Scientific Foundation SPIROSKI, Skopje, Republic of North Macedonia
South East European Journal of Immunology. 2025 Mar 31; 8(CITIM):029
https://doi.org/10.3889/seejim.2025.6090
eISSN: 1857-9388
Category: *CITIM - Cancer Immunotherapy & Immunomonitoring (CITIM2025)*
Section: *Invited Lectures*

Correlation of the tumor HLA-I expression (with LOH-HLA) with the immune response and clinical outcomes in NSCLC patients after perioperative neoadjuvant chemo-immunotherapy

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Citation: Aptsiauri N, Perea F, Molina-Alejandre M, Garrido F, Provencio M, Ruiz-Cabello F, Cruz-Bermúdez A. Correlation of the tumor HLA-I expression (with LOH-HLA) with the immune response and clinical outcomes in NSCLC patients after perioperative neoadjuvant chemo-immunotherapy. SEE J Immunol. 2025 Mar 27;8(CITIM):029. https://doi.org/10.3889/seejim.2025.6090
Keywords: HLA-I expression; Loss of heterozygosity (LOH-HLA); Neoadjuvant chemo-immunotherapy (CIT); Non-small cell lung cancer (NSCLC); Tumor mutational burden (TMB)
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Received: 22-Fev-2025
Accepted: 25-Mar-2025
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Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

Total or selective loss of tumor antigen presentation caused by the loss of HLA class I (HLA-I) haplotype due to the loss of heterozygosity at chromosome 6 (LOH-HLA) may result in reduced repertoire of antigenic peptides presented to cytotoxic T-cells and is known to facilitate cancer immune evasion. LOH involving HLA genes has been linked to increased resistance to immunotherapy, cancer recurrence and poor survival after treatment with checkpoint blockade therapy. Previous studies have shown that neoadjuvant chemo-immunotherapy (CIT) is effective in NSCLC tumors with low tumor mutational burden (TMB). However, there is no data on perioperative chemo-immunotherapy efficacy or response mechanisms in the context of HLA-I defects.

In the present study, using SNP arrays, we demonstrated that LOH-HLA is a common event in cancer samples with a prevalence of a copy neutral type of LOH (CN-LOH) that affects entire chromosome 6 or 15 and involves chromosomal duplications. LOH-6 and was associated with homozygous HLA genotype and partial loss of HLA-I expression. Moreover, we analyzed the baseline HLA-I expression and LOH-HLA at diagnosis in correlation with the characteristics of the tumor microenvironment (TME) and clinical outcomes in a cohort of 24 patients with NSCLC after perioperative chemo-immunotherapy (nivolumab plus chemotherapy). We integrated HLA-I tumor status with molecular data (PD-L1, TMB, TCR repertoire, TILs populations, bulk RNA-seq, spatial transcriptomics) and clinical outcomes (pathological response and survival data) to study the activity of perioperative CIT considering HLA-I defects.

Baseline LOH and/or decreased HLA protein levels occurred in 41.7% of tumors and were categorized as HLA-deficient status. These tumors showed a “desert”-like tumor microenvironment at baseline, with lower PD-L1 levels and immune cell infiltrate. Despite their “cold” microenvironment, perioperative CIT induced similar complete pathological response rates, as well as 3-year progression-free survival (PFS) and overall survival (OS) rates, in both HLA-deficient and HLA-positive tumors. HLA-deficient tumors had B-cell aggregates forming tertiary lymphoid structures (TLS), CD4+T cells in a close location with HLA class II positive cells, and activated CD8+T cells. These data suggest a positive important role of TLS and the coordinated action of helper and cytotoxic T-cells in tumor rejection. All patients with TMB high and HLA-positive tumors were free of disease progression and alive at 3 years.

In conclusion, our findings highlight the impact of antigen presentation status on the immune microenvironment of NSCLC, and its potential synergy with TMB as a promising prognostic biomarker for long-term survival following perioperative CIT. It can help to unveil a potential response mechanism to be therapeutically enhanced in non-responsive tumors.