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### TITLE

## Mechanism of DNA damage in Diabetes

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Systemic complications are the major causes of morbidity and mortality in patients with diabetes. Oxidative stress leads to protein, lipid, and DNA modifications that cause cellular dysfunction and contribute to the pathogenesis of macro- and microvascular complications of diabetes, including diabetic nephropathy. Mitochondrion and nucleus, two major targets of oxidative stress, contain a variety of DNA repair enzymes to repair oxidant-induced DNA modifications. Damage most likely occurs when the endogenous antioxidant network and DNA repair systems are overwhelmed. However, it is essential for the cell to repair DNA damage induced by oxidants. 8-Oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) is a sensitive marker of reactive oxygen species (ROS)-induced DNA damage. There is an increase in 8-oxodG levels in tissue of diabetic rats and in the urine of patients with type 1 and type 2 diabetes, with the levels being significantly higher in patients with albuminuria or with other diabetic complications. 8-OxodG in DNA is repaired primarily via the DNA base excision repair pathway. The DNA repair enzyme that recognizes and excises 8-oxodG is 8-oxodG-DNA glycosylase (OGG1). Deficiency in DNA repair enzyme OGG1 has important functional consequences, compromising the ability of cells to repair DNA. We have recently shown that OGG1 is regulated by tuberin, the product of the tumor suppressor gene, *TSC-2*. Tuberin normally exists in an active state physically bound to hamartin, the product of *TSC-1* gene, to form a stable complex. These two proteins function within the same pathway(s) regulating cell cycle, cell growth, adhesion, and vesicular trafficking. Activation of phosphatidylinositol 3-kinase (PI 3-kinase) and phosphorylation of serine/threonine kinase Akt/protein kinase B (PKB) by certain agonists lead to inactivation of tuberin. The PI 3-kinase/Akt pathway is activated in diabetes, and there is evidence that this activation is redox dependent in different cell types, including renal cells. Little is known about DNA repair disturbances potentially contributing to DNA damage in diabetes. In the present study, we determined a potential mechanism by which ROS result in 8-oxodG accumulation and explored the role of tuberin phosphorylation and OGG1 in the kidney cortex of rats with type 1 diabetes.

### Biography

Dr. Habib has completed his PhD from Roswell Park Cancer Institute, Buffalo, NY. He was a recipient of several research grant and awards from American Diabetes Association, American Heart Association, National Kidney Foundation, New Investigator Award and Merit Review Award from Veterans Affairs, and Pilot Research Award from NIH/NIDDK. He has recently received the Excellent of Performance Award from the VA. Dr. Habib has been a regular member of the Kidney Cancer Study Section of the Medical Research Program, Department of Defense. He is also an editor of two Journals and an editorial board member of 5 journals. He has published more than 30 papers.