Mutations

Major Finding: Microsatellite insertions and deletions generated antigenic mutant proteins shared among patients.

Concept: Common frameshifted peptides were strongly immunogenic, likely due to being presented by MHC-I.

Impact: This work suggests that microsatellite-unstable tumors may be targetable with off-the-shelf vaccines.

FRAMESHIFTS IN MICROSATELLITE-UNSTABLE TUMORS CREATE SHARED NEOANTIGENS

Because microsatellite instability–high (MSI-H) tumors can exhibit frameshift mutations caused by microsatellite expansions and contractions in coding regions of genes, a question of interest is whether MSI-H tumors from different patients may have overlapping neoantigen profiles, making off-the-shelf anticancer vaccines feasible. Roudko, Bozkus, and colleagues examined whole-exome sequencing data from The Cancer Genome Atlas, focusing on patients with colorectal, gastric, or endometrial adenocarcinoma, and found that those with MSI-H tumors had more frameshift mutations on average than those whose tumors did not have high MSI. Additionally, many of the frameshift mutations were expected to produce proteins with shared mutations from patient to patient. Further, the frameshift mutations found in these MSI-H tumors were predicted to affect long enough stretches of amino acid residues in the translated proteins to result in the generation of several new possible epitopes per protein. The identified frameshifted RNAs and the proteins they encode were abundant in cancer cells, indicating that the frameshifted DNA was not epigenetically silenced and that the frameshifted RNAs were not preferentially degraded and were effectively translated. Another analysis showed that frameshifted peptides in the MSI-H cancer cells were capable of being presented by MHC-I on the cell surface, suggesting that they could be detected by the immune system. Correspondingly, T cell–stimulation experiments showed that the frameshifted peptides were highly immunogenic to blood mononuclear cells from both healthy donors and patients with MSI-H cancers. Collectively, these findings confirm that MSI-H tumors have neoantigens shared among patients, which may make these cancers particularly suitable candidates for the development of anticancer vaccines. ■

Roudko V, Bozkus CC, Orfanelli T, McClain CB, Carr C, O'Donnell T, et al. Shared immunogenic poly-epitope frameshift mutations in microsatellite unstable tumors. Cell 2020;183:1634–49. E17.

Clinical Trial

Major Finding: In a phase II clinical trial, FLT3 ligand (FLT3L) enhanced immune cell and antibody responses.

Approach: Hematopoietic progenitor–activating FLT3L was used with a dendritic cell–targeting melanoma vaccine.

Impact: This suggests that FLT3L may provide needed aid to anticancer vaccines; larger trials are needed.

FLT3 LIGAND BOOSTS IMMUNE RESPONSE AND MAY ENHANCE ANTICANCER VACCINES

The efficacy of anticancer vaccines has been limited in part by failure to elicit strong immune responses in many patients, which may sometimes be due to lack of engagement of antigen-presenting cells such as dendritic cells (DC). In a phase II, open-label clinical trial, Bhardwaj and colleagues evaluated whether anticancer vaccine efficacy could be enhanced by exogenous FLT3L, a cytokine and growth factor that activates early hematopoietic progenitors, increasing the number of cross-presenting conventional DCs (cDC1 and cDC2) and plasmacytoid DCs (pDC). Sixty patients with resected stage II–IV melanoma and no signs of residual disease were randomized 1:1 to receive the vaccine CDX-1401—which consists of an antibody targeting the DC marker CD205 fused to the tumor-associated antigen NY-ESO-1—plus the immunostimulating TLR3 agonist poly-ICLC with or without exogenous FLT3L pretreatment. Antigen-specific T-cell immunity following vaccination occurred in more FLT3L-treated patients (63%) than non–FLT3L-treated patients (17%) and was of greater magnitude in FLT3L-treated patients on average. Further, antibody responses were more rapid and reached higher titers in FLT3L-treated patients. Consistent with the expected mechanism, FLT3L administration raised numbers of monocytes, DCs (including cDC1s, cDC2s, and pDCs), and natural killer (NK) cells and increased activation of NK cells, DCs, and $CD4^+$ and $CD8^+$ T cells. Transcriptional analyses of peripheral blood mononuclear cells collected at baseline and at 11 additional timepoints during and after treatment from 12 patients who received FLT3L and 11 patients who did not revealed marked gene expression changes over time that were indicative of an immune response in the former group, whereas gene expression in the latter group remained largely unchanged. This study was not statistically powered to detect differences in efficacy between the two groups, so larger trials will be needed to further investigate whether the observed immune responses translate into clinical benefit. In summary, this trial demonstrates that the addition of exogenous FLT3L to an anticancer vaccine can substantially increase the vaccine-induced immune response, with promising implications. ■

Bhardwaj N, Friedlander PA, Pavlick AC, Ernstoff MS, Gastman BR, Hanks BA, et al. Flt3 ligand augments immune responses to anti-DEC-205-NY-ESO-1 vaccine through expansion of dendritic cell subsets. Nat Cancer 2020;1:1204–17.