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Neutrophils are associated with resistance to anti-PD-1 monotherapy in mismatch repair-deficient tumors

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Background

Clinical studies have highlighted the efficacy of anti-PD-1 (αPD-1) treatment in patients with hypermutated tumors deficient in DNA mismatch repair (MMRD). However, the responsiveness of MMRD tumors to αPD-1 treatment is variable, and the cause to explain this variability remains unclear.

Methods

Two mouse tumor cell lines inactivated for *MSH2*, 4T1$^{MSH2-/-}$ and CT26$^{MSH2-/-}$, were generated to recapitulate MMRD phenotype. MSH2$^{-/-}$ cells were serially passaged *in vitro* to increase insertion/deletion mutational load which was assessed longitudinally by whole exome sequencing. Mice bearing *MSH2-/-* tumor cells were then treated with αPD-1 or αPD-1+αCTLA-4 plus or minus neutrophil depletion using the αLy6G-depleting antibody. Tumor volume was monitored and immune tumor microenvironments as well as blood neutrophil to lymphocyte ratio (NLR) were determined by flow cytometry. NLR was also evaluated retrospectively in 104 patients diagnosed with MMRD tumors and treated with aPD-(L)1.

Results

While αPD-1 treatment was effective in the CT26$^{MSH2-/-}$ model, no efficacy was observed in the 4T1$^{MSH2-/-}$ even in ultra-mutated 4T1$^{MSH2-/-}$ tumors (>280 mutations/Megabase). Unlike the CT26 model, 4T1 model is characterized by an accumulation of neutrophils. Neutrophils depletion with αPD-1 or the combination αPD-1+αCTLA-4 restored the response to immunotherapy in 4T1$^{MSH2-/-}$ model. Given that the combination treatment was accompanied by a decrease in neutrophils, it is likely that CTLA-4 blockade may hamper the accumulation of neutrophils. Consistent with this, we calculated the percentage of the NLR variation between baseline and two months after anti-PD-(L)1 initiation in 104 patients. Median overall survival was undefined for $\%NLR_{variation}$ <0% and 23.13 months for patients with $\%NLR_{variation}$ >0% ($HR_{logrank}$=0.40; $^{95\%}$IC: 0.18-0.91).

Conclusions

Accumulation of neutrophils is associated with resistance to αPD-1 monotherapy in MMRD tumors. We propose that αPD-1+αCTLA-4 combination may represent an effective strategy in patients with abnormal neutrophil accumulation.

Legal entity responsible for the study

The authors.

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Disclosure

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