1147-G  ERV-DERIVED PEPTIDES AS NOVEL IMMUNOTHERAPEUTIC TARGETS IN OVARIAN CANCER

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Background Ovarian cancer is one of the leading cause of cancer-related mortality in women worldwide.1 Due to its frequent late-stage diagnosis, effective treatment remains challenging, underscoring the urgency for novel therapeutic strategies.2 While multiple immunotherapeutic interventions have been explored, their outcomes remain poor, and their efficacy is most likely hampered by the immunosuppressive nature of the ovarian cancer tumor microenvironment, characterized by limited tumor infiltration.3 Understanding and targeting this microenvironment is crucial for the success of immunotherapies. A promising area of interest is the role of endogenous retroviruses (ERVs). Recent evidence suggests transcriptional reactivation of ERVs in different types of cancers, leading to retroviral RNA and protein expression.4,5

Methods and Results Herein, by using the ERVmap tool, we identified, in a large cohort of public available data, a distinct ERV signature in ovarian cancer, which included both ovary-specific and cancer-specific profile. Predictive analysis showed that this mRNA ERV signature could originate thousands of peptides with a spectrum of affinities, ranging from weak to strong, for multiple HLA class I molecules. The functional translation capability of this RNA fragments was then proven by the presence of a small fraction of these peptides on the cell surface bound to HLA class I molecules. HLA class I elution and consequent mass spectrometry analysis of 42 ovarian cancer samples revealed the presence of these ERV-derived peptides, conspicuously absent in normal ovarian tissue (n=15), and with predicted immunogenic properties. Importantly, the promiscuous nature of these peptides, predicted to be presented across diverse HLA class I molecules, augments their application for T-cell based therapies.

Conclusions The identification of immunogenic ERV-derived tumor specific peptides as potential targets offers a promising and exploitable vulnerability in ovarian cancer, opening new avenues for targeted immunotherapy.

REFERENCES

Ethics Approval All human data analyzed in this study is publicly available at TCGA, GTEX, and PRIDE databases.

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