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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 cells[1]. 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 arrest[1]. This study presents a novel mechanistic strategy to exploit ROS elevation in cancer by inhibiting OGG1.

References:

1. Visnes, T.; Benítez-Buelga, C.; Cázares-Körner, A.; Sanjiv, K.; Hanna, B.M.; Mortusewicz, O.; Rajagopal, V.; Albers, J.J.; Hagey, D.W.; Bekkhus, T. et al. Targeting OGG1 arrests cancer cell proliferation by inducing replication stress. *Nucleic acids research* **2020**; *48*, 12234–12251.
2. Visnes, T.; Cázares-Körner, A.; Hao, W.; Wallner, O.; Masuyer, G.; Loseva, O.; Mortusewicz, O.; Wiita, E.; Sarno, A.; Manoilov, A. et al. Small-molecule inhibitor of OGG1 suppresses proinflammatory gene expression and inflammation. *Science* **2018**, *362*, 834–839.

3. Hanna, B.M.F.; Helleday, T.; Mortusewicz, O. OGG1 inhibitor TH5487 alters OGG1 chromatin dynamics and prevents incisions. *Biomolecules* **2020**, *10*, 1–10.

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