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Authors
Yang, S
Zheng, ZI
Misner, B
et al.

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APE/Ref-1, a druggable target for the therapy of human melanoma
S. Yang, Z. I. Zheng, B. Misner, R. Chamberlin, F. L. Meyskens
University of California, Irvine, Orange, CA, USA

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 capacity. 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.