*Nature Reviews Clinical Oncology* | Published online 19 Dec 2017; doi:10.1038/nrclinonc.2017.203

IMMUNOTHERAPY

# dMMR presents opportunities to enhance immunotherapy

Tumours with DNA mismatch repair deficiency (dMMR) often develop and progress rapidly, but are paradoxically associated with a favourable prognosis. Such tumours are also particularly responsive to immune-checkpoint blockade, as underscored by the recent histology-agnostic approval of pembrolizumab for the treatment of dMMR tumours. The functional basis of these clinical observations remains unclear, but has been hypothesized to reflect an increased mutation rate that results in the generation of neoantigens by, and thus improved immunosurveillance of, dMMR cancer cells. New data from a preclinical study support the validity of this theory.

In this study, Alberto Bardelli and colleagues induced dMMR in mouse colorectal, breast, and pancreatic cancer cell lines by inactivating *Mlh1*, the MMR gene that is most frequently altered in colorectal cancers. Despite having similar growth kinetics to their MMR-proficient counterparts *in vitro* and in immunocompromised mice, the dMMR cells grew poorly when implanted in immunoproficient syngeneic mice. "We found that inactivation of dMMR increased mutability and concomitantly augmented the neoantigen burden that dynamically evolved over time," Bardelli explains. By contrast, the mutational load and neoantigen profile of the MMR-proficient cells remained stable. Accordingly, tumours comprising dMMR cells, but not their parental counterparts, effectively triggered immunosurveillance and regressed in response to immune-checkpoint inhibition in mice. "Overall, our results suggest that dMMR causes a dynamic hypermutation status that leads to continuous generation of neoantigens in tumours, which improves immune surveillance," Bardelli summarizes.

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He proposes several ways to translate these observations into improved clinical outcomes: "one could aim to turn an immunologically 'cold' tumour into a 'hot' one by triggering the emergence of neoantigens. Initially, we will look to do so by repurposing drugs that might trigger dMMR, such as temozolomide." Interestingly, the effects of *Mlh1* knockout were recapitulated in mouse tumours with acquired resistance to temozolomide. "Ultimately, however, one can envision strategies to directly target MLH1 or other proteins involved in DNA repair, many of which have enzymatic activity that can be inhibited pharmacologically," Bardelli concludes.

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**ORIGINAL ARTICLE** Germano, G. *et al.* Inactivation of DNA repair triggers neoantigen generation and impairs tumour growth. *Nature* **552**, 116–120 (2017)