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Cadmium induces matrix metalloproteinase-9 expression via NADPH oxidase/ROS-dependent EGFR signals in human endothelial cells

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Cadmium, a widespread cumulative pollutant is a known human carcinogen associated with inflammation and tumor. Matrix metalloproteinase-9 (MMP-9) plays a pivotal role in inflammatory reaction and tumor metastasis, however, the mechanisms underlying MMP-9 expression induced by cadmium remains obscure in human endothelial cells. Here, cadmium elevated MMP-9 expression and enzyme activity as well as MMP-9 promoter-driven luciferase activity in a dose and time dependent manner in ECV304 human endothelial cells. Moreover, cadmium activated phosphorylation of EGFR, Akt, Erk1/2, JNK1/2, P38MAPK and promoted NF- κ B and AP-1 binding. Specific inhibition and mutagenesis study shows that EGFR, Akt, Erk1/2, JNK1/2 and transcription factor NF- κ B and AP-1 were related to cadmium-induced MMP-9 expression in ECV304 cells. Akt and MAPKs (Erk1/2 and JNK1/2) functioned as upstream signaling molecules in the activation of NF- κ B and AP-1 respectively. Furthermore, Cadmium increased ROS production and the ROS-producing NADPH oxidase. Cadmium translocates p47phox, a key subunit of NADPH oxidase to the cell membrane. The exogenous H₂O₂ increased MMP-9 mRNA expression. And that, inhibition of ROS by ROS scavenger (NAC) or NADPH oxidase inhibitor (DPI) attenuated EGFR, Akt, MAPKs(Erk1/2, JNK1/2, p38 MAPK) activation and MMP-9 expression. Likewise, inhibition of EGFR phosphorylation prevented the activation of AKT, MAPKs (Erk1/2, P38 MAPK). Finally, ECV304 cells treated with cadmium displayed markedly invasiveness which was partially abrogated by MMP-9 neutralizing antibodies. These results demonstrated that cadmium induces MMP-9 expression via NADPH oxidase/ROS-dependent EGFR/Akt NF- κ B and EGFR/MAPKs (Erk1/2, JNK1/2)/AP-1 signaling pathways and in turn stimulates invasiveness in human endothelial ECV304 cells. These findings provide further insight into the molecular mechanisms in the carcinogenesis effect of cadmium.

Biography

Young Do Jung MD, PhD has completed his degree at the age of 26 years from Chonnam National University, Korea and Postdoctoral studies from MD Anderson Cancer Center, TX. He is a Vice Dean of from Chonnam National University Medical School. He has published more than 60 papers in reputed journals and has been serving as an Editorial Board Member of repute.

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