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Induction of miR-21 Expression by Freshly Fractured Silica Involves ROS-Mediated ERK Pathway

Min Ding[1], **Lichao Hou**[1], **Linda Bowman**[1], **Terence Meighan**[1], **Tabatha Settle**[1] **and Jun Liu**[2]

[+] Author Affiliations

Abstract

Silica particles are considered to be fibrogenic agents and established carcinogens, but the mechanisms for disease initiation and progression are not well understood. Earlier studies demonstrated that the tumor suppressor gene, PDCD4, and its upstream regulator, miR-21, may be considered as oncogenes for novel cancer prevention or anti-cancer therapies. The present study examined the alterations of miR-21-PDCD4 signaling in JB6 cells after exposure to freshly fractured silica particles. The results showed that (1) silica caused PDCD4 inhibition in JB6 cells; (2) exposure of cells to silica caused a significant increase of miR-21 expression and decrease of PDCD4 expression; (3) inhibition of ERKs or p38 with U0126 or SB 203580 reversed silica-induced PDCD4 inhibition; and (4) ROS scavengers, N-acetyl-L-cysteine, reversed the inhibitory effect of silica on PDCD4 expression; (5) chronically exposed human lung epithelial BEAS-2B or JB6 cells to low-dose silica resulted in neoplastic transformation assayed by soft agar. These findings demonstrate that freshly fractured silica particles induce miR-21 expression and PDCD4 inhibition, which may be mediated through ROS and ERK pathways. Unraveling the complex mechanisms associated with these events may provide insights into the initiation and progression of silica-induced carcinogenesis.