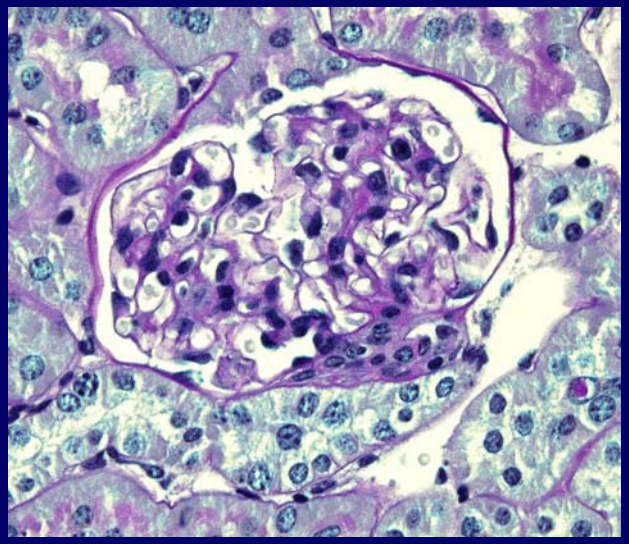


Decorin deficiency accelerates loss of renal function in diabetes



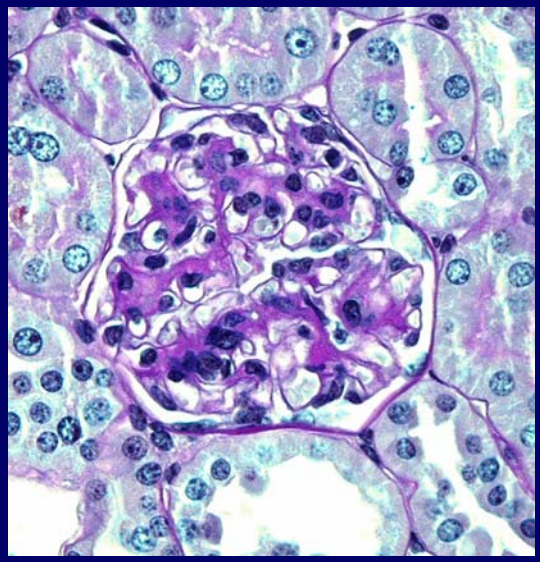


Loss of Decorin Leads to Accelerated Glomerular Lesions of Diabetic Nephropathy (perfused)



Diabetic (10-12 m)

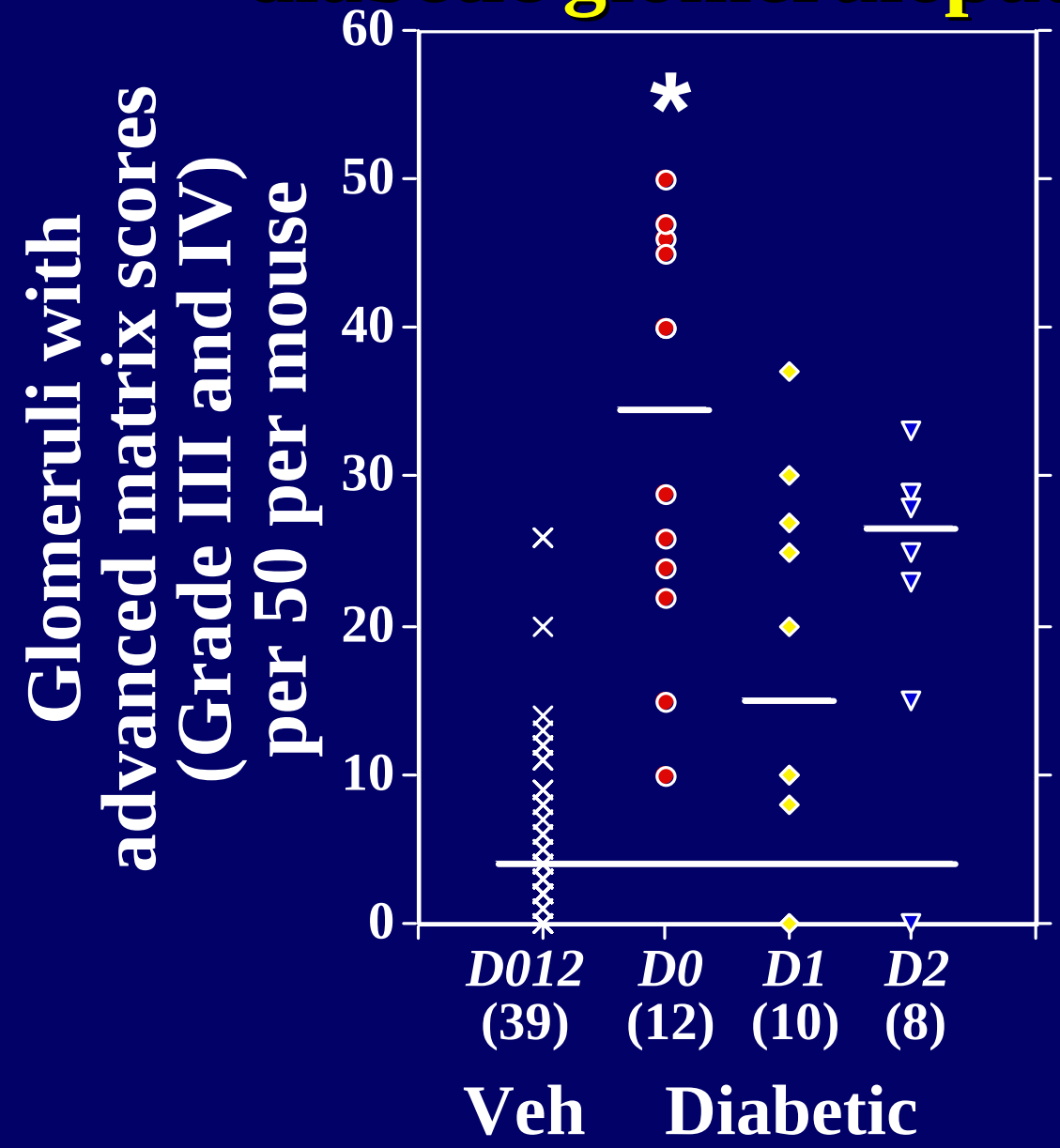
Wild type



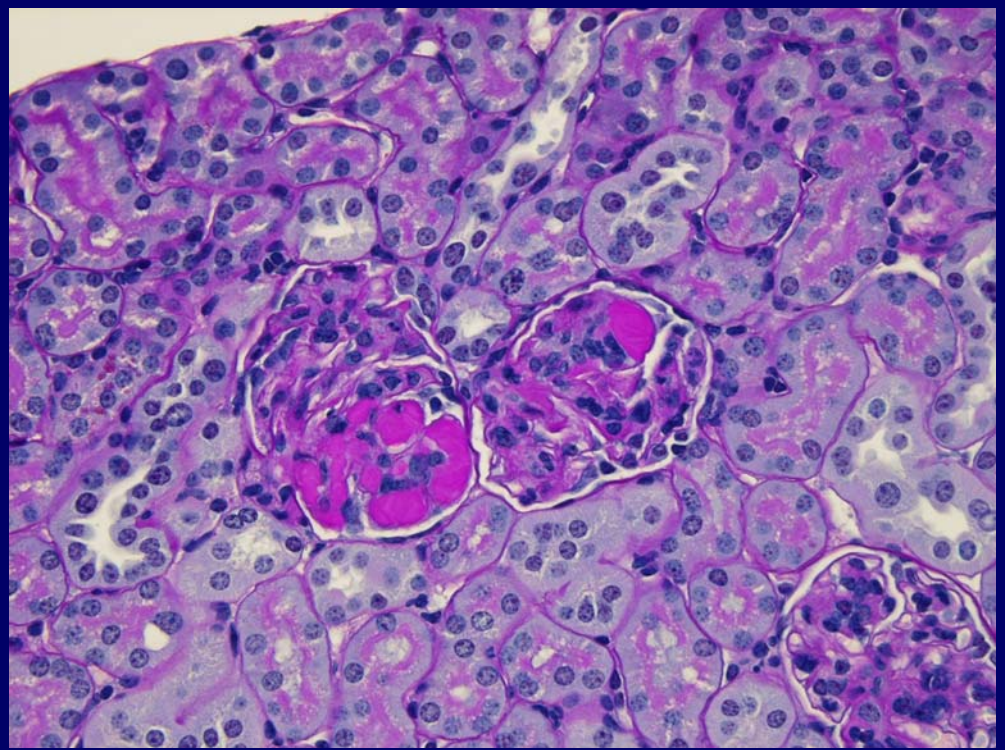
Diabetic (10-12 m)

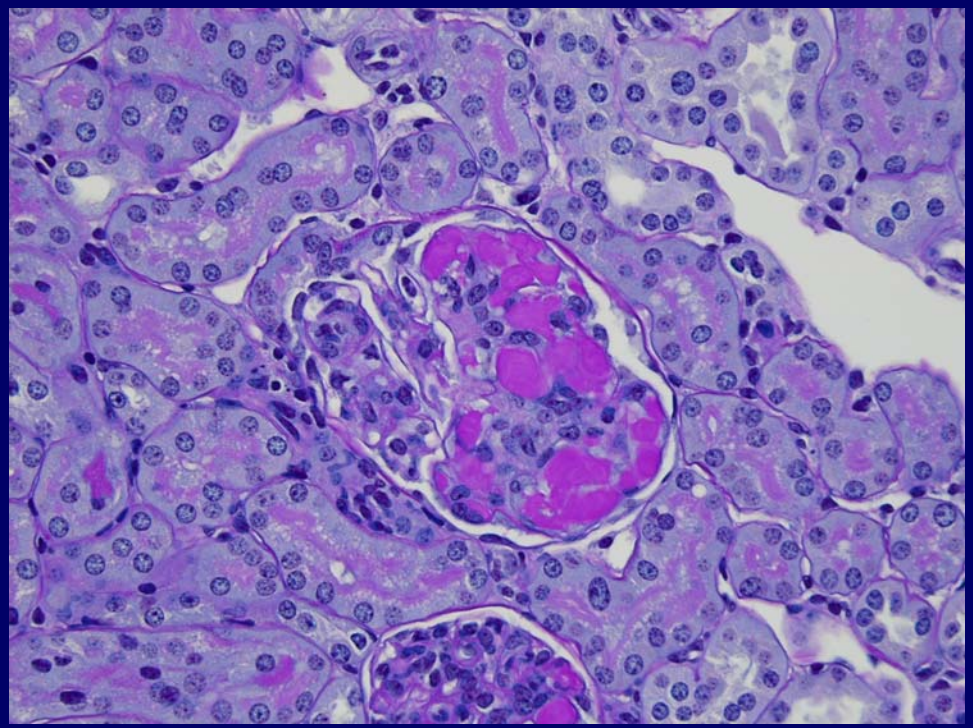
Dcn -/-

Decorin deficiency significantly worsens diabetic glomerulopathy



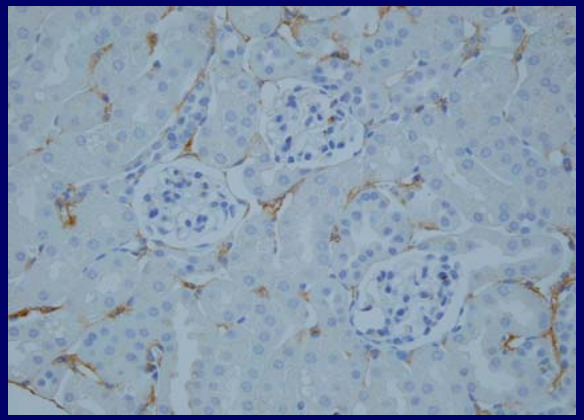
Fibrin caps, a feature of human diabetic nephropathy, occur only in *Dcn* KO diabetic mice

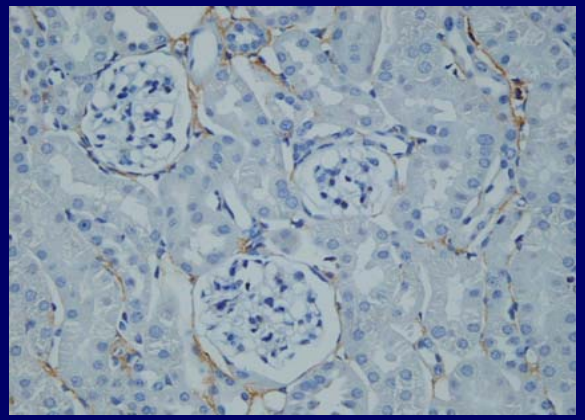




Decorin deficiency substantially increases glomerular accumulation of type I collagen in diabetes

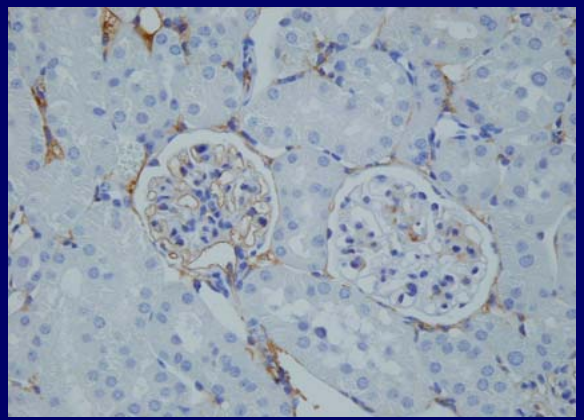
Veh, *Dcn*+/+

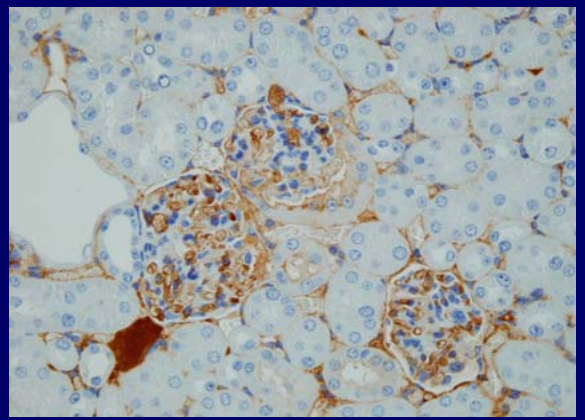




Veh, *Dcn*-/-

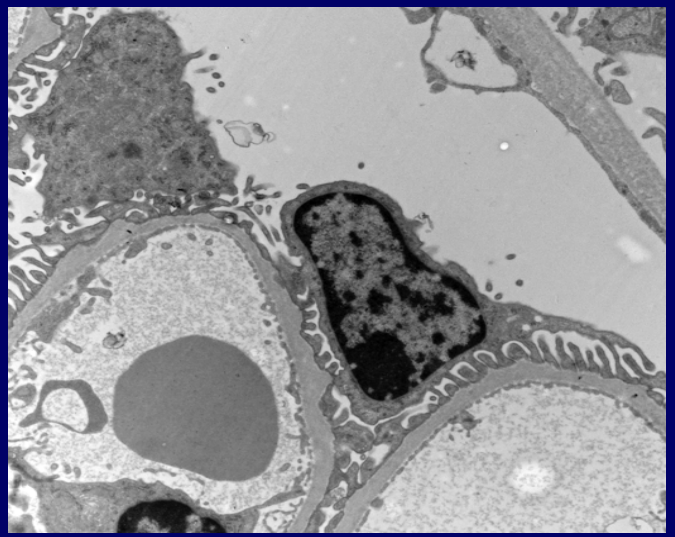
DM, *Dcn*+/+



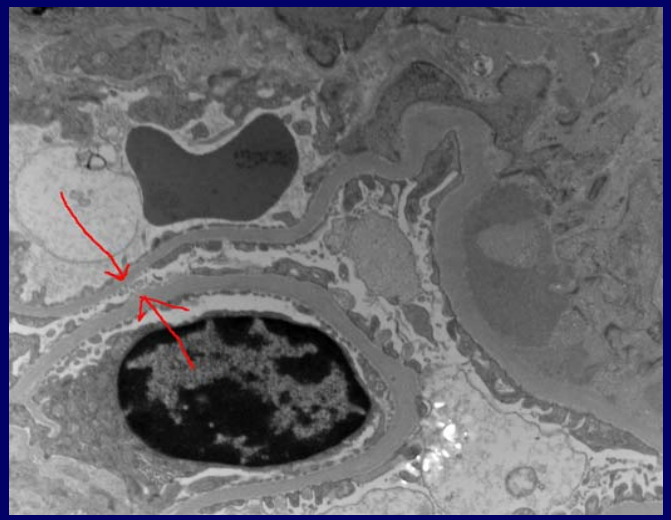


DM, *Dcn*-/-

GBM Thickness and Podocyte Effacement Observed in Decorin Deficient Diabetic Mice

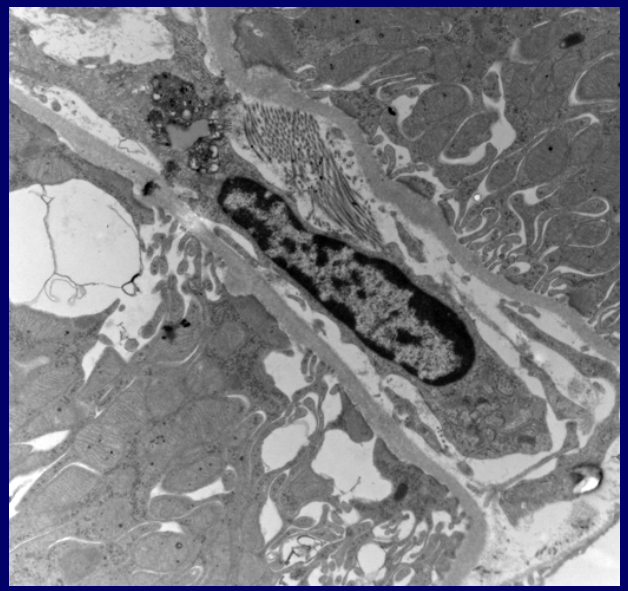


Normal
Foot processes
+/+ normal mouse

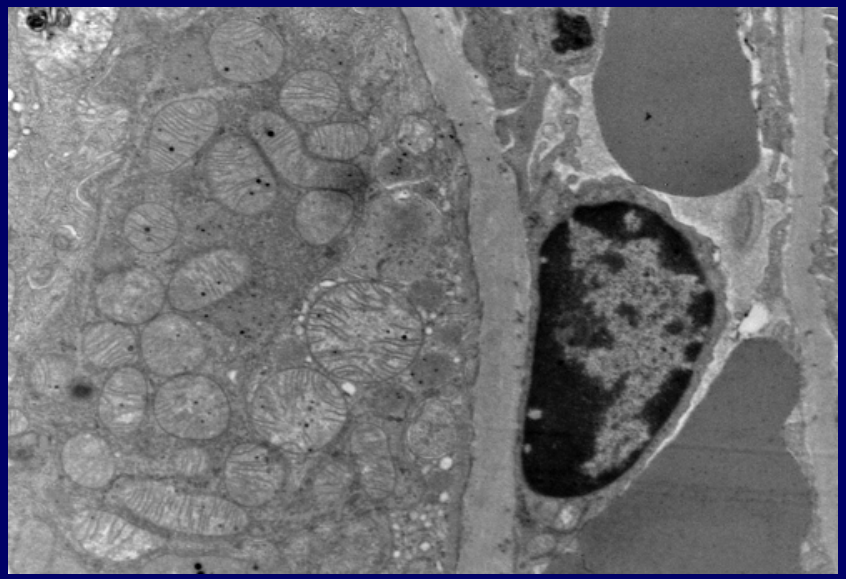


Denuded and thickened GBM
Dcn -/- diabetic mouse

Loss of Decorin leads to TBM Thickening in Diabetic Mice



Normal TBM in
+/+ Non-Diabetic Mouse



Thickened TBM in
Decorin -/- Diabetic Mouse

Summary

- Prolonged diabetes using a low-dose STZ protocol in C57Bl6J mice leads to stable diabetes (blood glucose 400-600) without weight loss for 10-12 months of diabetes
- No significant increases in urine albumin, plasma creatinine, or mesangial matrix expansion by 10 months of diabetes in STZ-diabetic C57Bl6J mice
- No evidence of advanced retinopathy in wild type or Dcn -/- diabetic mice (T. Kern)

Summary/Conclusions

- Loss of decorin (Dcn +/-, Dcn -/-) does not impact development and degree of diabetes with low dose STZ
- Loss of decorin (Dcn -/-) in diabetic mice is associated with excess mortality by 12 months of diabetes
- Loss of decorin (Dcn -/-) in diabetic mice leads to an accelerated course of diabetic nephropathy characterized by increased albumin/creatinine ratio and increased plasma creatinine
- Loss of decorin allele leads to severe diabetic glomerulopathy with diffuse mesangial matrix expansion and occasional fibrin cap formation
- Decorin is likely to be an endogenous protective agent in the diabetic kidney

Ongoing Studies

- To investigate a potential CV cause of increased mortality, a new cohort of Dcn -/- mice have been made diabetic and the following parameters will be studied
  - Blood pressure by tail cuff at 2, 4, 6, 8 m
  - Lipid profiles, CV risk markers at 2 and 6 m
  - Collaborate with Rockefeller and Utah group to assess atherosclerosis and cardiac function at serial time points
- With new cohort of Dcn -/- diabetic mice assessment of neuropathy (Michigan Core) and uropathy will be performed
- To accelerate course of diabetic nephropathy Dcn -/- mice have been crossed with LDLR -/- mice and will be made diabetic

Acknowledgements

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