ATM regulates 3-methylpurine-DNA glycosylase and promotes therapeutic resistance to alkylating agents.

Agnihotri S¹, Burrell K¹, Buczkwicz P¹, Remke M¹, Golbourn B¹, Chornenkyy Y¹, Gajadhar A², Fernandez NA¹, Clarke ID¹, Barsczyk MS¹, Pajovic S¹, Ternamian C¹, Head R¹, Sabha N¹, Sobol RW³, Taylor MD¹, Rutka JT¹, Jones C⁴, Dirks PB¹, Zadeh G⁵, Hawkins C⁶.

Abstract
Alkylating agents are a first-line therapy for the treatment of several aggressive cancers, including pediatric glioblastoma, a lethal tumor in children. Unfortunately, many tumors are resistant to this therapy. We sought to identify ways of sensitizing tumor cells to alkylating agents while leaving normal cells unharmed, increasing therapeutic response while minimizing toxicity. Using an siRNA screen targeting over 240 DNA damage response genes, we identified novel sensitizers to alkylating agents. In particular, the base excision repair (BER) pathway, including 3-methylpurine-DNA glycosylase (MPG), as well as ataxia telangiectasia mutated (ATM), were identified in our screen. Interestingly, we identified MPG as a direct novel substrate of ATM. ATM-mediated phosphorylation of MPG was required for enhanced MPG function. Importantly, combined inhibition or loss of MPG and ATM resulted in increased alkylating agent-induced cytotoxicity in vitro and prolonged survival in vivo. The discovery of the ATM-MPG axis will lead to improved treatment of alkylating agent-resistant tumors.

SIGNIFICANCE: Inhibition of ATM and MPG-mediated BER cooperate to sensitize tumor cells to alkylating agents, impairing tumor growth in vitro and in vivo with no toxicity to normal cells, providing an ideal therapeutic window.

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Sameer Agnihotri 2014 Aug 19 1:34 p.m. 1 of 2 people found this helpful
Dear Dr. Li, the uncorrected proof is currently online. Figure 7 will be corrected soon for the final edited version. Thank you for your observation.

Mengxia Li 2014 Aug 11 11:17 p.m. 1 of 1 people found this helpful
In Figure 7, the authors listed LIG4 as BER gene by mistake which is not a typical BER gene and functioning in NHEJ.