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# Endothelin signaling and actions in renal mesangium

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In renal mesangium endothelin-1 (ET-1) exerts excessive contraction, proliferation and extracellular matrix accumulation leading to glomerulosclerosis and kidney failure. The molecular mechanisms of ET-1 actions in renal mesangium are insufficiently studied. We have discovered novel signaling pathway stimulated by ET-1 in cultured glomerular mesangial cells (GMC) which involves the formation of multiunit signaling complex including adaptor protein p66 Shc. Our data suggest that p66 Shc promotes GMC proliferation via inactivation of transcription factor FOXO3a and restricts GMC contractility through regulation of calcium influx. We have found that ET-1-mediated signaling is responsible for increased p66 Shc renal expression in rat model of salt-sensitive hypertension induced nephropathy. To test whether this ET-1 mediated signaling pathway plays principal role in glomerular diseases *in vivo* when ET-1 production is increased and renal mesangium is dysfunctional we have generated unique rat strains deficient in p66 Shc using engineered Zinc Finger Nucleases (ZFNs). The possibility to generate targeted gene changes using ZFNs in inbred rat strains has become one of the major breakthroughs in the field dramatically increasing opportunities of investigators in utilizing rats for biomedical research. We hypothesize that ET-1 signaling via adaptor protein p66 Shc in renal mesangium *in vivo* is contributing to kidney pathologies associated with abnormal function of renal GMC. Abnormal GMC function is detected in the majority of patients with hypertension induced nephropathy and glomerulosclerosis. The elucidation of mechanisms of ET-1-induced renal pathologies is important for understanding of the mechanisms underlying proliferation-associated and oxidative stress related renal glomerular diseases.

## Biography

Andrey Sorokin graduated from the St. Petersburg State University and received his PhD from the Institute of Cytology Academy of Sciences of Russia in 1981. He is the Head of the Laboratory at the Medical College of Wisconsin where he is holding the position of Full Professor with secondary appointments at Department of Physiology and Department of Microbiology & Molecular Genetics. He has published more than 90 papers in reputed journals and serving as an editorial board member of a number of journals including *Frontiers in Renal and Epithelial Physiology*.

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