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

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Abstract 1937: APE/Ref-1, a drugable target for the therapy of human melanoma

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Abstract

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. 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 redox activity of APE/Ref-1 should be explored for therapeutic potential. Utilizing 3-dimensional modeling and virtual docking, we have screened compounds from 35 chemical vendors with total number of more than 7 million. Through extensive chemical modifications of our top ranked candidates, we have successfully synthesized novel APE/Ref-1 inhibitors (#598-5, #598-21, and #598-24) showing significant inhibition on the redox activity of APE/Ref-1. Notably, #598-21 exhibited promising anti-melanoma activities with IC_{50} below 1 μM. In addition, our studies have also identified two leading compounds whose mechanism of inactivation of APE/Ref-1 is due to the oxidation of APE/Ref-1 protein itself. Taking these molecules as lead compounds, we are evaluating their in vivo anti-tumor efficacies and synthesizing more potent inhibitors with enhanced activities.

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