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APE/Ref-1, a druggable target for the therapy of human melanoma

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Human malignant melanoma exhibits impaired redox status and abnormal redox-regulated signal pathways. Induced as an adaptive response to reactive oxygen species (ROS) and reactive nitrogen species (RNS), a multi-functional protein called APE/Ref-1 serves as a redox chaperone and modulator of many nuclear transcription factors and for maintaining intracellular redox status. Our previous studies showed that knockdown of APE/Ref-1 significantly sensitized melanoma cells to chemo-treatment and reduced metastatic potential markedly. In this study, we further characterized the role of APE/Ref-1 in the invasive properties of human melanoma. Two function-deficient Ref-1 constructs were stably transfected into melanoma cells; further studies with Scratch Migration and Matrigel assays showed that both ΔNLS-Ref-1 and RedoxD-Ref-1 markedly decreased migration and invasive c-apacity. Matrix metalloproteinase (MMP)-1 mRNA levels were also significantly reduced in transfectants, which was reversed by APE/Ref-1 cDNA overexpression.

In addition, nitric oxide (NO) stress induced by DETA (NO donor) treatment was associated with enhanced invasion potential of melanoma cells, which was significantly reversed by APE/Ref-1 depletion. These results suggest that specific and potent inhibitors targeting APE/Ref-1 should be explored for therapeutic potential. Accordingly, through 3-D modeling and virtual docking, we successfully screened compounds from 35 chemical vendors (total number of compounds is more than 7 millions) and synthesized a specific APE/Ref-1 inhibitor (#598-21) with IC50 below 1 μM, which also significantly reduced the invasion of metastatic melanoma Lu1205 cells. Taken this molecule as a lead compound, we are screening and synthesizing more potent inhibitors with enhanced anti-melanoma activities.