TTLL8, POTEE, AND PKMYT1 ARE TARGETABLE TUMOR ANTIGENS IN OVARIAN CANCER

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Background High-grade serous ovarian cancer (OC) is the most common and lethal subtype, with a 70% mortality rate and an 85% relapse rate within five years.1 Cancer testes (CT) antigens are tumor-associated antigens with restricted expression in immune-privileged tissues, as well as abnormal expression in cancer.2 This indicates that they can be targeted for their immunogenicity without the risk of toxicity to normal tissue. Currently, few antigens have been validated for OC. We thus hypothesized that the use of immunopeptidomics could reveal novel CT antigens that can be targeted for OC treatment.

Methods Immunopeptidomics was performed with the HLA-A2:01-positive OVCAR-5 cell line, and identified 10,197 peptides corresponding to 5,604 unique proteins. NetMHCcons was used to generate consensus affinity values for each peptide and identified high-confidence HLA-A02:01-restricted peptides. The expression profiles of each protein were analyzed in the Human Protein Atlas database. Tissue microarrays containing 120 patient samples were stained via immunohistochemistry (IHC) to assess tumor expression levels and survival analysis was carried out. Primary human T cell samples were stimulated with peptide candidates and intracellular cytokine staining (IC), tetramer-staining, and T cell killing assays against peptide-pulsed OC cells were performed.

Results We performed immunopeptidomics on an OC cell line that expresses the common HLA-A02:01 haplotype to find possible new tumor antigens that could be used as immunotherapy targets. From this dataset, we identified TTLL8, POTEE, and PKMYT1 peptides as candidate tumor antigens. Using tissue microarrays, TTLL8 was found to be expressed in 60% of OC and was significantly associated with a worse overall prognosis. POTEE was expressed in over 90% of OC patients and had no significant association with survival. Expression of POTEE was increased in OC cell lines by treatment with a DNA methyltransferase inhibitor as is characteristic of many CT antigens. In patient tumor samples, TTLL8-, POTEE-, and PKMYT1-specific CD8 T cell responses were identified by increases in cytokine production and tetramer-positive populations. TTLL8-, POTEE-, and PKMYT1-specific T cells induced tumor cell killing of antigen pulsed OC cells. The use of a blocking antibody targeting MHC class I demonstrated that the T cell-induced killing was dependent on CD8 T cell recognition of antigen.

Conclusions These results suggest that TTLL8, POTEE, and PKMYT1 are good targets for the development of antigen-targeted immunotherapy in OC.

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Ethics Approval This study was approved by the IRB of the Mayo Clinic. The number of the application is 20–001221.

Consent Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.