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Elevated expression of O-GlcNAc-modified proteins and O-GlcNAc transferase in corneas of diabetic Goto-Kakizaki rats.

Akimoto Y, Kawakami H, Yamamoto K, Munetomo E, Hida T, Hirano H.

Department of Anatomy, Kyorin University School of Medicine, Mitaka, Tokyo, Japan. yakimoto@kyorin-u.ac.jp

Abstract

PURPOSE: The hexosamine biosynthetic pathway is one of the possible mechanisms involved in diabetic keratopathy. The purpose of this study was to examine the role of O-glycoside-linked N-acetylglucosamine (O-GlcNAc) modification of proteins in the pathogenesis of diabetic keratopathy in the Goto-Kakizaki (GK) rat, which has spontaneous development of diabetes.

METHODS: An anti-O-GlcNAc antibody, an anti-O-GlcNAc transferase antibody, and digoxigenin (DIG)-labeled cRNA probes were used to examine the localization of O-GlcNAc-modified proteins, O-GlcNAc transferase protein and mRNA in the corneas of diabetic GK rats and in those of nondiabetic Wistar rats. The corneas from Wistar rats were organ cultured in control medium or in medium containing 100 micro M O-(2-acetamide-2-deoxy-D-glucopyranosylidene) amino-N-phenyl-carbamate (PUGNAc), an inhibitor of O-GlcNAcase, the enzyme that removes O-GlcNAc from proteins. The morphologic changes were examined by electron microscopy.

RESULTS: In normal corneas, immunoreactive O-GlcNAc and O-GlcNAc transferase were observed in the epithelial, endothelial, and stromal cells. In the diabetic corneas, their immunoreactivities in the epithelium were increased in intensity. Morphologically, the number of hemidesmosomes in the epithelial basal cells was lower than that in those cells from the nondiabetic rats. In some areas, the basement membrane had detached from the epithelial basal cells. The PUGNAc treatment of Wistar rat corneas increased the level of O-GlcNAc immunoreactivity and caused a decrease in the number of hemidesmosomes and the detachment of corneal epithelial cells from the basement membrane.

CONCLUSIONS: The elevated expression of O-GlcNAc-modified proteins and O-GlcNAc transferase may play a causative role in the corneal epithelial disorders of diabetic GK rats.

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