Inhibition of Ape1's DNA Repair Activity as a Target in Cancer: Identification of Novel Small Molecules that have Translational Potential for Molecularly Targeted Cancer Therapy

Inhibition of Ape1's DNA Repair Activity as a Target in Cancer: Identification of Novel Small Molecules that have Translational Potential for Molecularly Targeted Cancer Therapy

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Abstract:

The DNA Base Excision Repair (BER) pathway repairs DNA damaged by endogenous and exogenous agents including chemotherapeutic agents. Removal of the damaged base by a DNA glycosylase creates an apurinic / apyrimidinic (AP) site. AP endonuclease1 (Ape1), a critical component in this pathway, hydrolyzes the phosphodiester backbone 5′ to the AP site to facilitate repair. Additionally, Ape1 also functions as a redox factor, known as Ref-1, to reduce and activate key transcription factors such as AP-1 (Fos/Jun), p53, HIF-1α and others. Elevated Ape1 levels in cancers are indicators of poor prognosis and chemotherapeutic resistance, and removal of Ape1 via methodology such as siRNA sensitizes cancer cell lines to chemotherapeutic agents. However, since Ape1 is a multifunctional protein, removing it from cells not only inhibits its DNA repair activity but also impairs its other functions. Our hypothesis is that a small molecule inhibitor of the DNA repair activity of Ape1 will help elucidate the importance (role) of its repair function in cancer progression as wells as tumor drug response and will also give us a pharmacological tool to enhance cancer cells′ sensitivity to chemotherapy. In order to discover an inhibitor of Ape1′s DNA repair function, a fluorescence-based high-throughput screening (HTS) assay was used to screen a library of drug-like compounds. Four distinct compounds (AR01, 02, 03 and 06) that inhibited Ape1′s DNA repair activity were identified. All four compounds inhibited the DNA repair activity of purified Ape1 protein and also inhibited Ape1′s activity in cellular extracts. Based on these and other in vitro studies, AR03 was utilized in cell culture-based assays to test our hypothesis that inhibition of the DNA repair activity of Ape1 would sensitize cancer cells to chemotherapeutic agents. The SF767 glioblastoma cell line was used in our assays as the chemotherapeutic agents used to treat gliobastomas induce lesions repaired by the BER pathway. AR03 is cytotoxic to SF767 glioblastoma cancer cells as a single agent and enhances the cytotoxicity of alkylating agents, which is consistent with Ape1′s inability to process the AP sites generated. I have identified a compound, which inhibits Ape1′s DNA repair activity and may have the potential in improving chemotherapeutic efficacy of selected chemotherapeutic agents as well as to help us understand better the role of Ape1′s repair function as opposed to its other functions in the cell.

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