



复旦大学 中国红十字会

華山醫院

SIRT1 in Diabetic Nephropathy

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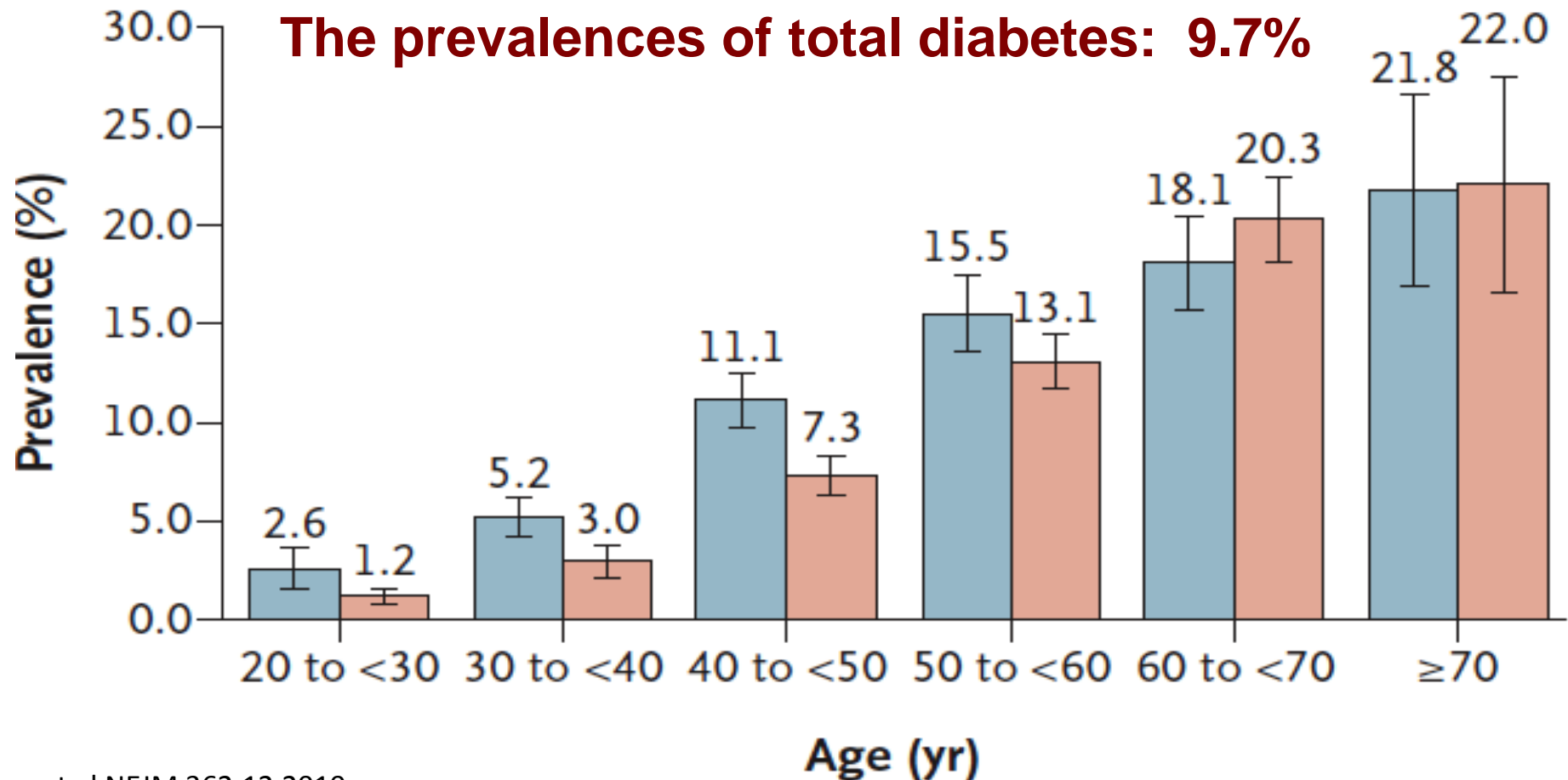
Shanghai, China

Content

- Diabetic nephropathy, a growing challenge in China
- Diabetic Nephropathy is a Prototypical Disease of Gene and Environmental Interactions
- New therapeutic target for diabetic nephropathy -- Role of SIRT1?

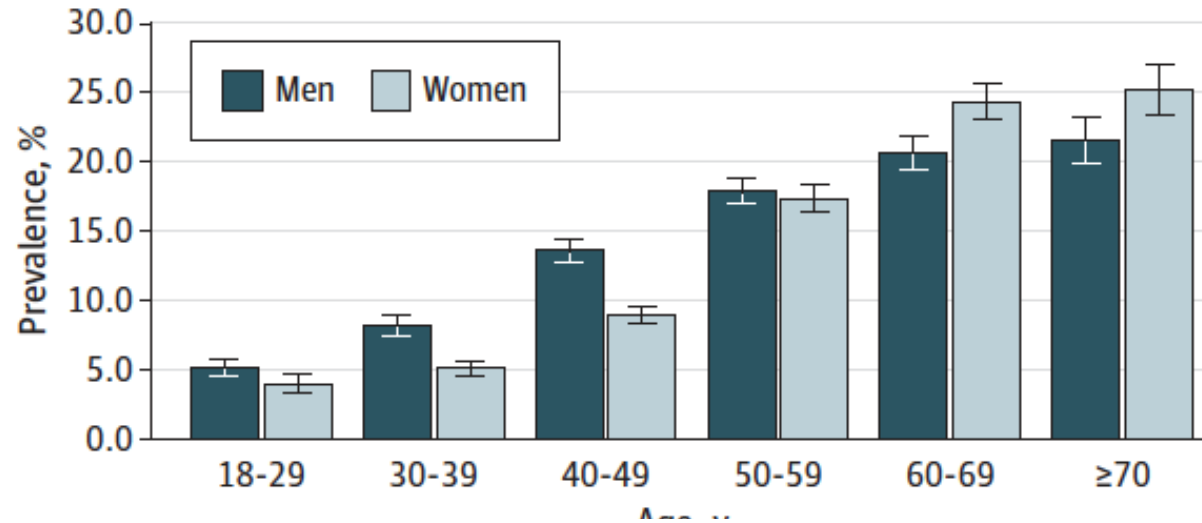
Prevalence of Diabetes in China

Total Diabetes



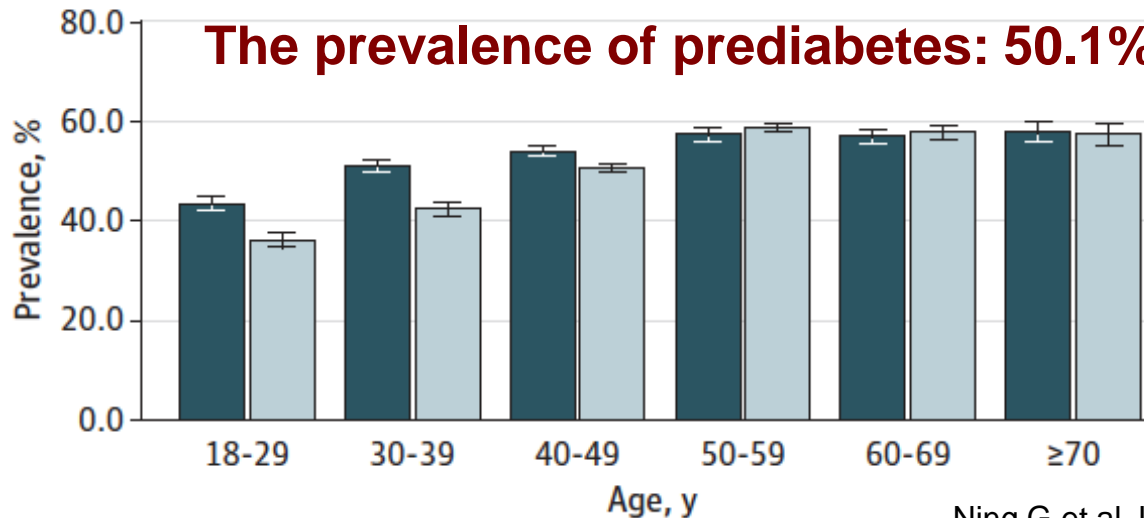
Prevalence of Diabetes in China

A Diabetes **The overall prevalence of diabetes: 11.6%**



B Prediabetes

The prevalence of prediabetes: 50.1%



Causes for ESRD in China

Data from Dialysis Registry of China

Causes	Prevalence				Incidence			
	2011	2012	2013	2014	2011	2012	2013	2014
Primary GN	59.47%	58.16%	55.65%	55.13%	54.28%	51.25%	46.50%	43.93%
Diabetic Nephropathy	15.08%	16.46%	17.83%	16.69%	18.04%	18.89%	20.82%	21.00%
Hypertensive	9.91%	10.07%	9.72%	9.58%	9.52%	9.43%	8.38%	8.71%
PKD	3.32%	3.31%	3.27%	1.53%	2.79%	2.45%	2.51%	1.33%
Kidney stone	2.17%	1.95%	1.87%	3.15%	2.53%	2.13%	2.00%	2.44%
Others	9.46%	8.58%	8.24%	8.52%	11.95%	12.11%	11.57%	11.27%
Unknown	0.59%	1.47%	3.43%	5.41%	0.88%	3.74%	8.21%	11.33%



Management of Diabetic Kidney Disease

- Behavioral therapy
 - Diet, exercise, and smoking cessation
- Pharmacologic intervention
 - Blood pressure
 - Blood sugar
 - Blood lipids
 - RAS blockade

Phase III trials for DN: A Barren Landscape

1	Recruiting	<u>Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy</u> Conditions: Diabetes Mellitus, Type 2; Diabetic Nephropathies Interventions: Drug: Canagliflozin; Drug: Placebo
2	Recruiting	<u>Pyridorin in Diabetic Nephropathy</u> Conditions: Diabetic Nephropathy; Diabetic Kidney Disease Interventions: Drug: Pyridorin; Drug: Placebo
3	Recruiting	<u>Study Of Diabetic Nephropathy With Atrasentan</u> Condition: Diabetic Nephropathy Interventions: Drug: Atrasentan; Drug: Placebo
4	Completed	<u>Go Fish: Omega-3 Fatty Acid Supplementation in Diabetes-Related Kidney Disease</u> Condition: Diabetes Intervention: Dietary Supplement: Lovaza (fish oil)
5	Terminated	<u>Bardoxolone Methyl Evaluation in Patients With Chronic Kidney Disease and Type 2 Diabetes</u> Conditions: Renal Insufficiency, Chronic; Diabetes Mellitus, Type 2 Interventions: Drug: Placebo; Drug: Bardoxolone Methyl: 20 mg
6	Not yet recruiting	<u>A Trial in Adults With Type 1 Diabetes Mellitus Evaluating the Effects of Fenofibrate Versus Placebo on Macular Thickness and Volume</u> Conditions: Type 1 Diabetes Mellitus; Retinopathy; Diabetic Nephropathy Interventions: Drug: Fenofibrate; Drug: Inert lactose placebo
7	Completed	<u>Vitamin-D Receptor Activation (VDRA) in Chronic Kidney Disease</u> Condition: Chronic Kidney Disease Intervention: Drug: Zemplar

Phase II: Few Proof of Concept Clinical Trials For Diabetic nephropathy

Disease State Search Term	Number of Active Phase II Trials*
Breast Cancer	206
Lung Cancer	167
Diabetes Mellitus	108
Congestive Heart Failure	51
Glioblastoma	50
Stroke	46
AIDS	46
Rheumatoid Arthritis	40
Colon Cancer	24
Influenza	17
Psoriasis	15
Glaucoma	15
Cirrhosis	14
Diabetic Nephropathy	9

Diabetic Nephropathy is a Prototypical Disease of Gene and Environmental Interactions

- Calorie excess is associated with type II diabetes
- Even in the setting of poor glycemic control, patients with diabetes will not always develop clinically evident DKD
- Familial aggregation of patients with diabetic renal disease

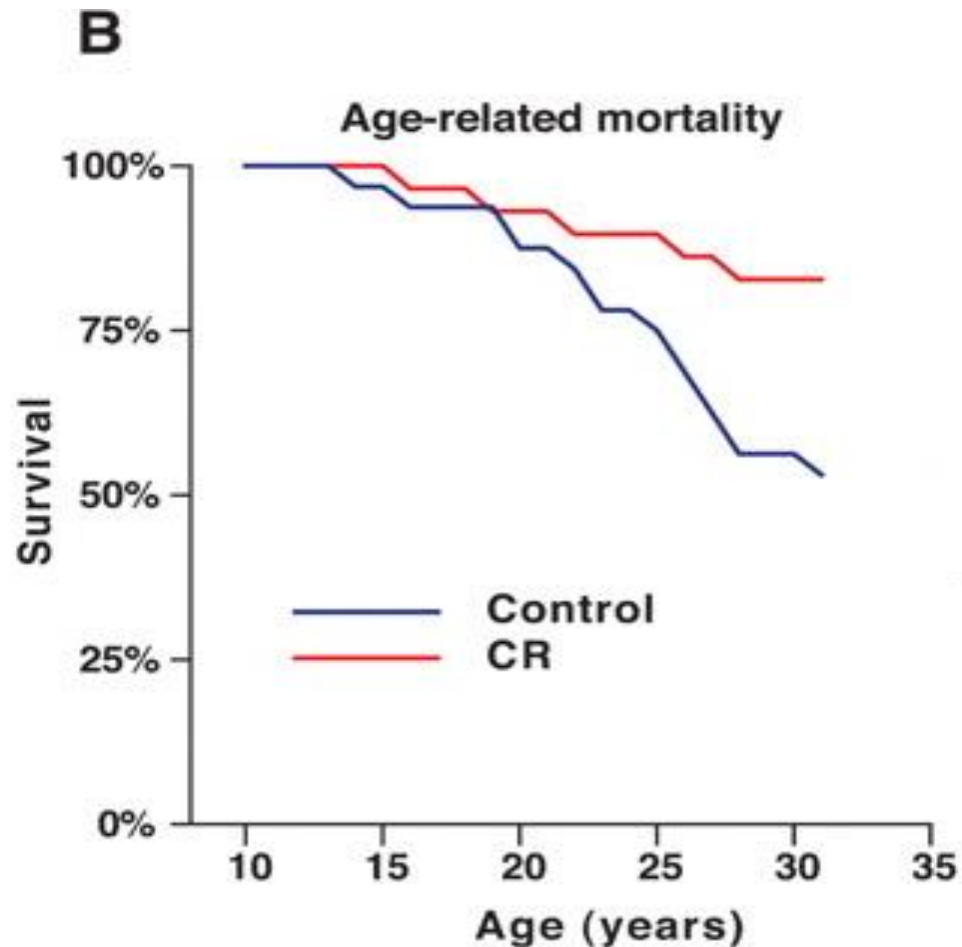
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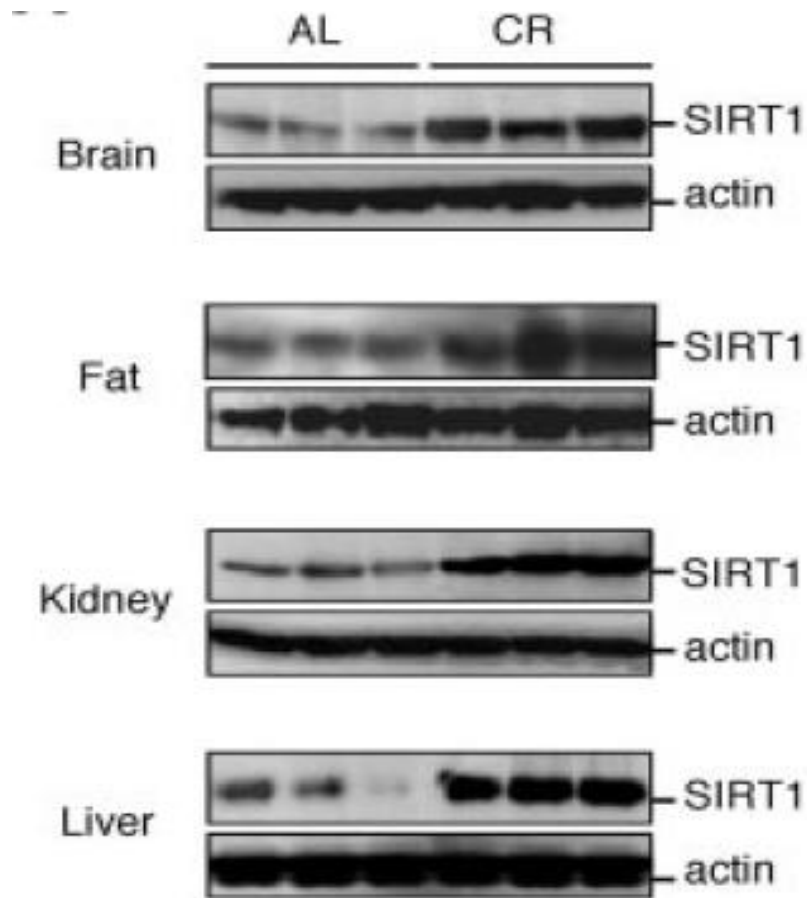
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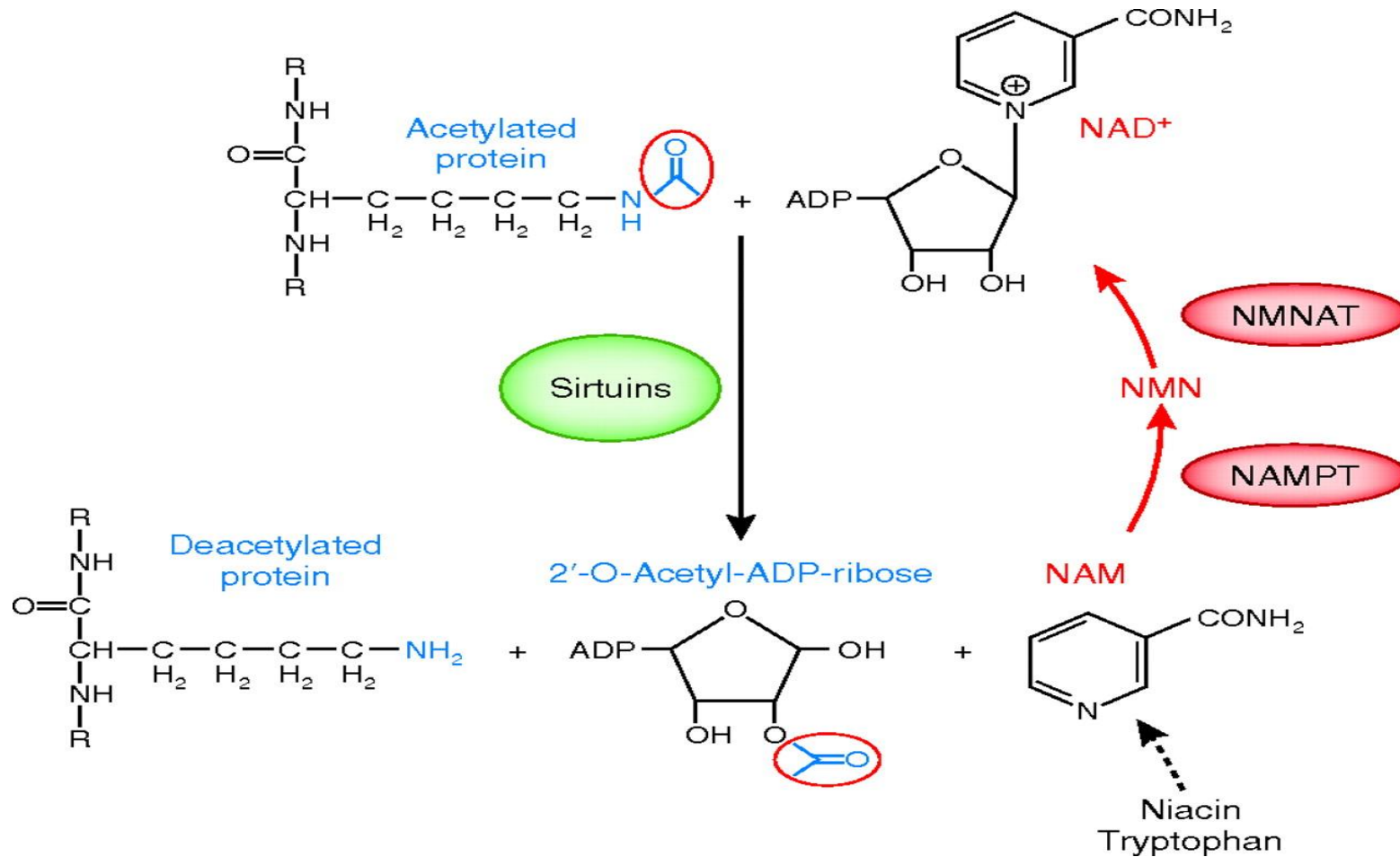
Calorie Restriction Reduces Mortality



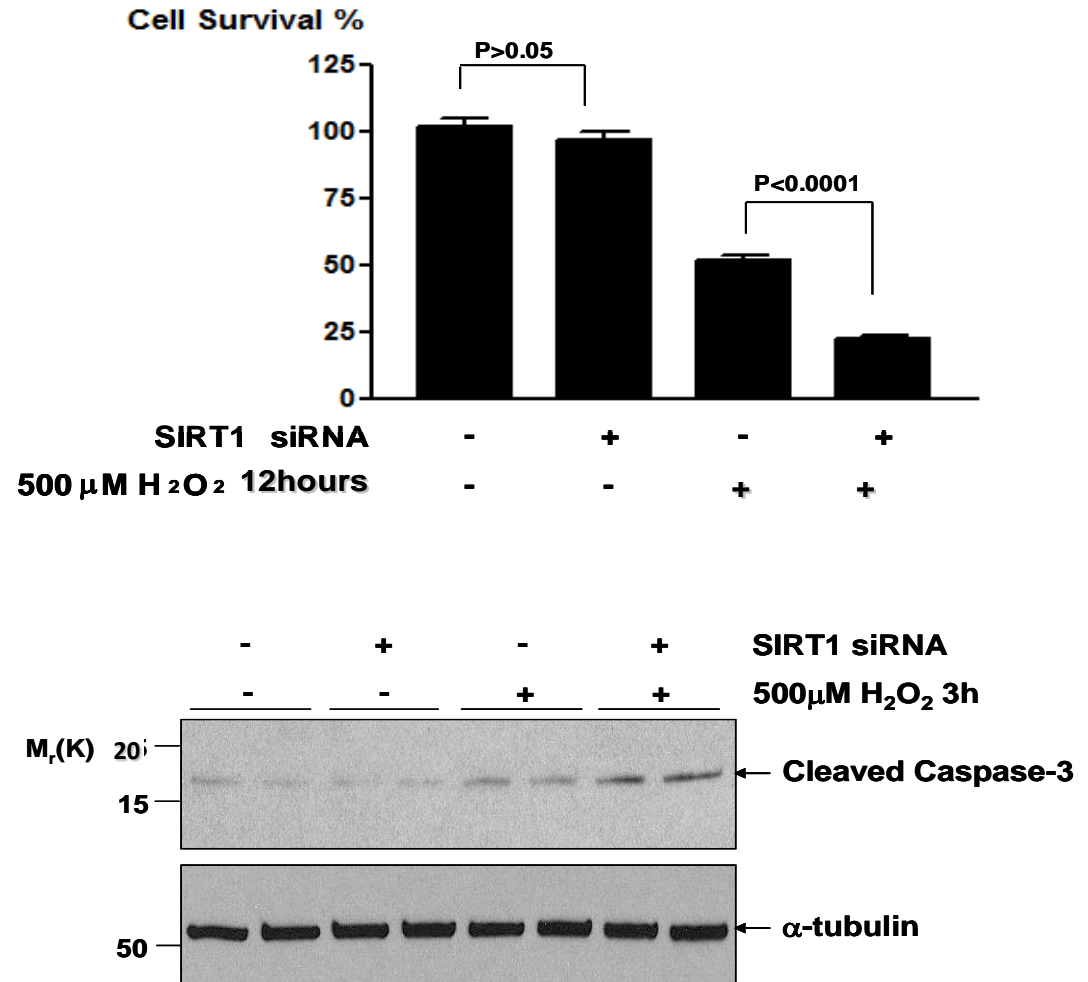
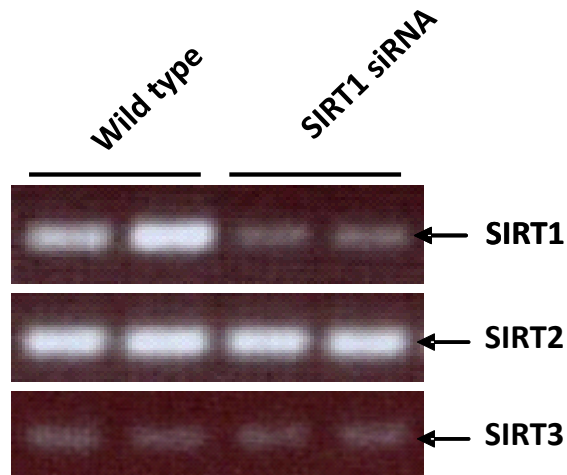
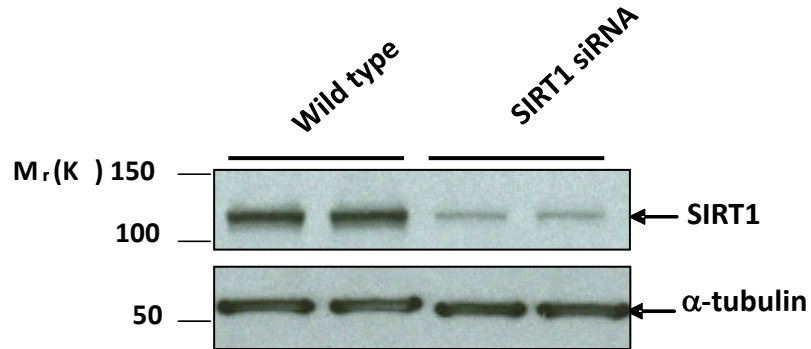
Calorie restriction increases Sirt1 expression



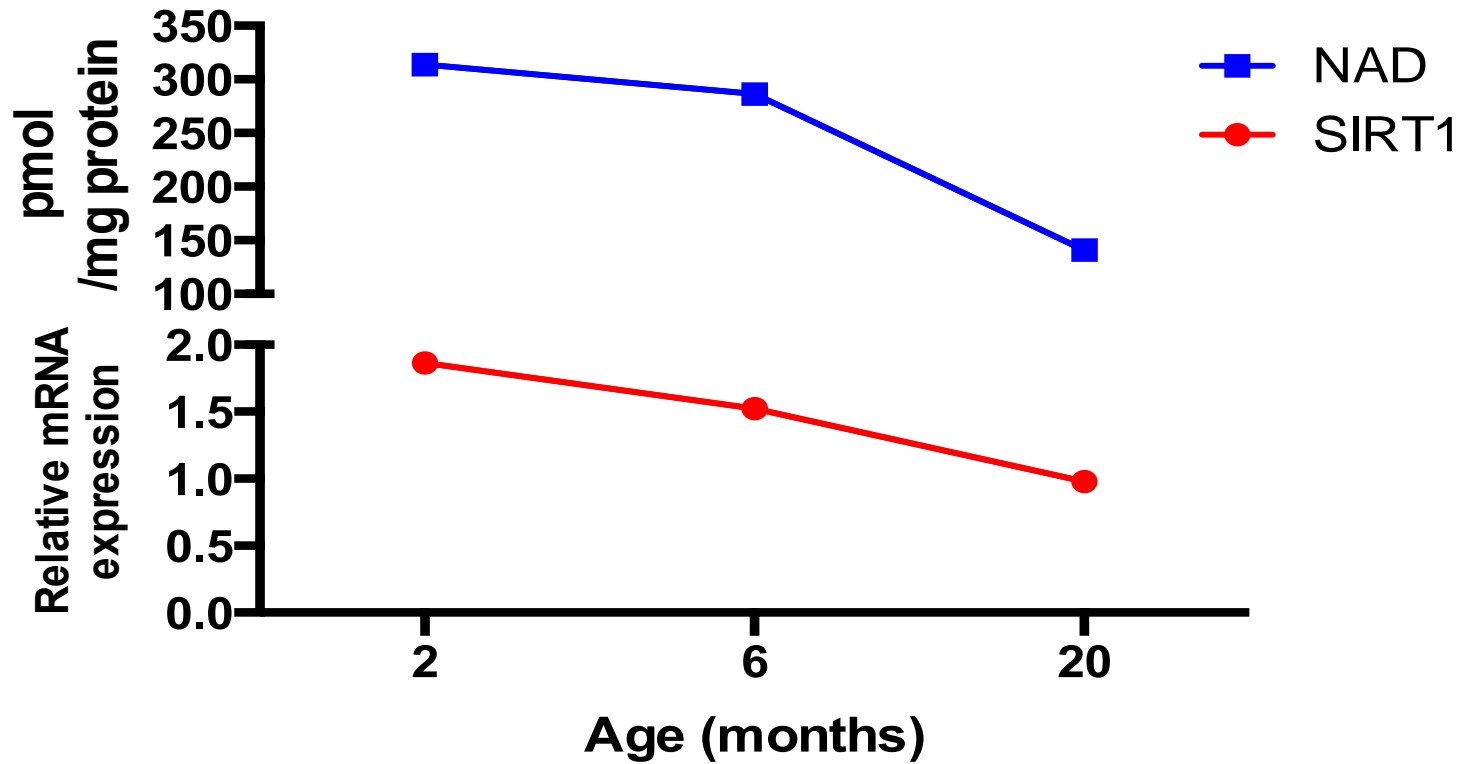
SIRT1



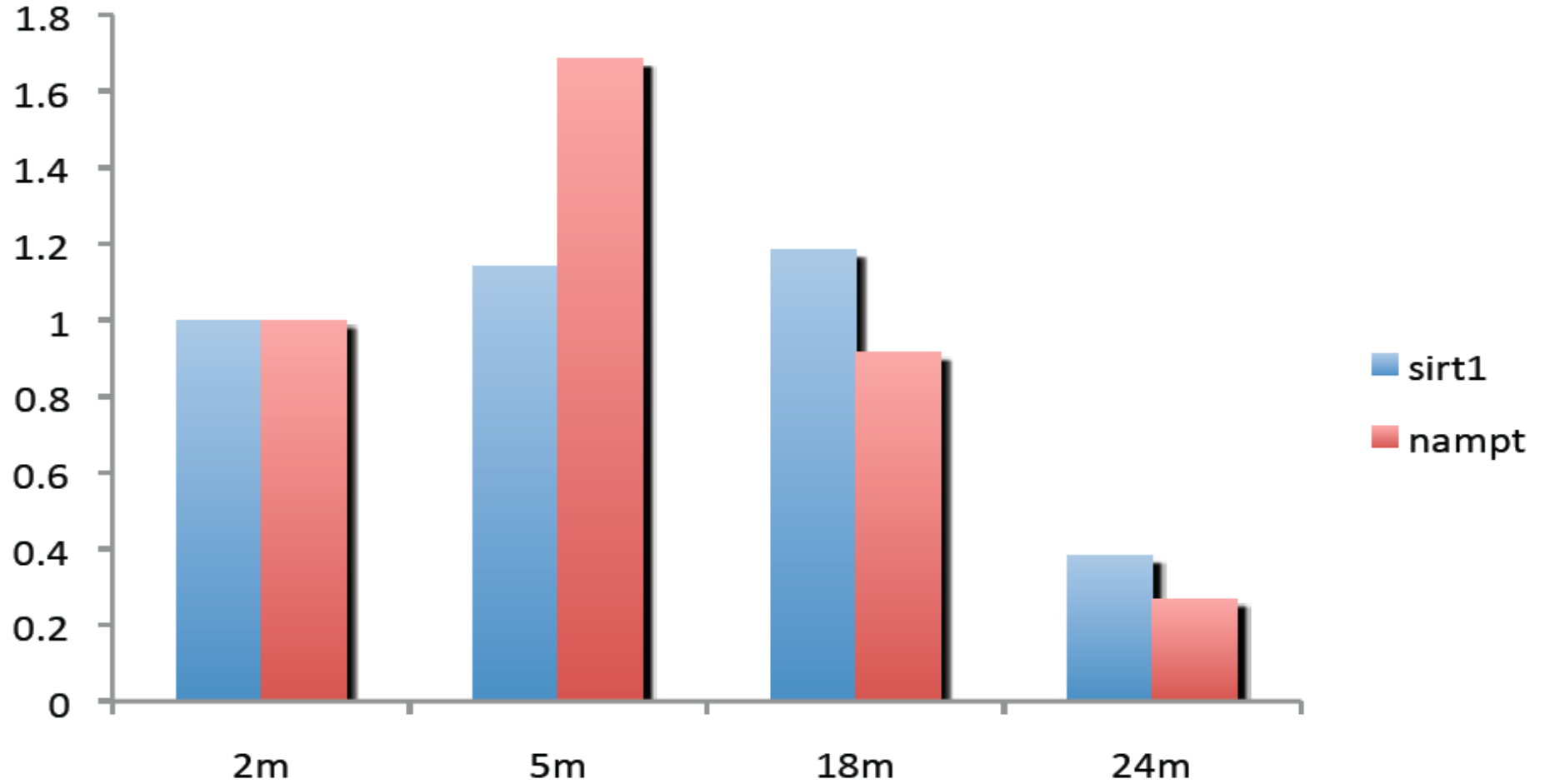
SIRT1-deficient Renal Medullary Interstitial Cells Exhibit Increased Cell Death following H_2O_2



SIRT1 IS NAD⁺ DEPENDENT STRESS RESPONSIVE

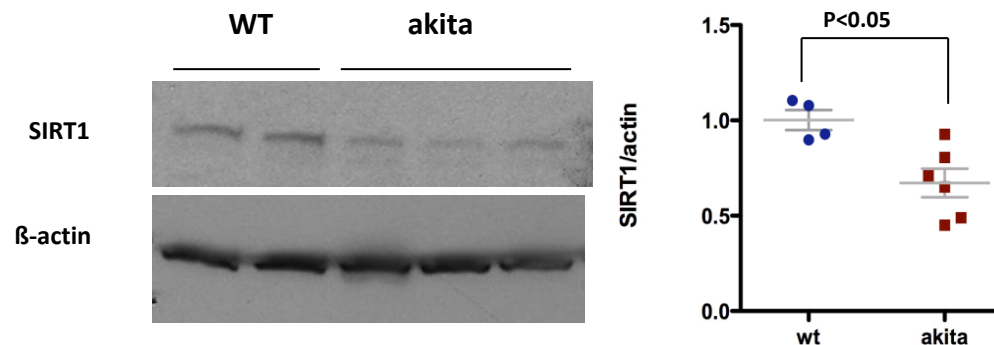
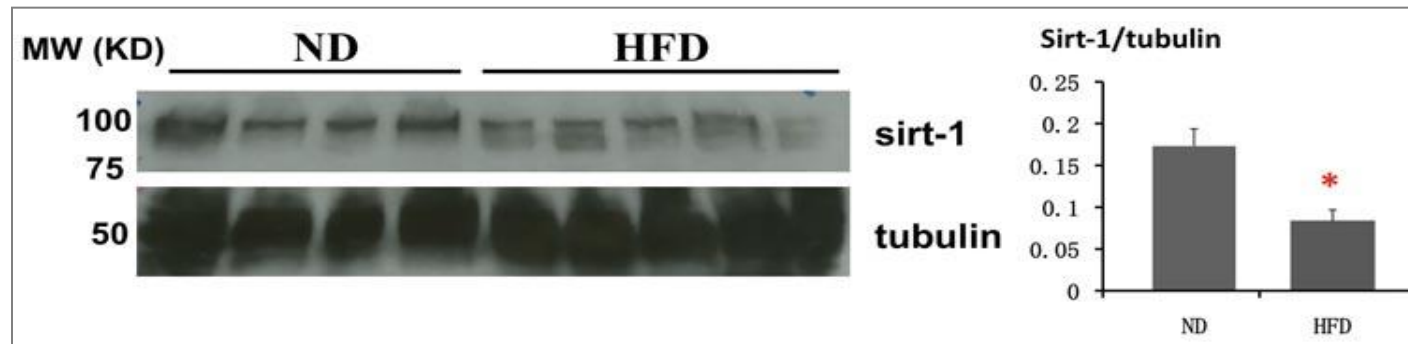


SIRT1 Expression in Aged Mouse Kidney

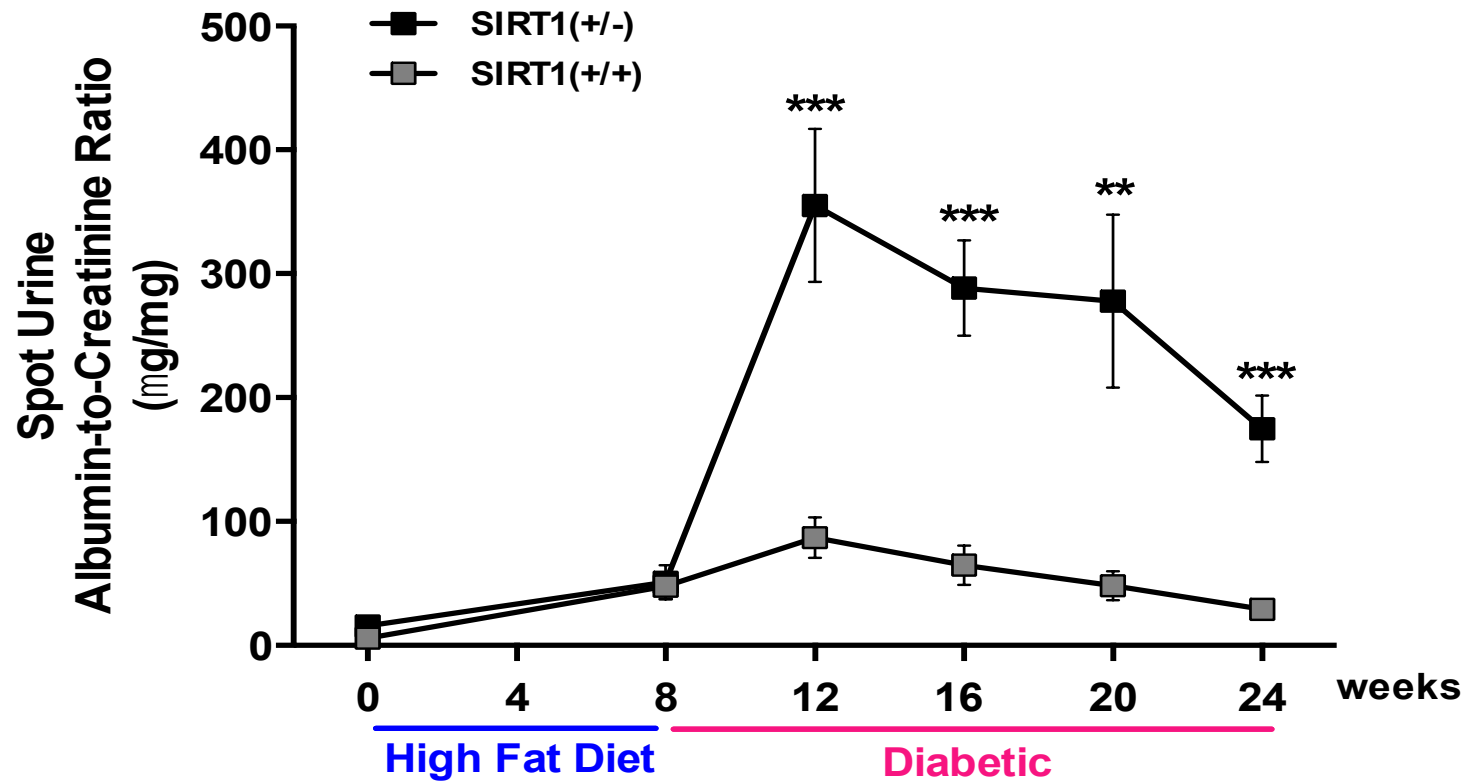


Guan Y & Hao C

Sirt1 Expression is Reduced in Diabetic Kidneys

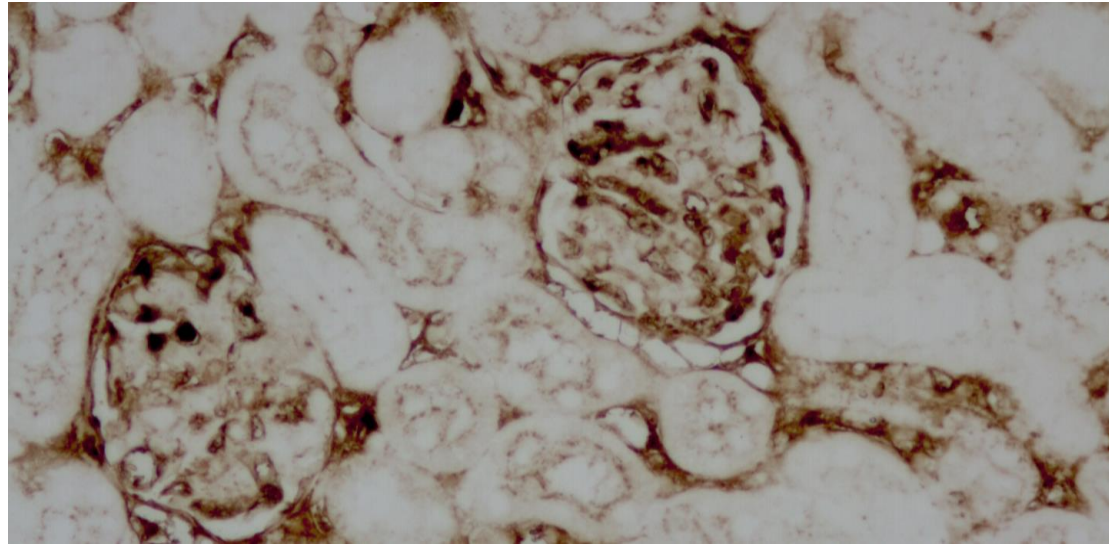


SIRT1 Deficiency Increases Urine ACR in Diabetic Mouse

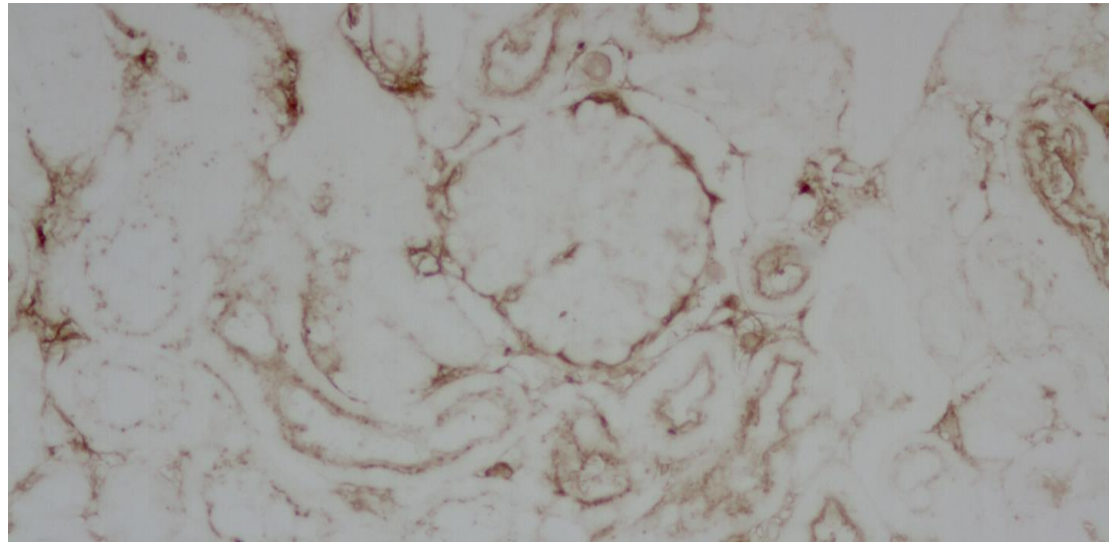


Signs of Renal Fibrosis in Diabetic SIRT1 Deficient Mice

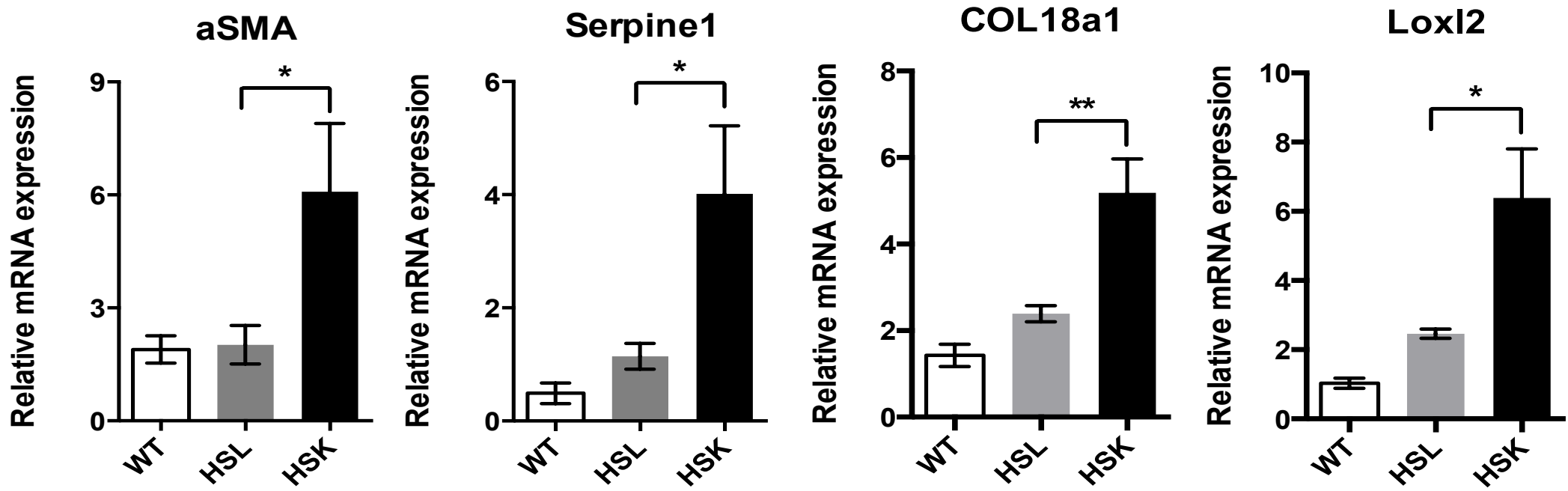
IHC of COL IV
SIRT1(+/-)
*400



IHC of COL IV
SIRT1(+/+)
*400

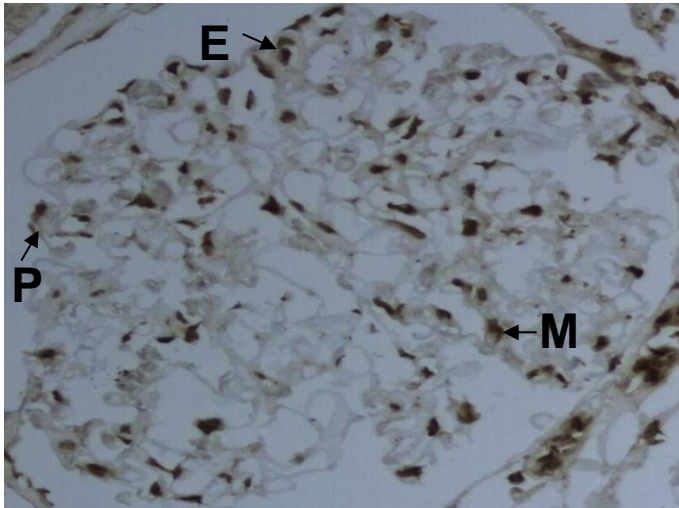


Renal Fibrosis in Diabetic SIRT1 Deficient Mice

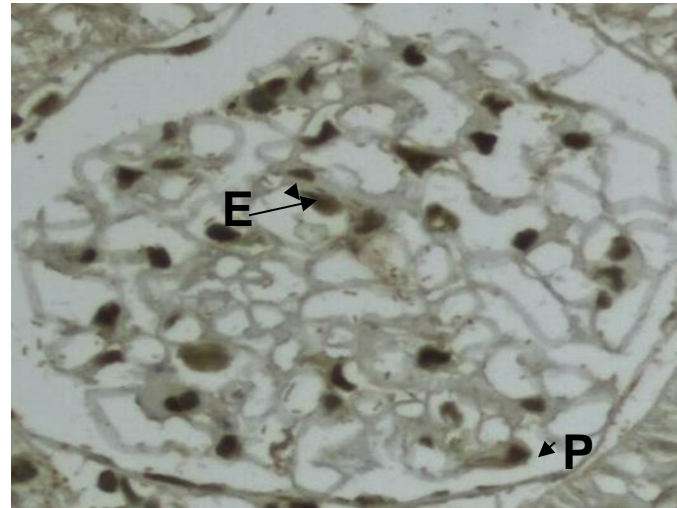


SIRT1 Expression in Glomerular Podocytes and Endothelial Cells

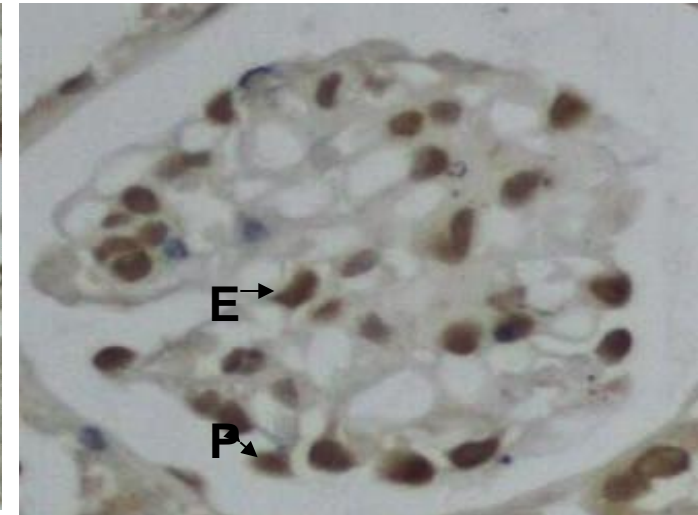
human



rat

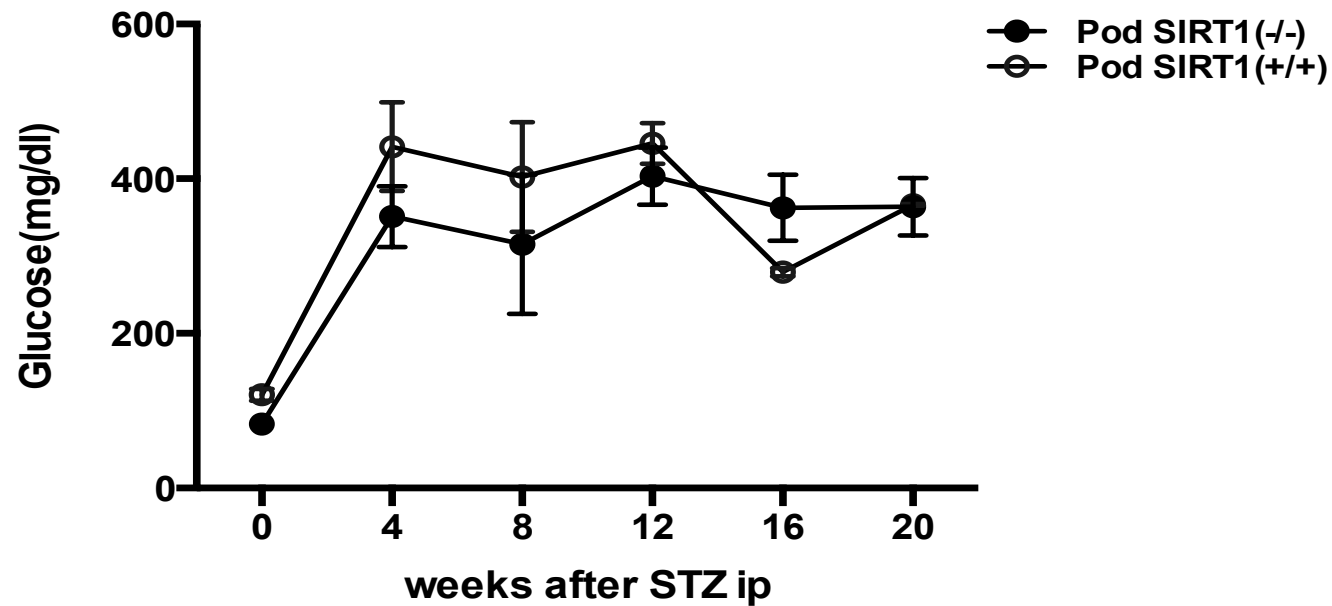


mouse



STZ induced Diabetes in Podocyte SIRT1 Knockout Mice

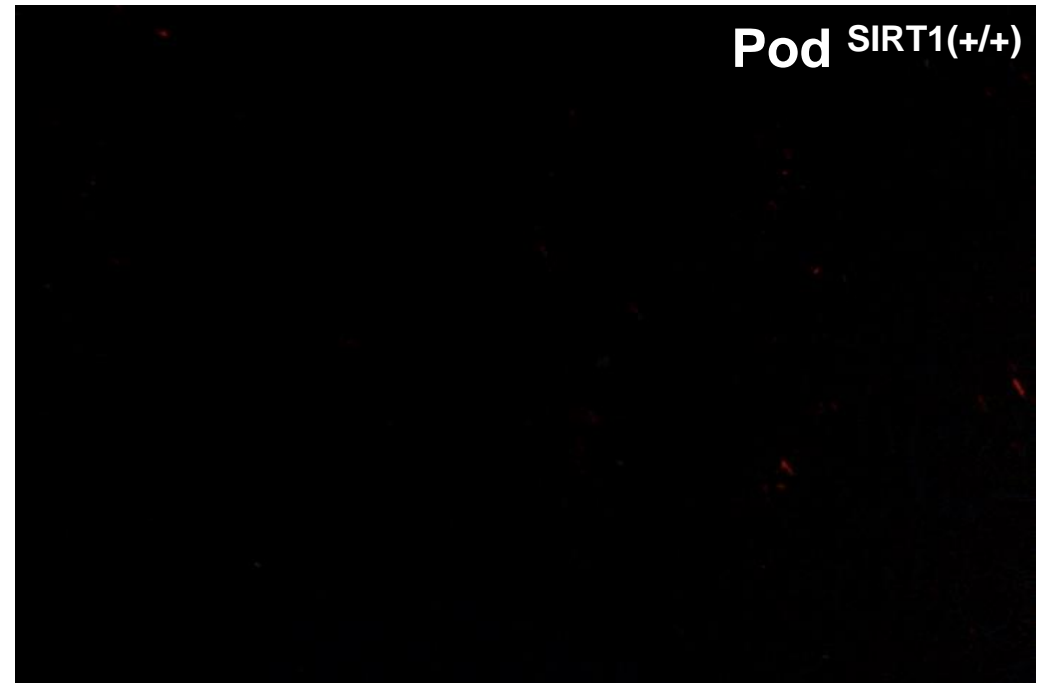
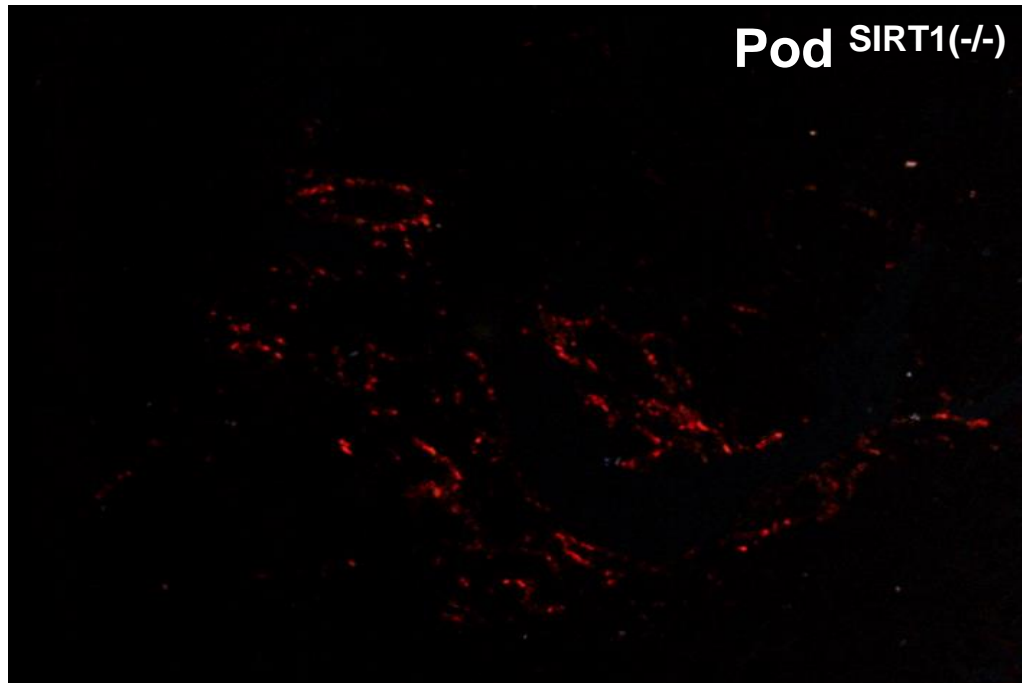
Podocin-Cre mice from JAX lab B6.Cg-Tg(NPHS2-cre)295Lbh/J



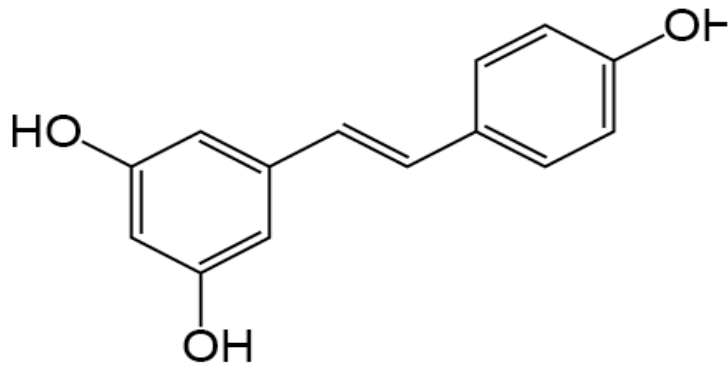
Podocyte SIRT1 Deletion Promotes Albuminuria in Diabetic Mice



Sirius Red Staining in Diabetic Mice with Podocyte SIRT1 deletion



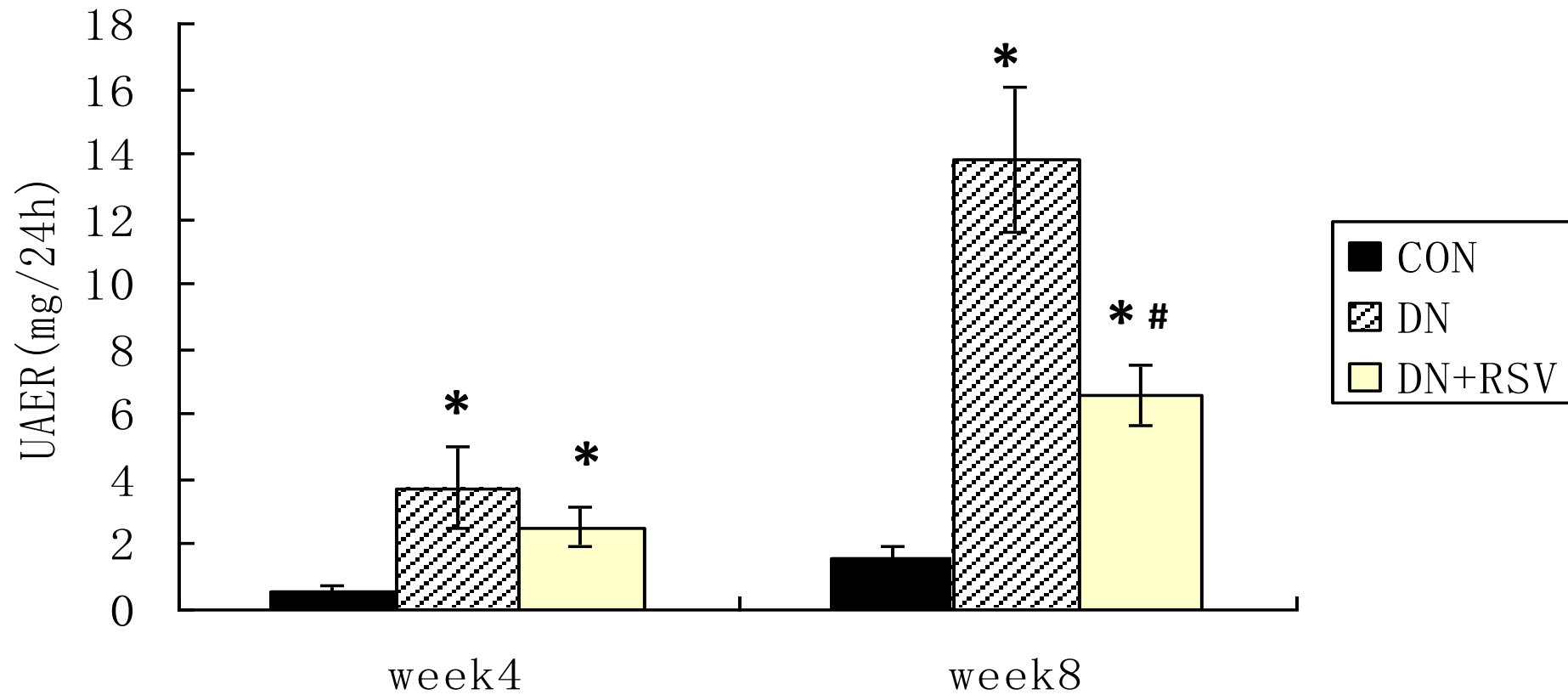
Resveratrol Reduces Urinary Protein Excretion in type 1 Diabetic Rats



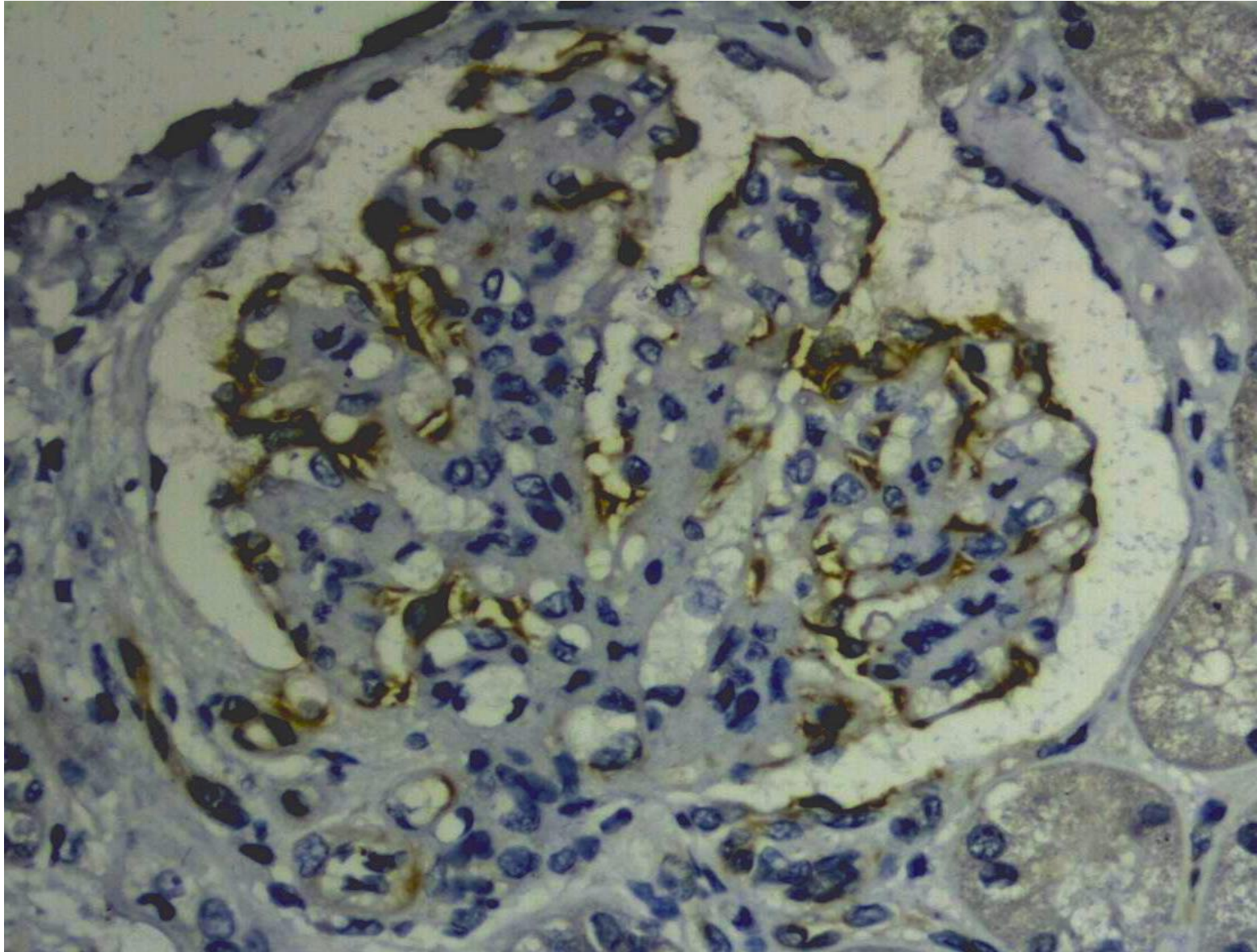
Resveratrol

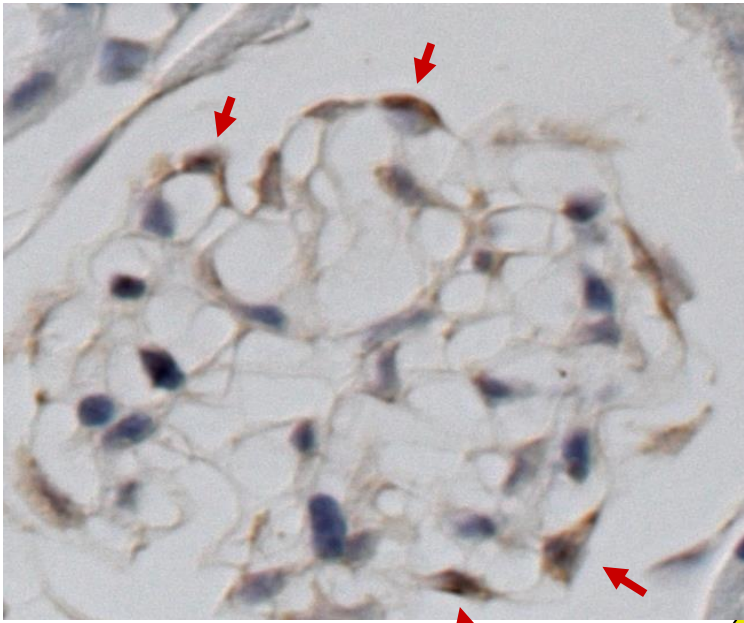


RSV Improves Albuminuria of Diabetic Rats

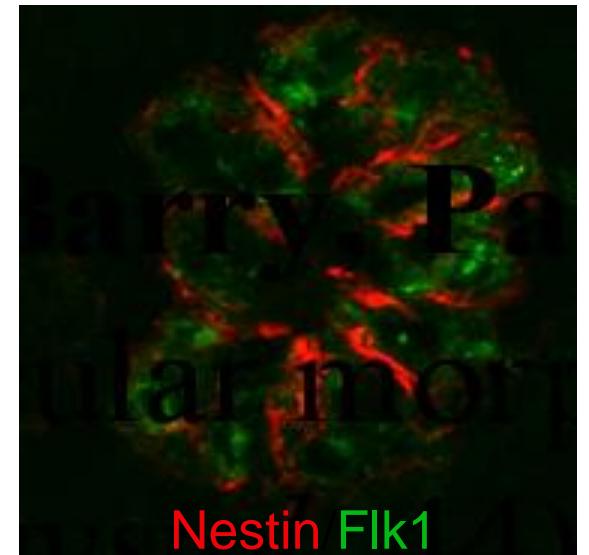
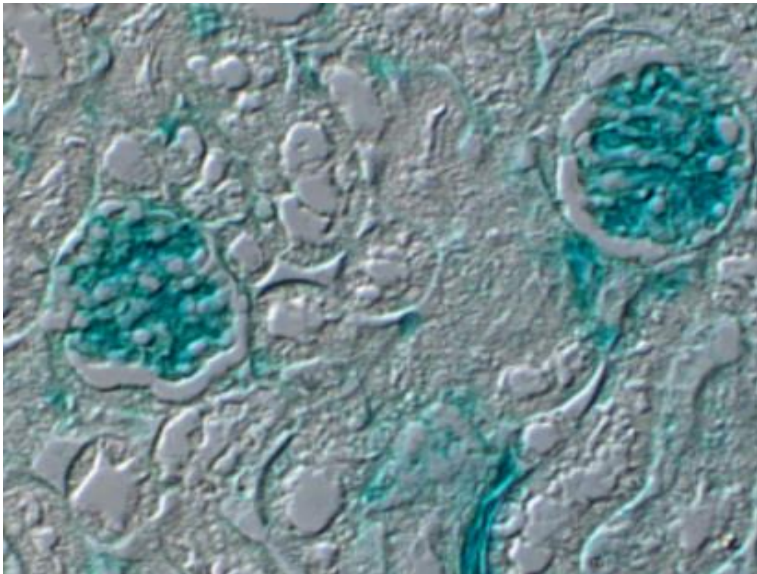
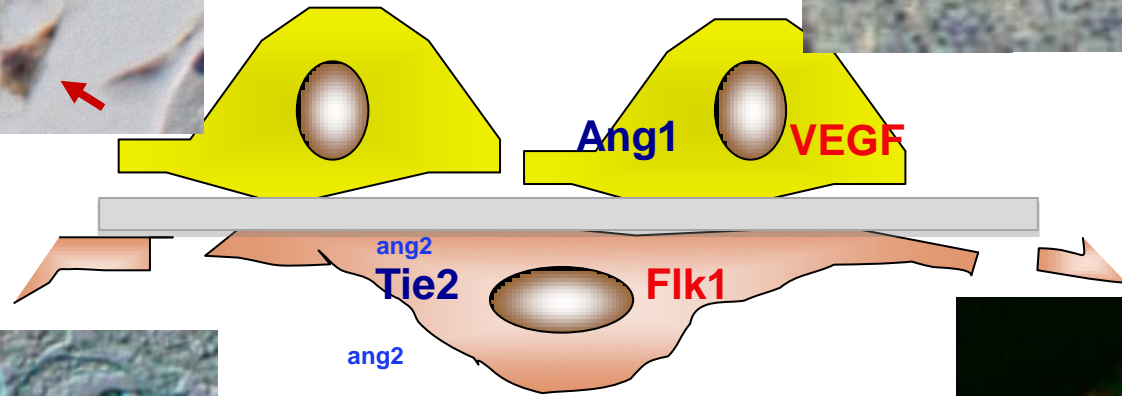
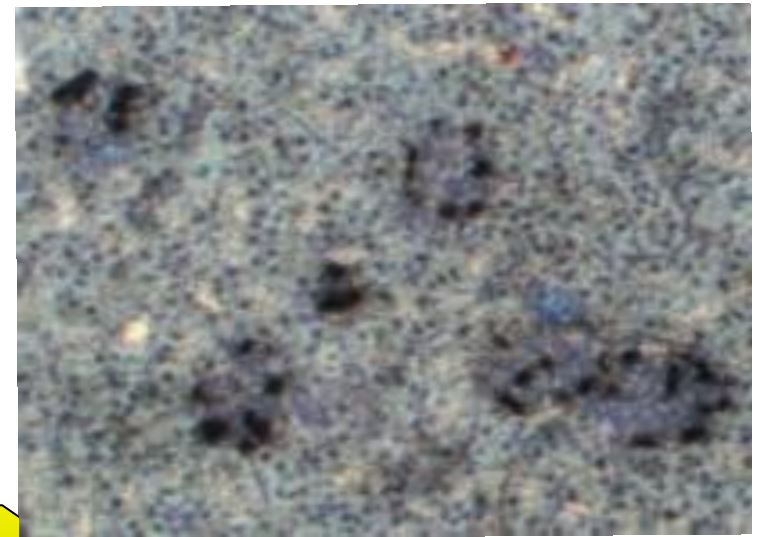


Angiogenesis in Diabetic Glomeruli in Human

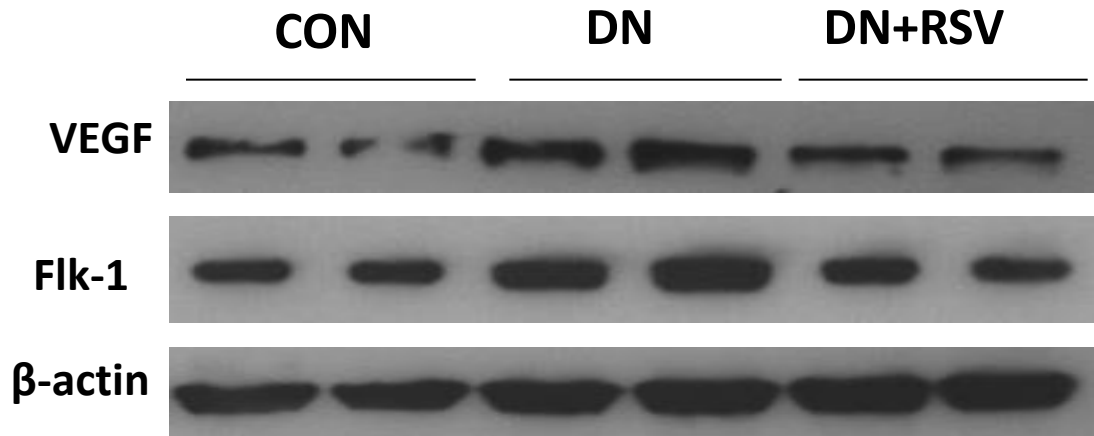




VEGF/FLK1
Ang1/tie2

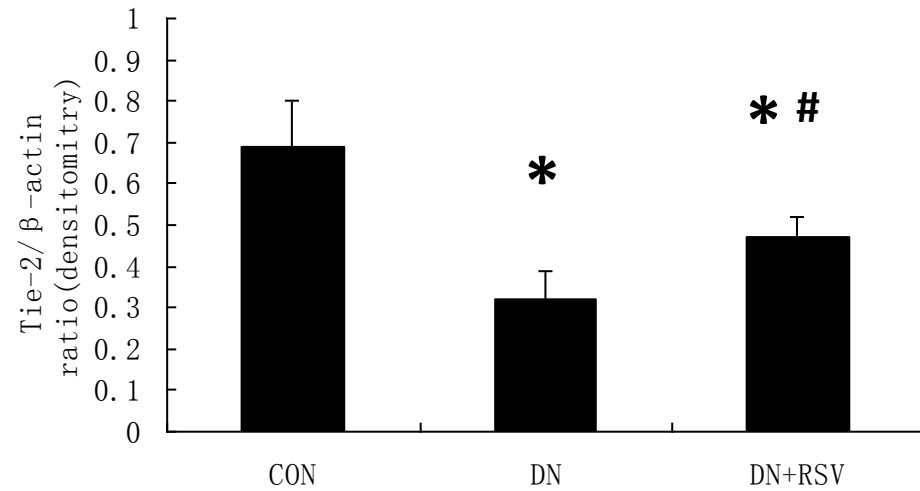
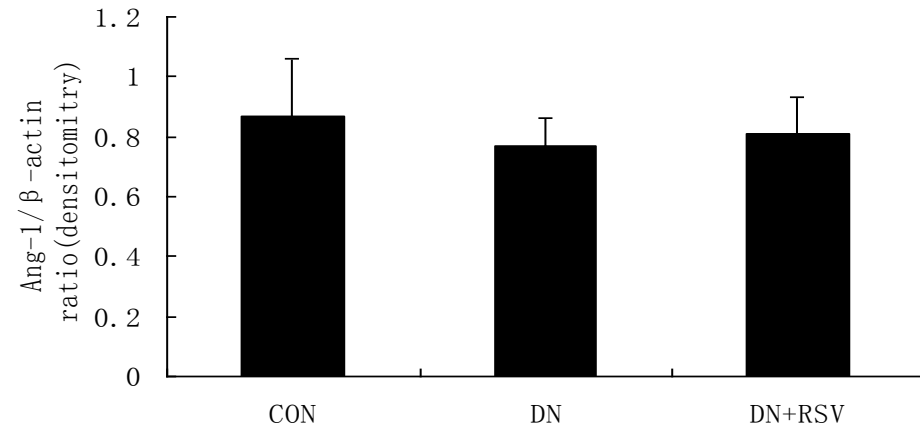
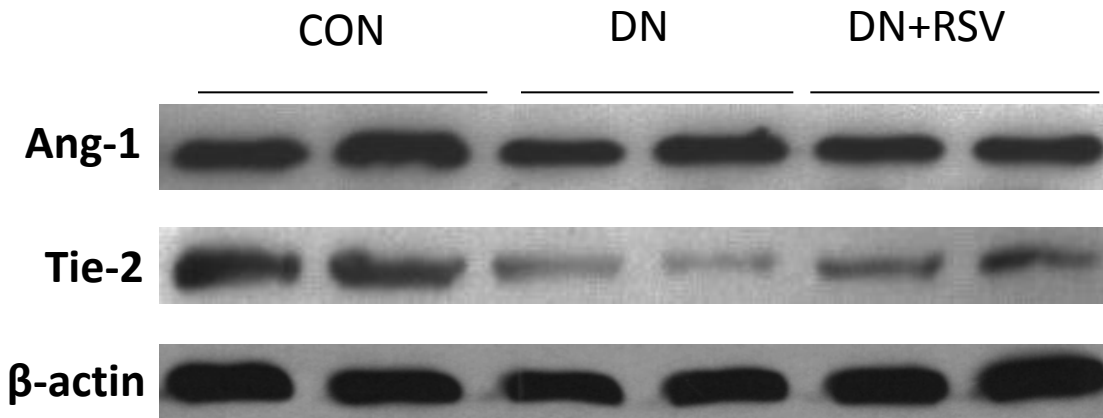


RSV Reduces VEGF and Flk-1 Expression in Diabetic Rats

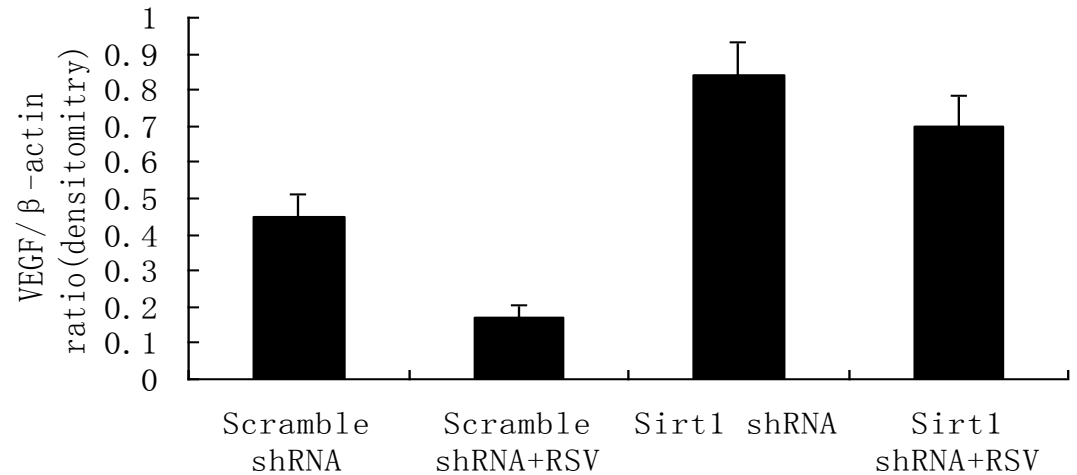
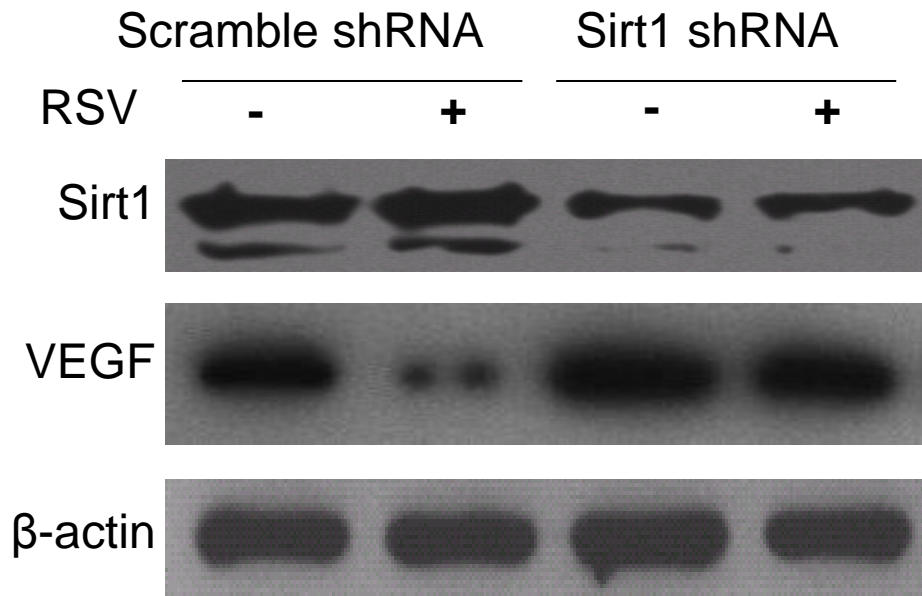


* $p < 0.05$, DN vs CON,
$p < 0.05$, DN+RSV vs DN

RSV Attenuated Tie-2 Inhibition in Diabetic Rats



Sirt1 Mediates RSV-induced Downregulation of VEGF Expression

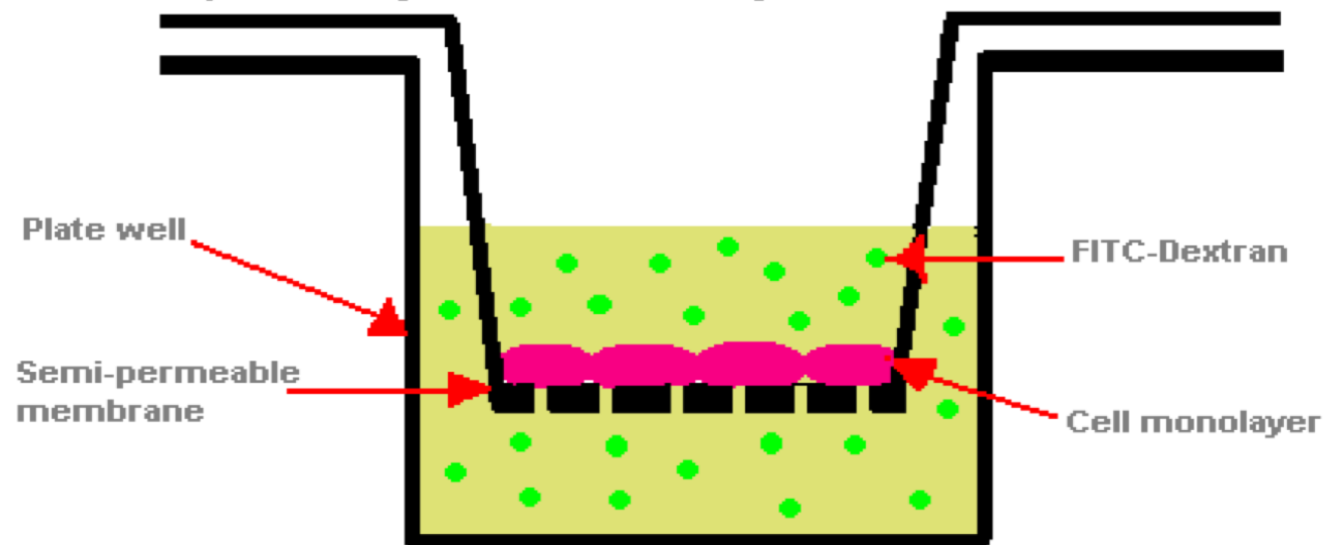


Diabetic kidney :

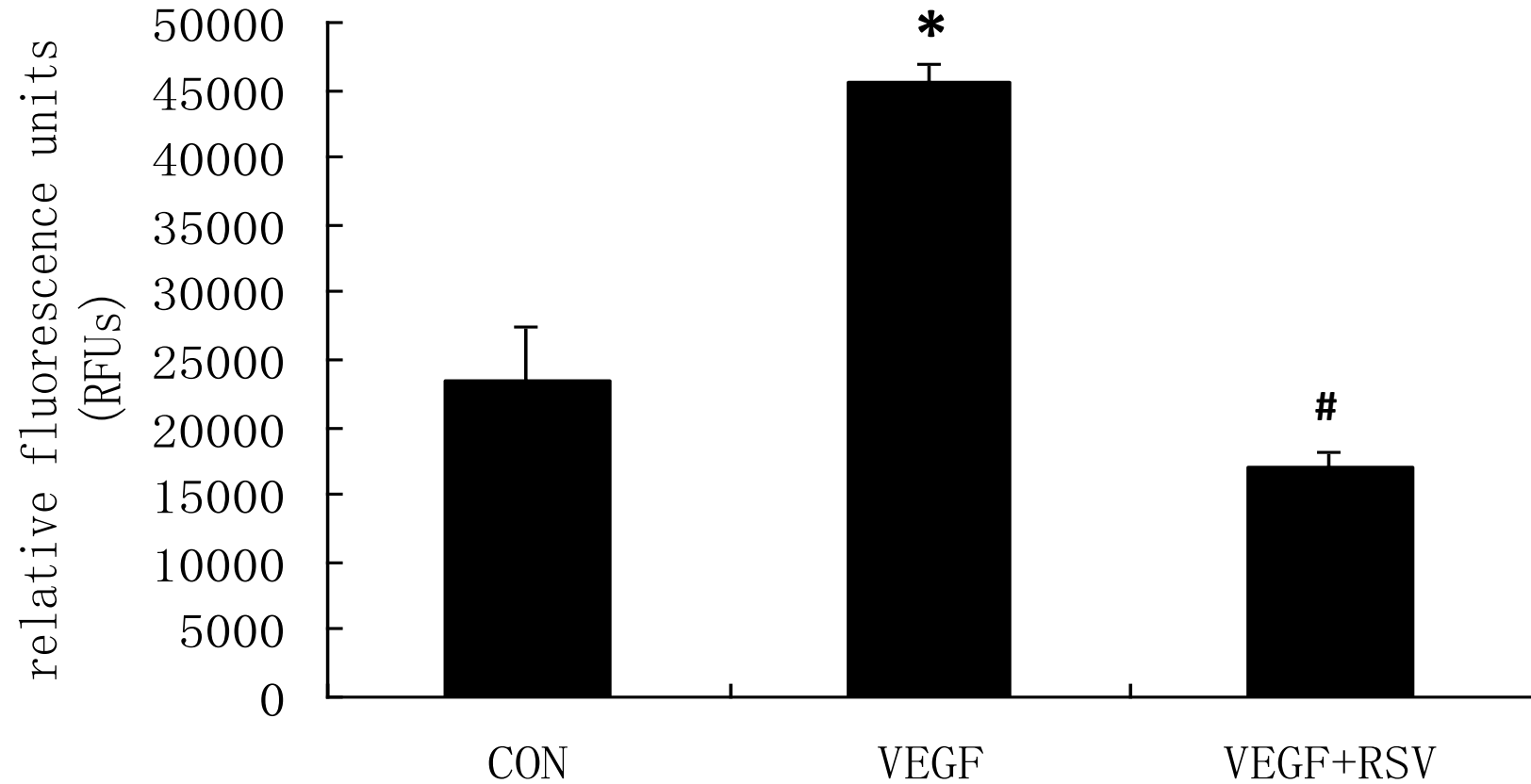
↑ VEGF/VEGFR

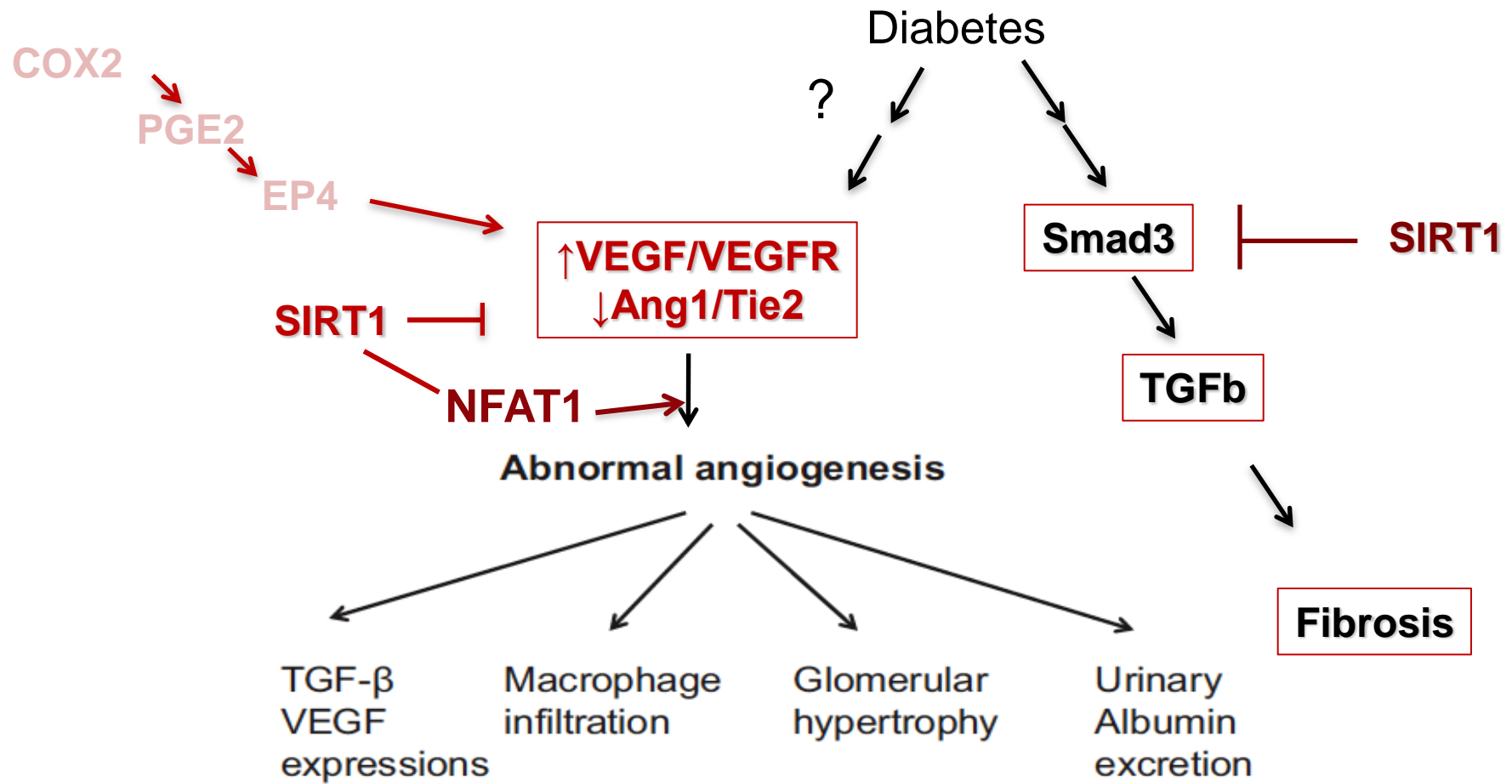
↓ Ang1/Tie2

FITC-Dextran permeates the treated cell monolayer into the plate well. The resulting fluorescence of the plate well is an indicator of the extent of the permeability for that cell monolayer.



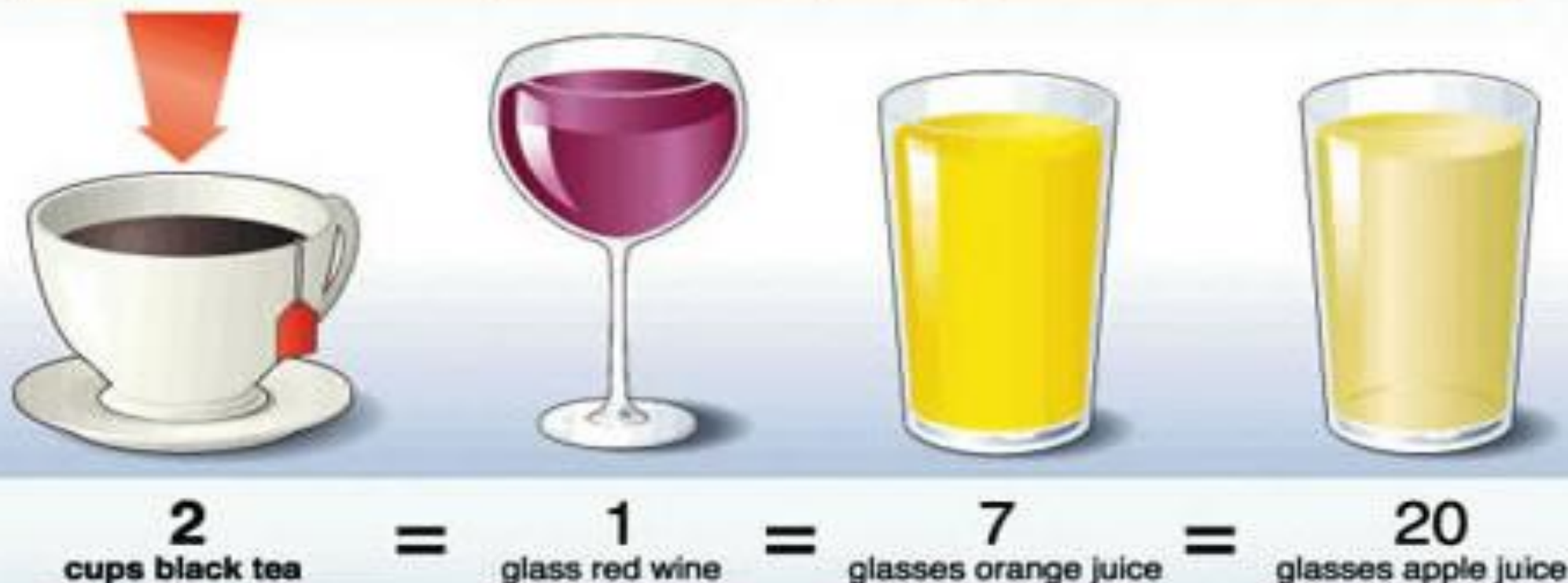
RSV decreased VEGF-induced hyperpermeability of endothelial cells





How do the popular beverages compare in antioxidant activity?

Antioxidant compounds are found in vegetables, fruits and many natural beverages like tea. Balanced diets are naturally-rich in antioxidants. Enjoy the variety, flavours and health potential in every serving!



Source: The Polyphenolic Content of Fruit and Vegetables and their Antioxidant Activities: What Does a Serving Constitute?, Paganga et al., Free Radical Research, Volume 30, February 1999

Acknowledgement

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Linda Davis
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Hong Fan

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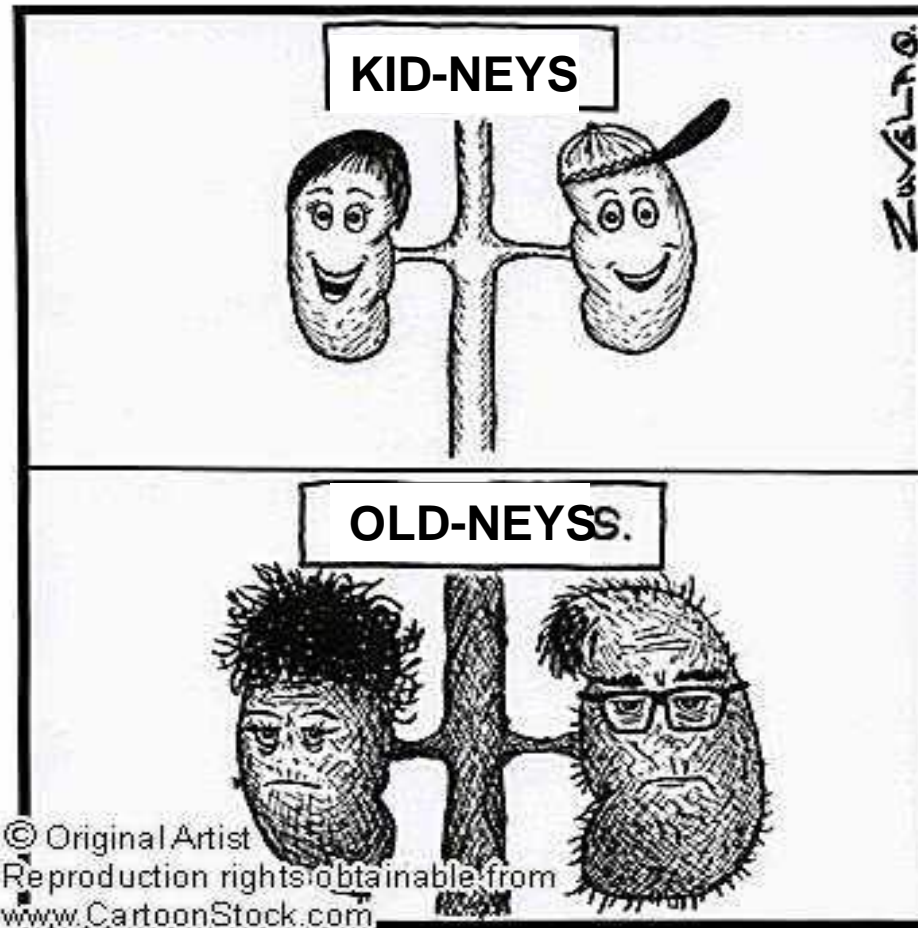
Yi Guan
Xinzhong Huang
Donghai Wen
Hong Fan
Li You

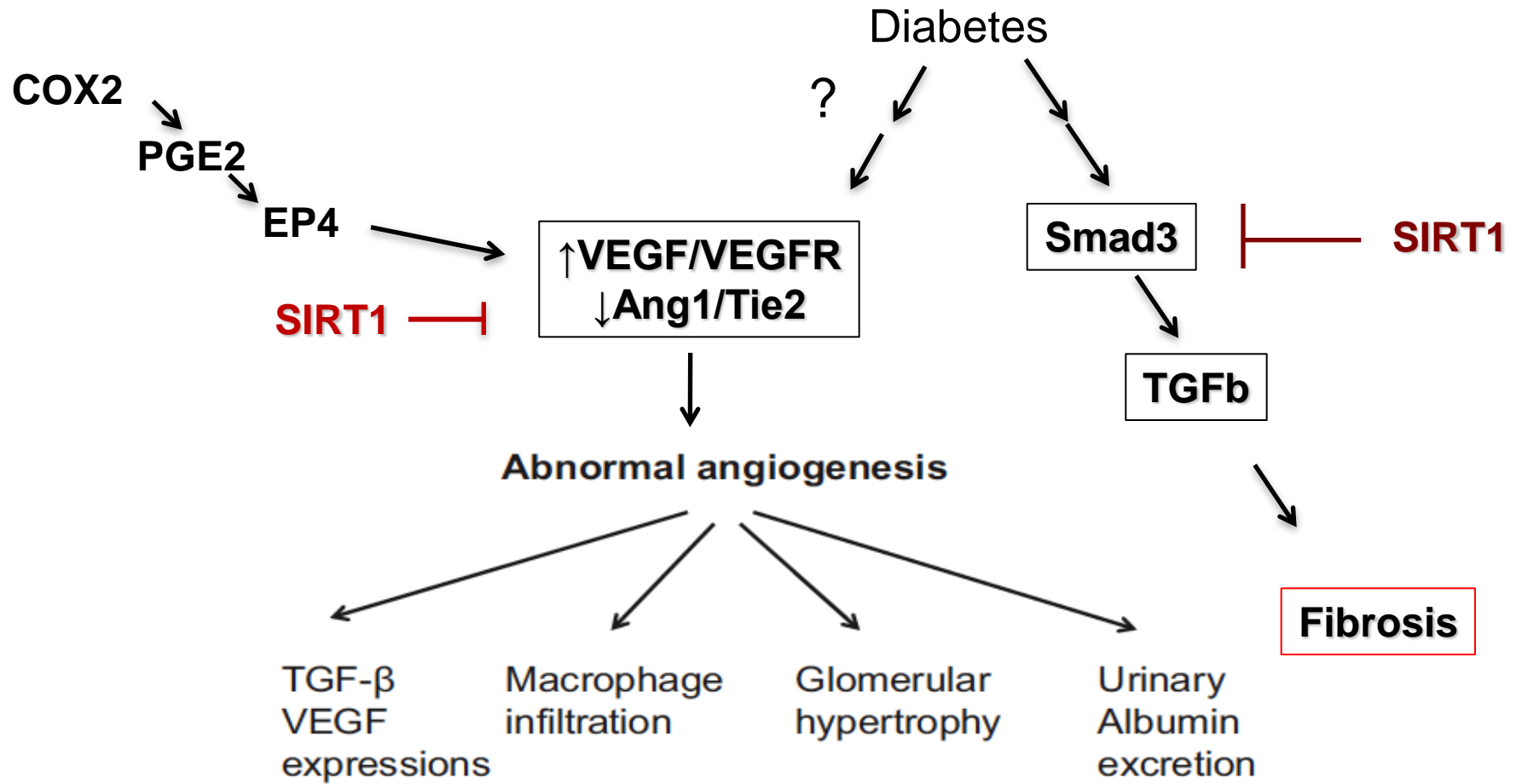
Collaborators

MingZhi Zhang
Matt Breyer
Ray Harris

GSK/Sirtis
NIDDK
NSFC

Aging kidneys





Acknowledgement

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Hong Fan
Yi Guan
Donghai Wen
XinZhong Huang
Li You
MingZhi Zhang
Ray Harris**

**GSK/Sirtis
973 program
NSFC**