Distinct immune gene programs associated with host tumor immunity, neoadjuvant chemotherapy and chemoimmunotherapy in resectable NSCLC

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Abstract #248

Introduction

- Neoadjuvant treatment with immune checkpoint inhibitors alone or in combination with chemotherapy have recently shown promising results in NSCLC[1,2]. However, mechanisms that promote response to these strategies remain inadequately understood[3].
- We analyzed three cohorts with resected NSCLC that underwent upfront surgery or neoadjuvant chemotherapy, as currently established standard of care in this setting, and compared with patients that received neoadjuvant chemoimmunotherapy (platinum-based plus anti-PD-1). Here we report immune programs that inform of host anti-tumor immunity and response in resectable NSCLC

Methods

- Targeted immune gene sequencing using the HTG Precision Immuno-Oncology panel was performed in localized NSCLCs from three cohorts based on treatment: naïve (n=190), neoadjuvant chemotherapy (n=38) and neoadjuvant chemoimmunotherapy (n=21). Detailed clinicopathological information are summarized in **Table 1**.
- Tumor immune microenvironment (TIME) phenotypes (inflamed, cold, excluded) were derived based on CD8$^+$ T cell infiltration.
- Signatures of immune cell abundance and immune genes were statistically compared based on tumoral PD-L1 expression, immune phenotypes, associated with pathological response, and were cross-compared across the three cohorts.

Table 1. Clinicopathological characteristics of the three cohorts: Treatment-naïve (n=190) and neoadjuvant chemotherapy cohort (n=38) from MD Anderson, and the neoadjuvant chemoimmunotherapy cohort from NADIM trial (n=21) (NCT03081689).

Clinicopathological variables	Treatment-naïve (n=190)	%	Neoadjuvant Chemotherapy (n=38)	%	Neoadjuvant Chemo-IO (n=21)	%
Age median (range)	67 (41 - 86)		62 (43 - 81)		64 (41 - 76)	
Sex						
Female	80	42.1	17	44.7	5	23.8
Male	110	57.9	21	55.3	16	76.2
Smoking Status						
Current	83	43.7	23	60.5	8	38.1
Former	92	48.4	15	39.5	13	61.9
Never	15	7.9	0	0.0	0	0.0
Histology						
LUAD	107	56.3	20	52.6	11	52.4
LUSC	83	43.7	18	47.4	10	47.6
TNM stage						
I	73	38.4	1	2.6	0	0.0
II	49	25.8	7	18.4	0	0.0
III	68	35.8	30	79.0	21	100.0
PD-L1 (IHC)						
<1%	80	42.1	4	10.5	8	38.1
≥1%	38	20	7	18.4	9	42.9
NA	72	37.9	27	71.1	4	19.0
Recurrence						
Yes	91	47.9	21	55.3	5	23.8
No	99	52.1	17	44.7	16	76.2
Survival						
Alive	56	29.5	8	21.1	19	90.5
Death	134	70.5	30	78.9	2	9.5

LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; IHC, immunohistochemistry; NA, not available.

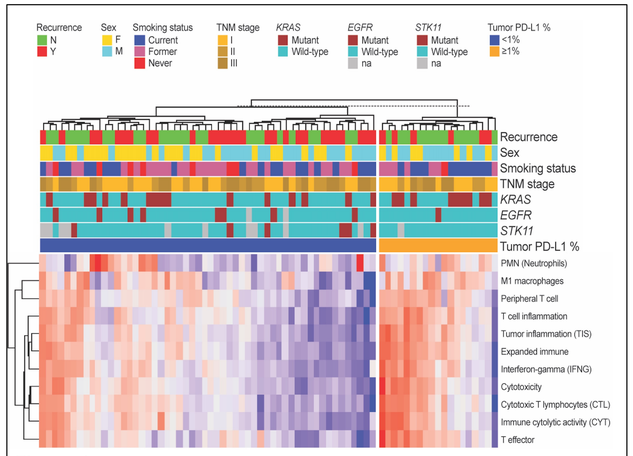

Figure 1. Immune expression programs differentially expressed in PD-L1 positive and negative treatment-naïve LUADs. Differential expression of functional gene signatures (red, higher expression; blue, relatively lower expression; adjusted p-value <0.05) between PD-L1 positive and negative LUADs.

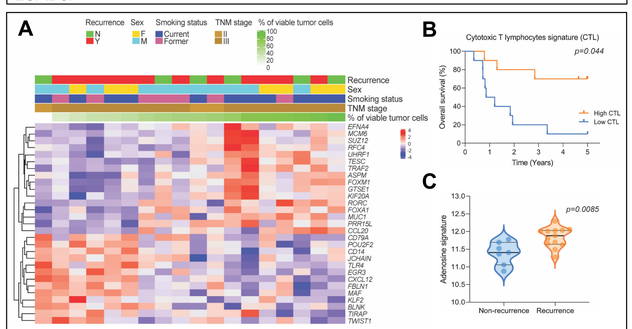

Figure 3. Immune expression changes linked with pathological response after neoadjuvant chemotherapy in early-stage NSCLC. A) Heat map showing 29 DEGs (un-adjusted p-value <0.01) that are associated with the percent of viable tumor cells in early-stage NSCLCs treated with neoadjuvant chemotherapy. **B)** Analysis of the association of signature score for cytotoxic T lymphocytes with OS. **C)** Adenosine signature with recurrence (p-value was calculated based on the Mann Whitney test, black lines represent the median, and gray lines correspond to 95% CI.

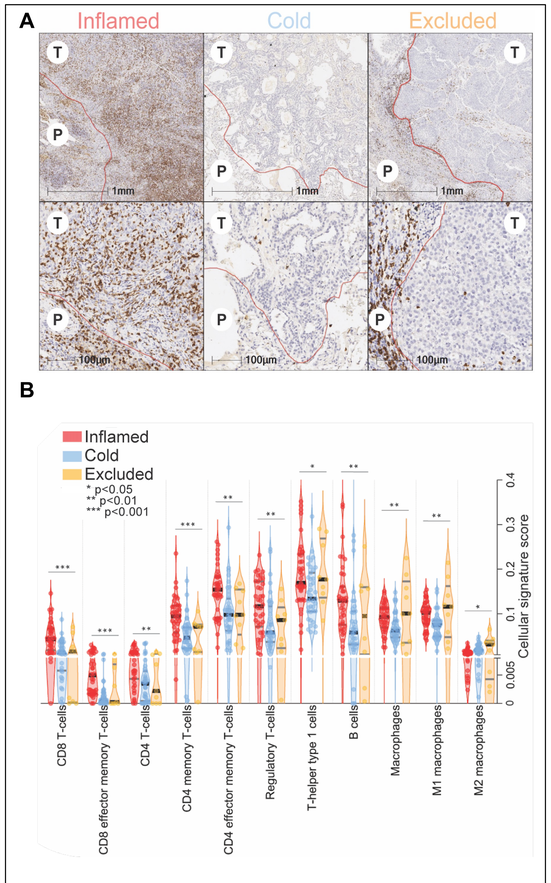

Figure 2. Gene expression programs associated with immunologically inflamed, cold, and excluded TIME phenotypes in treatment-naïve LUADs. A) Representative IHC images for the three different phenotype patterns at the bottom (P, peritumoral; T, tumor area). **B)** Violin plots depicting cellular signature scores across the three TIME phenotypes. P-values were calculated based on the Kruskal-Wallis test, black lines represent median levels, and gray lines correspond to 95% CI.

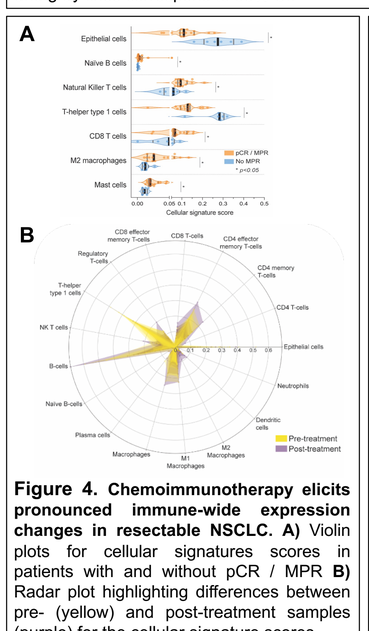

Figure 4. Chemoimmunotherapy elicits pronounced immune-wide expression changes in resectable NSCLC. A) Violin plots for cellular signatures scores in patients with and without pCR / MPR **B)** Radar plot highlighting differences between pre- (yellow) and post-treatment samples (purple) for the cellular signature scores.

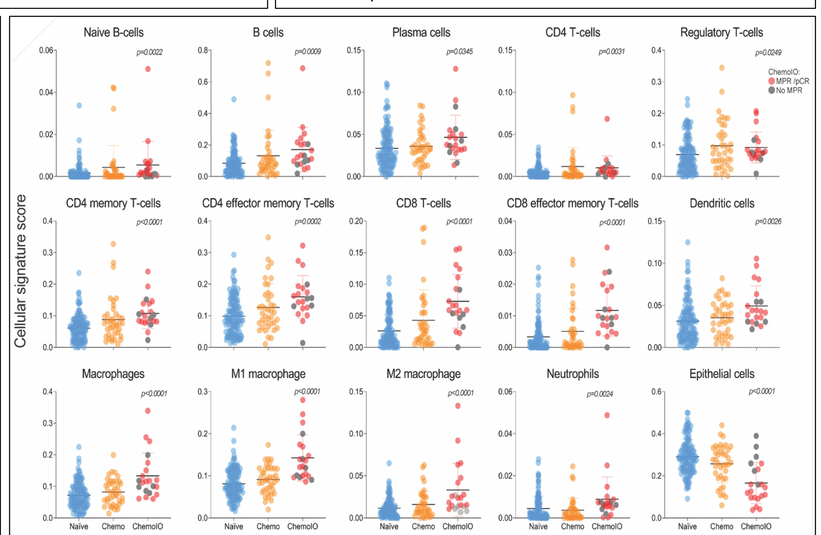

Figure 5. Immune gene programs that are differentially modulated between treatment-naïve NSCLCs and those treated with neoadjuvant chemotherapy and chemoimmunotherapy. Dot plots for cellular signature scores across the three cohort (blue, treatment-naïve; orange, neoadjuvant chemotherapy; red, neoadjuvant chemoimmunotherapy. P-values were calculated based on Kruskal-Wallis test, bars correspond to median values +/- 95% CI).

Results

- Augmented immune response is often observed in treatment-naïve patients with high tumor PD-L1 expression, while PD-L1 negative tumors exhibit heterogeneous host immune expression programs (**Figure 1**).
- TIME phenotypes (inflamed, cold and excluded, **Figure 2A**) based on the cell densities and spatial distribution of CD8+ T cells showed that inflamed LUADs exhibited significantly higher signature scores for effector memory T cells (p<0.0001) and increased abundance of B cell populations (p<0.0001). Macrophage and M1 macrophage subsets were significantly lower in cold LUADs (p=0.0008, and p=0.0003, respectively. While M2 macrophages were significantly increased in LUADs with an excluded phenotype (p=0.0219) (**Figure 2B**).
- Immune genes implicated in innate immune responses (*CD14, TLR4, MAF*) and those pertinent to B cell biology (*CD79A, JCHAIN, CXCL12, BLNK*) were significantly and positively associated with pathologic response (p<0.01) in patients receiving neoadjuvant chemotherapy (**Figure 3A**). Cytotoxic T cell and adenosine signature was associated with favorable survival in neoadjuvant chemotherapy-treated NSCLCs (**Figure 3B-C**).
- Patients achieving pCR or MPR after chemoimmunotherapy overall displayed higher immune scores for various cell subsets such as B cells (p=0.0110) and CD8 T cells (p=0.0293) (**Figure 4A**) while Th1 cells were significantly reduced post-chemoimmunotherapy (**Figure 4B**).
- Among the three cohorts, chemoimmunotherapy-treated NSCLCs significantly exhibited highest scores for immune cell subsets including T effector dendritic and B cells (**Figure 5**).

Conclusions

- Our findings highlight immune gene programs that may underlie host tumor immunity and response to neoadjuvant chemotherapy and chemoimmunotherapy in early-stage NSCLC.

References

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3) Chaft et al. Nat. Rev. Clin. Oncol. (2021)

Acknowledgements

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