TUMOUR BIOLOGY AND PATHOLOGY

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Integration of tissue and circulating parameters identifies a favorable immune profile in NSCLC patients treated with nivolumab

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Background: To define prognostic and potentially predictive immune profiles in NSCLC patients receiving nivolumab, an integrated analysis of tissue and circulating parameters was performed.
Methods: Peripheral blood (PB) from 31 advanced NSCLC patients was analyzed by FACS to assess CD3, CD8, CD4, NK, Treg, and MDSC ($CD14^{pos}/CD33^{pos}/DR^{neg}$) number, function (PD-1, CD3ζ, Granzyme B, Perforin) and proliferation (Ki67). Data were collected at baseline (T0), and after 2 (T1) and 4 (T2) cycles of bi-weekly nivolumab. PD-L1 (H-score) and TILs subpopulations were immunohistochemically investigated. Merged tissue and circulating parameters were correlated to clinico-pathological features, response to treatment (RECIST 1.1) and survival outcomes.
Results: T cells were more represented in PB from ADC patients ($p < 0.01$ vs SqCC), while KRAS mutation conditioned higher number of CD3, CD8, CD4, and NK, and lower MDSC ($p < 0.05$). Active smoking and BPCO directly correlated with T and NK cells proliferation ($p < 0.05$). Additionally, steroid naïve patients had increased effector and reduced immune suppressive ($p < 0.05$) phenotypes. Clinical benefit (CB, n = 19) group, compared to non-responder (NR, n = 12), displayed a distinctive PB immune profile at baseline, including higher NK (tot, CD3ζpos, Pfnpos, GrzBpos) and CD8pos/PD-1pos cells ($p < 0.01$). These CB immune features were maintained during nivolumab, while MDSC progressively rose in NR ($p < 0.05$). Prolonged OS ($p < 0.05$) and PFS ($p < 0.01$) were recorded in cases with high NK and CD8pos/PD-1pos number at T0. At tissue level, while high PD-L1 score had a modest clinical impact, low PD-1 expression in CD8pos TILs was a distinctive feature of CB ($p < 0.001$ vs NR) and correlated with better OS (ns) and PFS ($p < 0.01$). Strikingly, the combination of predetermined PB (high NK and CD8pos/PD-1pos) and tissue (low CD8pos/PD-1pos) positive prognostic factors characterized an immune privileged context provided by significantly prolonged PFS ($p < 0.001$) and OS ($p < 0.01$).
Conclusions: A divergent PD-1 expression in blood and tissue cytotoxic cells associated with a preserved functional pool of circulating NKs portrays an immune profile prone to nivolumab efficacy.
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MET activation in lung cancer up-regulates PD-L1 expression independently of JAK-STAT pathway, promoting an immunosuppressive phenotype

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Background: The ability of tumors to avoid immune surveillance has emerged as therapeutically approachable in several types of cancer, especially through the blockade of immune checkpoints such as PD-L1/PD-1. Our purpose is to determine the contribution of somatic genomic alterations in lung cancer (LC) to the capability of tumour cells to escape the immune surveillance checkpoints.
Methods: The mutation status of recurrent driver genes in lung cancer (e.g. *EGFR, KRAS, MET*) and the expression of immune-related molecules (PD-L1, HLA-complex, and tumour infiltrating lymphocytes CD8+, TILs) were assessed in a cohort of 155 primary resected non-small cell lung cancer (NSCLC). Correlations between genomic alterations and immune markers were determined by Chi-square test and validated in genetically characterized cancer cell lines. Functional assays were performed using appropriate treatments, including IFNγ, to modulate selected pathways. RNA-Seq analysis was performed to analyse differential gene expression with these treatments.
Results: *MET* activation, comprising *MET* exon 14 skipping mutations and *MET* amplification, was found in 3% of samples in our cohort and these tumors were more