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Title: Prx1 modulates the chemosensitivity of lung cancer to docetaxel through suppression of FOXO1-induced apoptosis

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Body: The level of Prx1, a major 2-Cys peroxiredoxin family member, is frequently elevated in several human cancers, including lung cancer, and this may confer increased resistance to treatment. Although Prx1 suppresses radiation-induced c-Jun NH_2-terminal kinase (JNK) activation and apoptosis in non-small cell lung cancer (NSCLC), the precise mechanism of chemoresistance is not yet clear. In this study, we investigated the role of Prx1 in docetaxel-induced apoptosis in A549 lung cancer cells. We generated shRNA targeting Prx1 in A549 cells to test the sensitivity to docetaxel treatment. The effects of docetaxel on the growth of scrambled- and shPrx1-infected A549 xenograft tumors in nude mice were measured. We found that Prx1 knockdown resulted in enhanced docetaxel-induced cytotoxicity in a dose-dependent fashion. In vivo, the growth rate of shPrx1-infected A549 tumors was significantly reduced compared to that of scrambled shRNA-infected A549 tumors. Prx1 knockdown also augmented the inhibitory effects of docetaxel on tumor growth. In addition, Prx1 knockdown increased apoptotic potential through activation of the caspase cascade and suppressed docetaxel-induced phosphorylation of Akt and its substrate forkhead box O1 (FOXO1). Moreover, treatment with the phosphatidylinositol 3-kinase (PI3K) inhibitor LY294002 reduced the phosphorylation of FOXO1 and increased the cytotoxicity of docetaxel in A549 cells. Our findings suggest that Prx1 may modulate the chemosensitivity of lung cancer to docetaxel through suppression of FOXO1-induced apoptosis.