XIX CONGRESSO NAZIONALE SIES2026
Firenze | 4-6 marzo 2026
Palazzo degli Affari

XIX Congress of the Italian Society of Experimental Hematology ABSTRACT N. P083

Lymphomas

THE LNCRNA MTAAT REGULATES PD-L1 TRAFFICKING VIA ARF6 IN T-CELL LYMPHOMA: IMPLICATIONS FOR IMMUNOTHERAPY

S. Mallia[1], G. Gambarelli[1|2], M. Zanelli[3], B. Donati[1], D. Fiore[4], I. Tamagnini[3], F. Torricelli[1], P. Di Chiaro[1], F. Reggiani[1], N. Puccio[1], F. Sanguedolce[5], S. Ascani[6], S. Luminari[7], F. Merli[7], A. Neri[8], A. Ciarrocchi[1], V. Fragliasso[1]

[1]Laboratorio di Ricerca Traslazionale dell'AUSL-IRCCS di Reggio Emilia; [2]Medicina Clinica e Sperimentale Ph. D. Program dell'Università di Modena e Reggio Emilia, [3]Unità di Patologia dell'AUSL-IRCCS di Reggio Emilia, [4]Dipartimento di Medicina Molecolare e Biotecnologia Medica dell'Università Federico II, [5]Unità di Patologia Policlinico Università di Foggia, [6]Unità di Patologia dell'Azienda Ospedaliera di Santa Maria di Terni, [7]Unità di Ematologia dell'AUSL-IRCCS di Reggio Emilia, [8]Direzione Scientifica dell'AUSL-IRCCS di Reggio Emilia.

Introduction: Immune checkpoint blockade (ICB) has redefined cancer therapy, including hematologic malignancies. Nevertheless, in T-cell lymphomas, responses to PD-1/PD-L1 inhibitors are unpredictable, ranging from complete remission to disease progression. Understanding molecular mechanisms controlling PD-L1 homeostasis is essential to guide clinical decisions.

Long non-coding RNAs (lncRNAs) regulate immune escape, but their value as clinical biomarkers is still unclear. Having identified the lncRNA MTAAT as a potential biomarker in the stratification of Anaplastic Large Cell lymphoma (ALCL) patients, we investigated its role in modulating PD-L1 localization and its potential as a predictive biomarker for ICB response in ALK-negative (ALK$^-$-ALCL)-ALCL.

Methods: Retrospective ALCL samples were examined for PD-L1 and MTAAT expression. MTAAT was silenced in ALK$^-$-ALCL cells using CRISPR/dCas9-KRAB to study effects on PD-L1 localization, ICB response, and identify regulatory pathways (RNA-seq).

Results: To assess the clinical relevance of PD-L1 in ALCL, we performed PD-L1 immunohistochemistry in 25 ALCL cases (ALK$^-$ n=17; ALK$^+$ n=8). PD-L1 positivity was more heterogeneous ALK$^-$-ALCL compared with ALK$^+$-ALCL (59% vs 77%), often showing mixed membranous and Golgi-like patterns (60%). In ALK$^-$-ALCL, MTAAT expression inversely correlated with PD-L1 localization, identifying MTAAT as a potential regulator of PD-L1 trafficking.

To further explore the role of MTAAT in PD-L1 localization, we silenced MTAAT expression in ALK$^-$-ALCL cell lines, revealing an increase in PD-L1 surface and its localization from the cytoplasm to the membrane.

Moreover, MTAAT depletion restored T-cell activation in co-culture assays and enhanced sensitivity to Nivolumab, highlighting the functional relevance of MTAAT-mediated PD-L1 localization.

Since MTAAT depletion did not alter total PD-L1 levels, we hypothesized a transcriptional control on PD-L1 recycling. RNA-seq analysis and pathway analysis of MTAAT-depleted cells, revealed changes in membrane trafficking and endocytosis pathways.

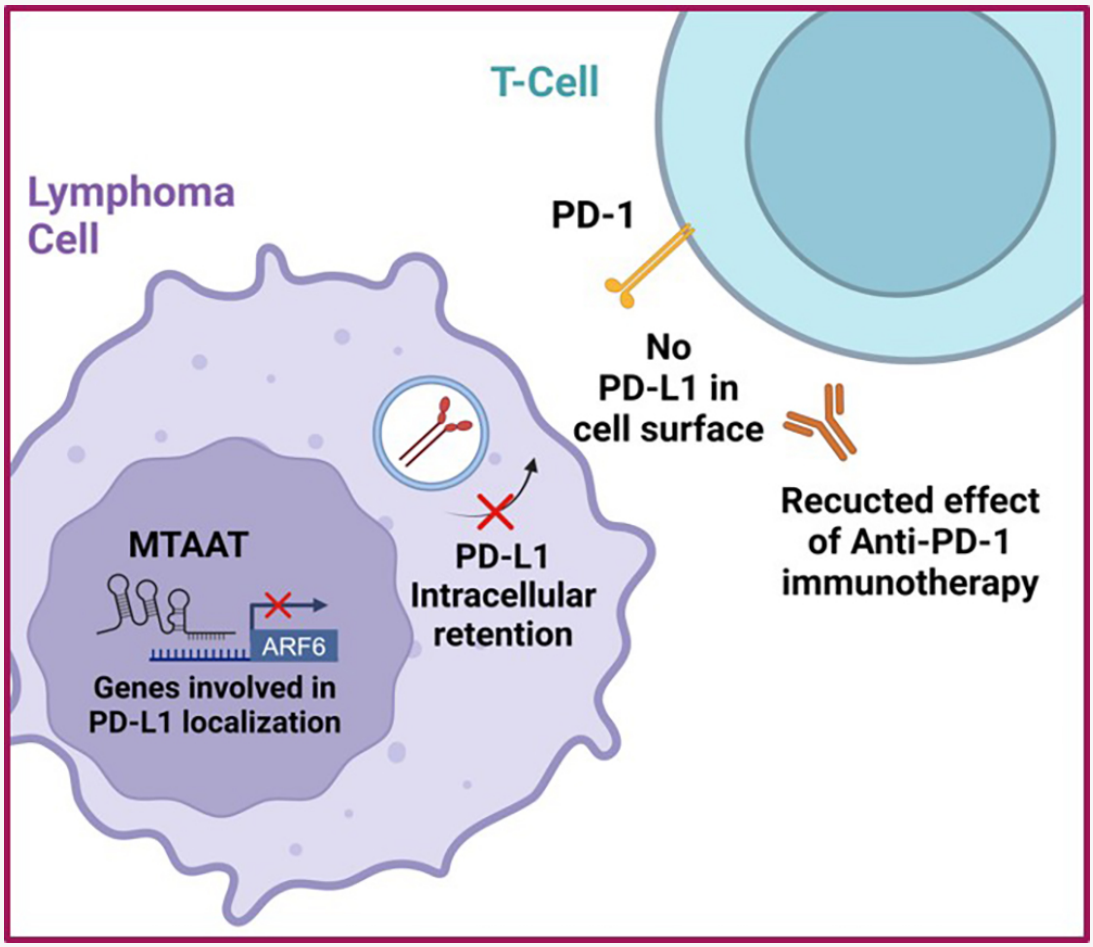
Specifically, MTAAT knockdown upregulated ADP-Ribosylation factor 6 (ARF6), a small GTPase critical for membrane trafficking and its activator CYTH3, causing both ARF6 and PD-L1 shift from cytoplasm to the membrane.

At the molecular level, MTAAT represses ARF6 transcription by restricting the binding of the transcription factor STAT3 to its promoter.

Finally, in silico analysis in ALK$^-$-ALCL cohort showed a correlation between high ARF6 levels and higher Tumor Immune Dysfunction and Exclusion (TIDE) score, indicating that low ARF6 expression could predict poor response to ICBs.

Conclusions: Our findings identify MTAAT as a key regulator of PD-L1 localization in ALK$^-$-ALCL, controlling immune evasion though ARF6/STAT3 regulation. The MTAAT/ARF6 axis uncovers a novel immune resistance mechanism and positions both MTAAT and ARF6 as potential biomarkers and therapeutic targets to improve immunotherapy.

Lymphomas


T-Cell
Lymphoma Cell
PD-1
No PD-L1 in cell surface
Recucted effect of Anti-PD-1 immunotherapy
MTAAT
ARF6
Genes involved in PD-L1 localization
PD-L1 Intracellular retention