331

Vanadate Induces cell Growth arrest through MAPKs and Reactive Oxygen Species

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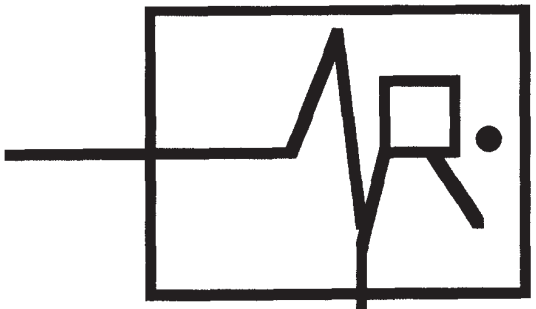
Cell growth arrest is an important mechanism in maintaining genomic stability and integrity in response to environmental stress. Using human lung epithelial cell line, A549, the present study investigates the role of reactive oxygen species (ROS) and ERK and p38 protein kinase in vanadate-induced cell growth arrest. Exposure of the cells to vanadate led to cell growth arrest at G_2/M phase and caused up-regulation of p21 and phospho-cdc2 and degradation of cdc25C. Vanadate activated phosphorylation of ERK and p38. PD98059 and SB202190 not only decreased phosphorylation of ERK and p38 activated by vanadate, also inhibited vanadate-induced G_2/M arrest, up-regulation of p21 and cdc2 and degradation of cdc25C. Cellular reduction of vanadate generated hydroxyl radical as determined by electron spin resonance (ESR) and superoxide radical and hydrogen peroxide as determined by flow cytometry and confocal microscopy in combination with specific antioxidant enzymes, superoxide dismutase and catalase. Among ROS generated by cellular reduction of vanadate, both hydroxyl radical and hydrogen peroxide play an important role in vanadate-induced activation of ERK and p38, up-regulation of p21 and phospho-cdc2, and degradation of cdc25C. These results suggest that cellular reduction of vandate generates hydroxyl radical and hydrogen peroxide via superoxide anion as an intermediate. ROS activate ERK and p38, which in turn up-regulate p21 and cdc2 and cause degradation of cdc25C leading to cell growth arrest at G_2/M phase. ROS affect different MAPK family members and cell growth regulatory proteins with different potencies.



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