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Exogenous ATP Drives Transcriptomic Changes Related to DC Activation that are Elevated by Neoadjuvant Chemoradiotherapy in Esophageal Cancer

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Background

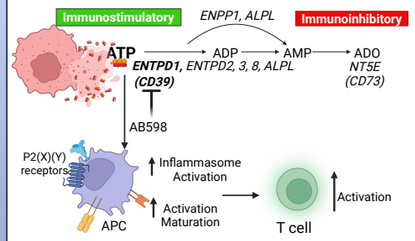


Figure 1. CD39 inhibition promotes anti-tumor immunity through DC activation. ATP, elevated by chemotherapy-driven ICD, is rapidly degraded by CD39. AB598 inhibits CD39 enzymatic activity and elevates eATP levels. eATP activates DCs to mediate T cell and immune activation, leading to tumor control.

- Immune checkpoint inhibitors exhibit reduced efficacy in PD-L1 low gastroesophageal tumors, which have correspondingly lower levels of immune infiltrate relative to PD-L1 high tumors.
- AB598, a therapeutic anti-CD39 antibody, preserves extracellular adenosine triphosphate levels (eATP) that are elevated by chemotherapy-driven immunogenic cell death (ICD).
- eATP activates Dendritic cells (DCs) which mediate immune activation, leading to tumor control (Fig 1).

Results

PD-L1 Low ESCA patients have low DC lineage gene expression

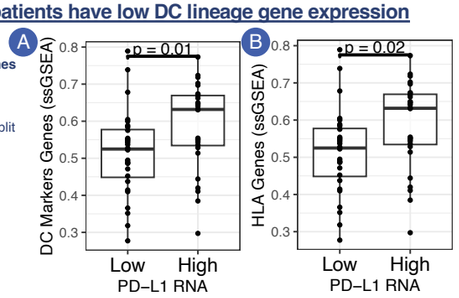


Figure 2. Association of DC marker genes with PD-L1 RNA expression. ssGSEA scores for **(A)** DC markers and **(B)** HLA genes in PD-L1 low and high esophageal carcinoma (ESCA) cancers from TCGA, split by median PD-L1 RNA expression.

DC markers: *CLEC10A, CD1C, CLEC9A, CCR7, ITGAX*
MHC Class II genes: *HLA-DMA, HLA-DMB, HLA-DOA, HLA-DOB, HLA-DPA1, HLA-DPA2, HLA-DPB3, HLA-DPB1, HLA-DPB2, HLA-DQA1, HLA-DQA2, HLA-DQB1, HLA-DQB1-AS1, HLA-DQB2, HLA-DQB3, HLA-DRA, HLA-DRB1, HLA-DRB5, HLA-DRB6, HLA-DRB9*

eATP generative treatment increases DC lineage in ESCA

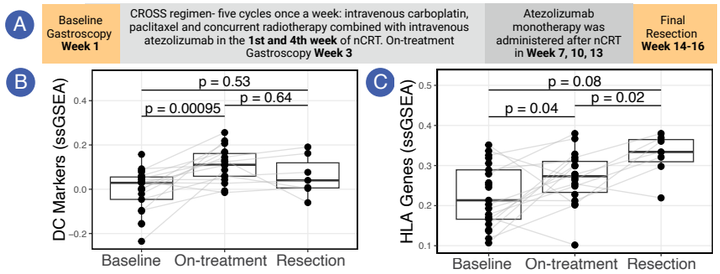
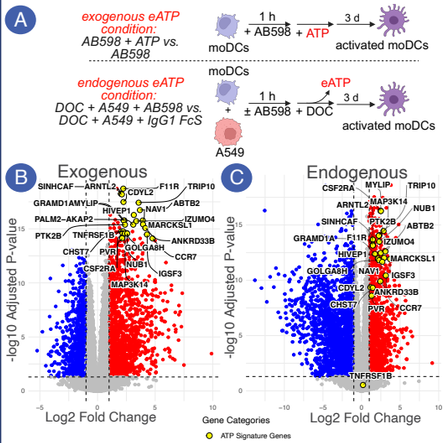


Figure 3. DC markers increased with eATP generative CROSS regimen in ESCA. A) Clinical trial design and sample biopsy (GSE165252) timeline of the PERFECT trial (NCT03087864) for ESCA. **B/C)** DC marker and HLA signature (genes in Fig 2) ssGSEA plots across treatment timepoints. eATP generative CROSS regimen increases DC lineage markers. Lines connect paired longitudinal biopsies. *nCRT: Neoadjuvant Chemoradiotherapy*

Results

Generation and validation of an ATP signature using a moDC coculture system



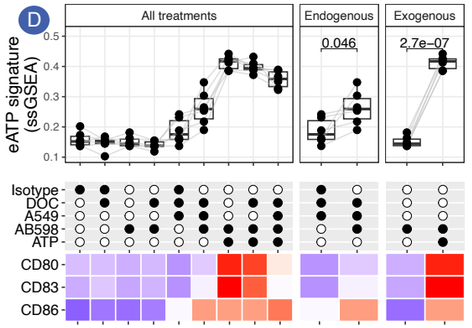


Figure 4. ATP signature generation using an endogenous coculture system. A) Monocyte-derived dendritic cells (moDCs) were exposed to combinations of treatments and coculture with NSCLC A549 cells followed by RNA sequencing. **B/C)** Volcano plots of (B) exogenous and (C) endogenous comparisons DEGs, 23-gene signature highlighted. **D)** (Top) Boxplot of ATP signature ssGSEA score. Lines connect matching donors. (Bottom) Heatmap of mean Z-score RNA expression of DC activation markers for each condition. Significance was determined with paired t-test. *DOC: docetaxel.*

ATP signature captures transcriptomic changes reflecting DC maturation and is independent of adenosine signaling

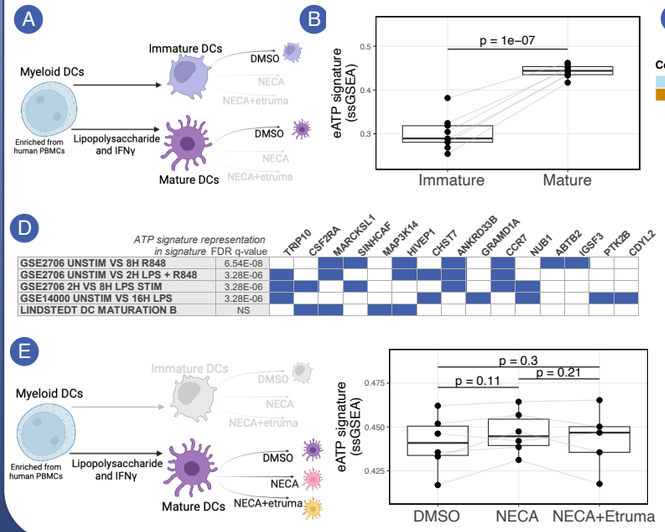


Figure 6. Assessment of the ATP signature in independent experiments.
A) Myeloid DCs enriched from human PBMCs were cultured as immature DCs or matured using LPS and IFNγ. Vehicle treated cells were used to assess DC maturation. **B)** ATP signature is increased in mature DCs. **C)** Heatmap of ATP signature genes show consistent upregulation in mature DCs. **D)** The ATP signature genes were tested for overrepresentation in the MSigDB. Pathways related to DC maturation and shared genes with the ATP signature are highlighted in blue. **E)** Adenosine signaling was assessed using mature DCs described in (A) exposed to DMSO, adenosine receptor A2$_{A/B}$R agonist NECA, and NECA + etrumadenant (etruma), a dual A2$_{A/B}$R antagonist. **F)** eATP signature is unchanged with adenosine exposure.

Results

Exogenous ATP increases CD39 and PD-L1 RNA expression

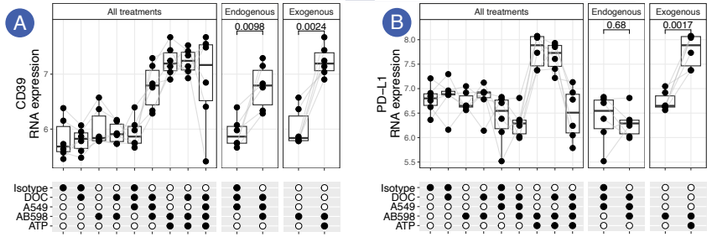


Figure 7. PDL1 and CD39 RNA expression increase with exogenous ATP in the presence of AB598. A/B) CD39 and PD-L1 RNA expression in the moDC experiment. Significance was determined with paired t-test.

eATP generative regimen increases the ATP signature score, PD-L1, and CD39 RNA expression in ESCA

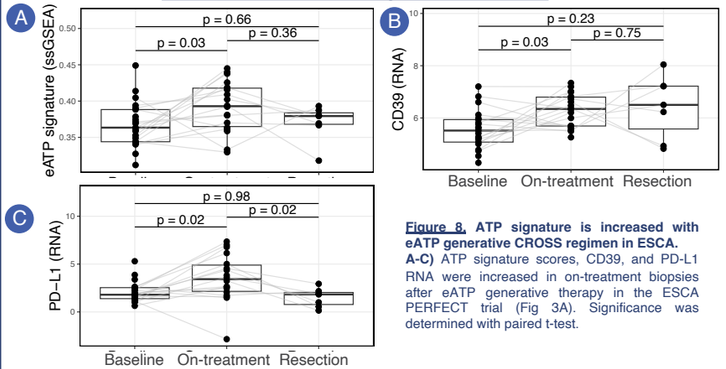


Figure 8. ATP signature is increased with eATP generative CROSS regimen in ESCA.
A-C) ATP signature scores, CD39, and PD-L1 RNA were increased in on-treatment biopsies after eATP generative therapy in the ESCA PERFECT trial (Fig 3A). Significance was determined with paired t-test.

Conclusions

- We generated an ATP signature defined by eATP added to the system, while inhibiting CD39. The signature increased with endogenous eATP generated by A549+DOC, and eATP generative therapy in ESCA.
- eATP-generating therapies increased the levels of PD-L1 and CD39 RNA expression which could result in eATP degradation and immunosuppression if CD39 activity is not inhibited.
- PD-L1 low patients may derive benefit from inhibiting CD39 and preserving the eATP generated by ICD chemotherapies that will increase DC activation and result in an enhanced immune response.

References: 1. van den Ende et al., (2021) Clin Cancer Res. 15;27(12):3351-3359; 2. Jin et al., (2025) The Journal of Immunology, vkaf187; 3. TCGA Research Network: https://www.cancer.gov/tcga; 4. Anderson et al., (2024) Molecular Cancer Therapeutics, 1;23(10):1471-1482; 5. Seitz et al., (2018) Invest New Drugs 37, 711–721.
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