Cadmium toxicity toward autophagy through ROS-activated GSK-3b in mesangial cells

施純明

Wang SH;Shih YL;Kuo TC;Ko WC;Shih CM

摘要.

Abstract

We previously demonstrated that cadmium (Cd) is able to induce autophagic cell death through a calcium-extracellular signal-regulated kinase pathway. Here, the object of this study is to investigate the role of glycogen synthase kinase-3beta (GSK-3beta) in the induction of autophagy. After treatment with Cd, MES-13 mesangial cells were determined to have undergone autophagy based on the formation of acidic vesicular organelles and autophagosomes as well as on the processing of microtubule-associated protein 1 light chain 3, using flow cytometry with acridine orange staining, electron microscopy, and immunoblot, respectively. Use of the GSK-3beta inhibitor SB 216763 or the small interfering RNA technique to knockdown the expression of GSK-3beta resulted in a decrease of Cd-induced autophagy. In contrast, overexpression of GSK-3beta by transient transfection potentiated Cd toxicity toward the mesangial cells, suggesting that GSK-3beta plays a crucial role in regulating Cd-induced autophagy. Moreover, a decrease of the phosphorylated level at Ser9 of GSK-3beta was observed by immunoblot after treatment with Cd, indicating GSK-3beta was activated by Cd. This phenomenon was reversed by the reactive oxygen species (ROS) scavenger N-acetylcysteine (NAC), demonstrated that ROS might activate GSK-3beta. In fact, intracellular hydrogen peroxide (H2O2) was 2.6-fold elevated after 3 h of exposure to Cd. Both Cd-induced ROS bursts and autophagy were reduced by NAC and vitamin E. In summary, this study demonstrated that, in MES-13 mesangial cells, Cd-induced autophagy was mediated through the ROS-GSK-3beta signaling pathway. 10.1093/toxsci/kfn266