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Defects of mitochondrial genome in diabetic nephropathy: Role and clinical relevance

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Mitochondria play important roles in cellular energy metabolism and reactive oxygen species (ROS) generation. Hyperglycemia-induced overproduction of mitochondrial ROS contributes to mitochondrial dysfunction and the development diabetic complication, including diabetic nephropathy (DN). We investigated changes in the mitochondrial DNA copy number (mtDNA-CN), gene expression of mtDNA-encoded subunits of electron transport chain (ETC) complexes and mitochondrial biogenesis in DN. ROS production, mitochondrial function, mtDNA-CN, gene expression of mtDNA-encoded ETC subunits and mitochondrial biogenesis regulatory factors were analyzed in human mesangial cells cultured for 1, 4 and 7 days in normal and high glucose in the presence and absence of manganese superoxide dismutase mimic (MnTBAP) or catalase. Additionally, mtDNA-CN was analyzed in peripheral blood of type-2 diabetes (T2D) patients with normoalbuminuria, DN patients with microalbuminuria or macroalbuminuria and healthy control subjects. In the renal cells, high glucose induced a significant increase in ROS production, which was accompanied by a progressive decrease in ATP. mtDNA-CN, expression of mtDNA-encoded genes and mitochondrial biogenesis were increased at 1 day in high glucose but were decreased at 4 and 7 days. Treatment of cells with MnTBAP or catalase during high-glucose incubation attenuated ROS production and all these changes. In the subject groups, peripheral blood mtDNA-CN was significantly lower in DN patients compared with T2D patients and controls, declined with the severity of DN and showed a significant diagnostic ability to differentiate DN patients from T2D patients and healthy controls. Lower mtDNA-CN was independently associated with the progression of DN, negatively correlated with albuminuria and conventional risk factors of DN and positively correlated with eGFR. Our data show that defects of mitochondrial genome play important role in DN. Protection of mitochondria from high glucose-induced ROS may provide a potential approach to retard the development of DN. Our data also propose the mtDNA-CN as a novel blood biomarker for the early diagnosis of DN and the significance of decreased mtDNA-CN as another risk factor in the development of DN.

Biography

Ghada Al-Kafaji is an Associate Professor of Molecular Genetics in the Department of Molecular Medicine and the Director of Personalized Medicine Master Program at the College of Medicine, Arabian Gulf University, Bahrain. She has obtained her PhD degree in Molecular Genetics from King's College London, University of London, UK. Following her PhD, she has worked in UK as a Postdoctoral Research Fellow at the School of Medicine, King's College London and as an Assistant Professor of Genetics at the College of Science, University College Kensington. Currently, she is involved in lecturing and tutoring undergraduate and graduate students and supervising graduate Thesis. She has abundant publications in the area of molecular genetics that have been cited over 150 times. She has participated as an active member in many international scientific associations. She acted as a potential Reviewer for many journals and received several certificates of excellence in reviewing scientific articles. She also received a number of awards for best presentations and outstanding work in regional and international conferences.

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