POLE proofreading mutation, immune response and prognosis in endometrial cancer

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ABSTRACT
Endometrial cancers (ECs) with POLE proofreading mutations are typified by ultramutation and excellent prognosis. We investigated whether these were related, and found that POLE-mutant ECs display a robust T cell response that corresponds to an enrichment of antigenic tumor neopeptides. Enhanced immunogenicity may explain the favorable outcome of POLE-mutant ECs.

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The proofreading exonuclease activity intrinsic to the replicative DNA polymerases epsilon and delta (Pols ε and δ) is essential to maintain fidelity of DNA replication and prevent mutagenesis. While a role for defective polymerase proofreading in human cancer has long been postulated, this has only recently been confirmed, with the demonstration that germline mutations in the exonuclease domains of POLE and POLD1 (which encode the principal subunits of Pols ε and δ respectively) predispose to cancer. Subsequently, we and others have shown that somatic POLE proofreading mutations occur in 7–12% ECs, 1–2% colorectal cancers (CRCs), as well as cancers of the brain, stomach and pancreas (TCGA unpublished, http://www.cbioportal.org, accessed June 2015). In keeping with the essential contribution of polymerase proofreading to replication fidelity, POLE proofreading-mutant ECs are ultramutated. However, perhaps less predictably, they also have an excellent prognosis. We hypothesized that these two characteristics may be related—more specifically, that tumor neopeptides caused by ultramutation may stimulate a cytolytic immune response, analogous to previous observations in hypermutated mismatch repair-deficient CRCs. In a recent study, we investigated this in two large EC cohorts.

Following the observation that POLE proofreading-mutants had a higher density of tumor-infiltrating lymphocytes (TILs) than other ECs, we confirmed that this represented a CD8+ cytotoxic T cell infiltrate likely to be capable of cytolytic activity, as evidenced by co-staining for the activation marker TIA-1. Consistent with these data, examination of RNAseq data from the independent TCGA EC series confirmed significant enrichment for immune-related pathways and a highly specific 200-gene tumor T cell infiltration signature in POLE proofreading-mutant ECs. This analysis also demonstrated that POLE-mutant tumors displayed significantly increased expression of CD8A (gene) and other T cell cytotoxic differentiation and effector markers known to predict favorable outcome in cancer, including T-bet, Eomes, IFNγ, perforin and granzymes B, H, K and M. Using a bio-informatic approach to investigate the possible contribution of antigenic tumor neopeptides to the antitumor immune response, we found that POLE proofreading-mutant ECs were predicted to display substantially more antigenic peptides than other ECs, providing a potential explanation for our findings.

Taken together, our data suggest that enhanced immunogenicity contributes to the excellent prognosis of POLE proofreading-mutant ECs, and are concordant with a recent study, which showed that dendritic cells pulsed by POLE-mutant tumor lysates stimulated greater CD4+ and CD8+ cell proliferation than those pulsed by ECs lacking POLE mutations. However, this begs the question of why POLE-mutant ECs are not eliminated by this enhanced cytotoxic T cell response? We found no evidence of an increased frequency of loss of HLA class I protein expression in POLE-mutant ECs, and functional mutations in the antigen presentation machinery also appeared relatively uncommon (2 of 18 cases). In contrast, we found striking increases in the expression of immunosuppressive checkpoint molecules and Treg markers, including LAG3, TIM-3, TIGIT, PDL1, CTLA4 and FOXP3, in POLE-mutant ECs, suggesting that this may be the principal mechanism of immune evasion in these tumors.

In short, our data suggest that POLE proofreading-mutant ECs evoke a striking antitumor immune response, which is likely to contribute at least partly to their excellent prognosis (Fig. 1). In addition to validating our results in further independent EC series, it will be important to determine whether an enhanced cytotoxic T cell reaction also occurs in other POLE proofreading-mutant cancers. Interestingly, recent data suggest this may be the case in glioblastomas. Given the association between benefit from immune checkpoint inhibitors and tumor mutation burden, our study also suggests that the few patients with advanced or recurrent POLE proofreading-mutant cancers may be promising candidates for these agents. Finally, a pressing question is why some POLE-mutant tumors do not appear to stimulate as potent an immune reaction as others? Is it simply that these tumors are less mutated? Or do they harbor novel mechanisms of immune escape? Thus, while much remains unknown, further study of POLE-mutant
cancers may provide insights into antitumor immune response and evasion that are generalizable more broadly, with potential benefits for a wide range of cancer patients.

Disclosure of potential conflicts of interest

No potential conflict of interest was disclosed.

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