mTOR-dependent dysregulation of autophagy in diabetic retinopathy

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Abstract

Diabetic retinopathy (DR) is a severe ocular complication of diabetes mellitus, affecting over 400 million adults worldwide and causing blindness in millions of them. Neurodegeneration is an early event in DR pathogenesis, preceding clinically detectable vascular damage. One potential cause of neuronal loss in DR is the dysregulated autophagy. Unfortunately, the mechanisms underlying autophagy dysregulation in DR remain unclear. A new study focused on the role of a central signaling molecule in this process, mTOR (mechanistic target of rapamycin) is a ubiquitous molecule that integrates diverse underlying signals to coordinate biological processes. Using a mouse model of DR, researchers found that mTOR-related proteins were upregulated shortly after diabetes induction but were then downregulated. Diabetes-induced neurodegeneration observed in this study was evaluated by an increase of apoptosis markers and a decrease in the total cell number. Insulin-independent glycemic control restored the regulation of mTOR and glucose transporter 1 (GLUT1) and decreased the quantity of autophagic and apoptotic proteins. Blocking autophagy using an mTOR activator, MHY1485, had a protective effect on ganglion cells. These results shed light on the mechanisms of neurodegeneration through the hyperglycemia/mTOR/autophagy/apoptosis pathway.