

Title: Excessive activation of autophagy aggravated oxidative stress-induced apoptosis of trabecular meshwork cells though inhibiting p62-Nrf2 pathway

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Apoptosis of trabecular meshwork cells (TMCs) is the cellular basis of glaucoma, although its specific mechanism is not fully understood. We collected trabecular meshwork tissues from healthy donor eyes, and observed increased level of autophagy in apoptotic TMCs, especially in elder healthy donors. In cultured human TMCs, autophagy was triggered by low dose of oxidative stress (50μM H_2O_2). After prolonged exposure to strong oxidative stress (200μM H_2O_2), autophagy was further enhanced with exhaustion of SQSTM1/p62 protein and decreased cell viability. Ablation of autophagy-related gene 7 (ATG7) or overexpression of autophagy adaptor protein p62 effectively reduced the oxidative stress-induced TMCs apoptosis. By RNA sequencing analysis, we found that Nrf2 pathway was activated after ATG7 knockout (ATG7-KO). To evaluate the role of Nrf2 pathway in oxidative stress-induced TMCs apoptosis, we knocked down the expression of p62 protein in ATG-KO TMCs using the lentiviral shRNA system, and observed less Nrf2 phosphorylation and decreased expression of its downstream antioxidative genes, as well as lower cell viability with H_2O_2 treatment. Moreover, knockdown of Nrf2 expression in ATG-KO TMCs would aggravate oxidative stress-induced cell apoptosis. We conclude that oxidative stress would induce excessive activation of autophagy, and lead to TMCs apoptosis by inhibiting the p62-Nrf2 signaling pathway.

Biography

Qin He has completed her MD at the age of 26 years from Zhejiang University and postdoctoral studies from Zhejiang University School of Medicine. She is an ophthalmologist in the First Affiliated Hospital of Zhejiang University. She has published 6 papers in ophthalmology field.

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