Abstract

Targeting OGG1 as a Novel Anti-Cancer Strategy†

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Due to oncogene expression and altered metabolism, reactive oxygen species (ROS) production is augmented in cancer cells resulting in oxidative DNA damage. 8-oxoguanine (8-oxoG) is one of the most abundant oxidative DNA lesions. This premutagenic lesion is eliminated from duplex DNA by 8-Oxoguanine DNA Glycosylase (OGG1), a key player in the base excision repair (BER) pathway. Here, we validate OGG1 as a potential anti-cancer target. OGG1 depletion impairs the growth of A3 T-cell lymphoblastic acute leukemia both in vitro and in vivo, but is well tolerated in non-transformed immortalized cells1. To further validate our findings, we developed TH5487, a potent small-molecule inhibitor that targets OGG1’s active site [1,2]. We show that TH5487 suppresses the growth of a wide range of tumor cells, with a favorable therapeutic index compared to non-transformed cells [1]. Mechanistically, TH5487 treatment inhibits the repair of potassium bromate-induced 8-oxo(d)G lesions, affects OGG1-chromatin dynamics, and hinders OGG1 recruitment to DNA damage regions [3]. Importantly, TH5487 induces replication stress and proliferation arrest1. This study presents a novel mechanistic strategy to exploit ROS elevation in cancer by inhibiting OGG1.

References:


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