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Abstract 5723: Inactivation of DNA repair triggers neoantigen generation and impairs tumor growth

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Abstract

Colorectal, ovarian, endometrial and other tumors carrying defects in DNA mismatch repair often show favorable prognosis and indolent progression. The genomes of these tumors bear hundreds of thousands of somatic mutations, a feature which fosters cancer progression and might lead to rapid evolution of resistance to targeted therapies. Recent evidences that a subset of MSI (microsatellite instable) tumors respond prominently to immune checkpoint blockade led to the hypothesis that the presence of high number of somatic mutations may be responsible for effective immune-surveillance. However, several reports indicate that a relevant fraction of hyper-mutated tumors have unfavorable prognosis and do not respond to immune-modulators. To understand the molecular and functional bases of response to immune checkpoint inhibitors, we genetically inactivated MutL homolog 1 (MLH1) in colorectal, breast and pancreatic mouse cancer cells. The growth of MMR deficient cells was comparable to their proficient counterparts in vitro and upon transplantation in immune-compromised mice. However, isogenic MMR deficient cancer cells, acquiring alterations over time, were unable to form tumors when injected subcutaneously or orthotopically in syngeneic mouse models according to cell-passage number. Moreover, we found that MMR-driven dynamic generation of neoantigens, when restricted to a clonal population, further increases immune detection. Mechanistically, MLH1 inactivation increased the mutational burden and led to dynamic mutational profiles, resulting in persistent renewal of neoantigens in vitro and in vivo, while control cells exhibited stable mutational loads and neoantigen profiles over time. These results led us hypothesize that enforced increase of the number of mutations in cancer cells could restrict cancer growth and might be beneficial for therapeutic purposes. We therefore performed a pharmacological screen to identify agents capable of permanent inactivation of MMR in colorectal, breast and PDAC cancer cells. We found that temozolomide triggers MLH1 inactivation in cancer cells that -as a result- are unable to form tumors in syngeneic animals. Genomic analysis of temozolomide resistant cells revealed that fluctuating levels of neoantigens, rather than the absolute number of mutations, might be critical to provoke immune surveillance. Overall, these results provide the rationale for developing innovative anticancer therapies based on inhibition of DNA repair mechanisms.

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