

Oxidative Stress and Tubular Apoptosis in Diabetic Nephropathy

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Abstract

Tubular atrophy and interstitial fibrosis are major features of late stage of diabetic nephropathy (DN) and they are closely associated with loss of renal function. The mechanisms underlying **tubular atrophy** are incompletely understood. One mechanism is – **apoptosis** –, which has been shown to mediate cell death in various renal diseases.

Hyperglycemia, oxidative stress and renin-angiotensin system (RAS) dysfunction have been implicated in the progression of DN, however, the underlying molecular mechanisms are far from being fully understood. We established that reactive oxygen species (ROS) mediate high glucose (HG) stimulation of angiotensinogen (Agt, the sole precursor of angiotensins) gene expression and RAS activation in renal proximal tubular cells (RPTCs) *in vitro*. Transgenic (Tg) mice specifically overexpressing catalase (CAT) in their RPTCs attenuates hypertension and RPTC apoptosis in diabetic mice, supporting the view that enhanced ROS generation plays a central role in RPTC apoptosis in diabetes. To identify the down-stream target genes of ROS action in diabetic kidneys, we used gene chip microarray analysis. We discovered that two pro-apoptotic genes, caspase-12 (Csp-12¹) and Bcl-2-modifying factor (Bmf) are differentially upregulated in RPTCs of diabetic db/db mice but normalized in db/db CAT-Tg mice. Bmf and Csp-12 overexpression or knockdown enhances or decreases RPTC apoptosis, respectively, in HG milieu *in vitro*. Furthermore, CAT and Bmf expression is markedly enhanced and localized to apoptotic RPTCs in human diabetic kidneys. Taken together, our recent data suggest that ROS-induced Csp-12 and Bmf expression are implicated in RPTC apoptosis and tubular atrophy, leading to kidney failure in diabetes.

Biography

John S.D. Chan has completed his Ph.D, at the University of Manitoba (Canada) and research training in Canada and the USA including National Institutes of Health (NIH) and Harvard Medical School (Boston). He is the Professor of Medicine at the Université de Montréal and the Director of the Laboratory of Molecular Nephrology and Endocrinology at the Research Centre of Centre hospitalier de l'Université de Montréal (CRCHUM)-Hotel Dieu Hospital. He has published more than 110 papers in reputed journals and is the Editor of the eBook, "Diabetic Nephropathy"