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Crosstalk between endoplasmic reticulum stress and oxidative stress in the progression of diabetic nephropathy

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Abstract

Increasing evidence in substantiating the roles of endoplasmic reticulum stress, oxidative stress, and inflammatory responses and their interplay is evident in various diseases. However, an in-depth mechanistic understanding of the crosstalk between the intracellular stress signaling pathways and inflammatory responses and their participation in disease progression has not yet been explored. Progress has been made in our understanding of the cross talk and integrated stress signaling network between endoplasmic reticulum stress and oxidative stress towards the pathogenesis of diabetic nephropathy. In this present study, we studied the crosstalk between the endoplasmic reticulum stress and oxidative stress by understanding the role of protein disulfide isomerase and endoplasmic reticulum oxidase 1α, a key player in redox protein folding in the endoplasmic reticulum. We had recruited a total of 90 subjects and divided into three groups (control (n = 30), type 2 diabetes mellitus (n = 30), and diabetic nephropathy (n = 30)). We found that endoplasmic reticulum stress markers, activating transcription factor 6, inositol-requiring enzyme 1α, protein kinase RNA-like endoplasmic reticulum kinase, C/EBP homologous protein, and glucose-regulated protein-78; oxidative stress markers, thioredoxin-interacting protein and cytochrome b-245 light chain; and the crosstalk markers, protein disulfide isomerase and endoplasmic reticulum oxidase-1α, were progressively elevated in type 2 diabetes mellitus and diabetic nephropathy subjects. The association between the crosstalk markers showed a positive correlation with endoplasmic reticulum stress and oxidative stress markers. Further, the interplay between endoplasmic reticulum stress and oxidative stress was investigated in vitro using a human leukemic monocytic cell line under a hyperglycemic environment and examined the expression of protein disulfide isomerase and endoplasmic reticulum oxidase-1α. DCFH-DA assay and flow cytometry were performed to detect the production of free radicals. Further, phosphorylation of eIF2α in high glucose-exposed cells was studied using western blot. In conclusion, our results shed light on the crosstalk between endoplasmic reticulum stress and oxidative stress and significantly contribute to the onset and progression of diabetic nephropathy and therefore represent the major therapeutic targets for alleviating micro- and macrovascular complications associated with this metabolic disturbance. Graphical abstract.

Keywords: Crosstalk; Diabetic nephropathy; ER oxidase 1α; Endoplasmic reticulum stress; Oxidative stress; Protein disulfide isomerase.

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