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Characterization of the tumor microenvironment in a cohort of KRAS- and EGFR mutant non-small cell lung cancer

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Introduction: Immune Checkpoint Blockade (ICB) led to better outcomes in non-small cell lung cancer (NSCLC) but only a subset of patients benefits from current treatment regimens. Different molecular subtypes show diverse treatment responses. It was reported that patients with KRAS-mutant tumors respond better to ICB therapy, in contrast, EGFR-mutant tumors show higher resistance to this type of therapy. In order to evaluate distinctions between these subtypes, a thorough characterization of the immune environment (IE) was performed in patients with untreated NSCLC. Methods: To characterize the immune environment, flow cytometry and multiplex immunohistochemistry was used. Additionally, TCR sequencing, and RNA sequencing was performed. The findings were validated in public datasets. Therapeutic blockage of CCL20 was tested in a murine in-vivo flank tumor model comparing CCL20-neutralizing antibody to its isotype control. Results: No apparent difference of immune cell composition was found between the molecular subgroups. Tumor Mutational Burden (TMB) and PDL1 expression on cancer cells was higher in KRAS-mutant NSCLC. Expression of CCL20 were upregulated in the same subgroup which could be validated in the TCGA lung adenocarcinoma cohort. Additionally, higher CCL20 expression was associated with lower survival probability. In-vivo experiments with a CCL20-blocking antibody showed reduced tumor growth in treatment group with reduced regulatory T cells and monocyte-derived dendritic cells. Conclusion: Higher TMB and PDL1 expression, both suggested biomarkers for the prognosis of ICB response, could explain better results in KRAS-mutant NSCLC. Targeting of CCL20 may be a new option for therapy in this subgroup. In-vivo experiments show promising results for therapeutic usage of blockade of CCL20 with minor modulation of the IE. In EGFR-mutated lung cancer, additional research is needed to assist therapy decisions.