Assessment of inflammatory marker expression and immune phenotypes in lung cancer

Ph.D. thesis

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1. Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide, with non-small cell lung cancer (NSCLC) representing approximately 85% of all cases. Lung adenocarcinoma (LADC) is the most prevalent NSCLC subtype and is often associated with oncogenic driver mutations such as Kirsten rat sarcoma viral oncogene (KRAS). Despite recent advances in targeted and immune-based therapies, the treatment of KRAS-mutant LADC remains challenging due to the heterogeneity of KRAS mutation subtypes and the variable response to immunotherapy.

In parallel, lung neuroendocrine neoplasms (LNENs) comprise a histologically and biologically diverse group of tumors, ranging from well-differentiated typical carcinoids (TC) to highly aggressive small cell lung cancer (SCLC) and large cell neuroendocrine carcinoma (LCNEC). Immunotherapeutic strategies for high-grade LNENs are still limited, and the tumor immune microenvironment (TIM) in these subtypes remains insufficiently characterized.

This study explores the immune phenotypes and inflammatory profiles of KRAS-mutant LADC and LNENs, with the aim of identifying potential immunotherapeutic targets.

2. Objectives

In the treatment of advanced LADC, alongside the traditionally used chemotherapy and radiotherapy, the role of immune checkpoint inhibitors: the programmed cell death protein 1 (PD-1)/PD-L1 has become increasingly significant. However, the therapeutic response to these agents varies considerably among individuals. Consequently, there is a clear need for predictive markers to determine the expected therapeutic response to specific treatments. In addition to immune checkpoint inhibitors, biomarkers such as tumor mutational burden and microsatellite instability have emerged as effective predictors of immunotherapeutic response. Comprehensive mapping of the tumor immunogenicity and immunophenotype is thus essential in determining the appropriate therapeutic strategies.

Genetic mutations, such as KRAS alterations in LADC, are known to affect several signaling pathways and enhance cell proliferation. These signaling pathways also impact the TIM by triggering inflammatory processes. Different KRAS mutant tumors have a distinct response to immunotherapy. A detailed analysis of the cytokines, regulatory proteins, and effector immune cells involved in tumor-associated inflammation may provide valuable insight into the relationship between inflammation and immunomodulation induced by KRAS

mutations. One of the key regulators of the hereditary inflammatory response is the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome, which can be activated through specific signaling pathways. Overactivation of NLRP3 leads to increased production of pro-inflammatory cytokines. Thus, NLRP3 inhibitor therapy may offer a novel approach to managing KRAS mutant adenocarcinomas.

Typical and atypical carcinoids (AC), although relatively rare subtypes of neuroendocrine lung tumors, are of growing importance. TC accounts for 2% of lung tumors, while AC accounts for about 0.2%, but their incidence is increasing worldwide. TC tumors are generally associated with better prognosis and longer overall survival (OS) compared to AC tumors, which demonstrate more aggressive clinical behavior. In cases of metastatic carcinoid tumors, occurring in 10-20% of TCs and 40-50% of ACs, therapeutic options remain limited, mainly due to the high resistance of these tumors to radiotherapy and chemotherapy. The identification of new therapeutic targets for treating malignancies is therefore essential.

3. Methods

3.1. KRAS -study

This retrospective study included 87 patients diagnosed with early-stage LADC, classified as stage I. A to II.B, all of whom had their diagnosis histologically confirmed. These patients underwent surgical resection at the National Koranyi Institute of Pulmonology in Budapest, Hungary, between 2012 and 2017. The selection criteria required the presence of a presumed KRAS mutation identified through previous direct sequencing.

During clinical data collection, we retrospectively processed the data obtained from the hospital's medical records on the patient's age, gender, comorbidities, and smoking habits at the time of diagnosis. To analyze morphological heterogeneity, tumor tissue samples were obtained through surgical resection, and three tissue microarray (TMA) punctures were extracted from each formalin-fixed, paraffin-embedded (FFPE) block. TMA tissue cores were retrieved from distinct representative regions within viable tumor areas. The TMA blocks were cut into four-micron-thick sections and stained with hematoxylin and eosin (H&E) and alcian blue to highlight histological patterns.

The extent of tumor-associated lymphocyte (TIL) and macrophage infiltration in the peritumoral region was assessed

through immunostaining. The following antibodies were used for IHC staining: CD3, CD163 , and NLRP3.

All staining procedures were conducted following the manufacturer's protocols using the fully automated BenchMark ULTRA IHC/ISH system. Antibody binding was detected using the ImmPACT DAB Substrate Kit from Vector Laboratories, and the nuclei were counterstained with hematoxylin. All antibodies were validated by utilizing appropriate tissue controls. The expression levels of the specific markers were assessed on a categorical, semi-quantitative scale by two experienced pulmonary pathologists who were blinded to the clinical data. In addition to the analysis of tumorous lesions, one pathologically verified non-tumorous lung tissue core was retrieved from each patient for control purposes. We performed IHC and molecular analyses on both tumor and non-tumor samples. In our study, RT-PCR reactions were performed in 96-well plates according to the manufacturer’s protocol, which was used for the quantification of the mutant allele frequency in the samples. We used a pairwise chi-square test to examine the relationships between categorical variables. Since none of the results were statistically significant even before adjusting for multiple testing, no corrections were applied in this analysis. While expression levels were originally defined on a categorical

scale (none/ slight, diffuse plasma staining/ medium plasma staining with dominant spots/ strong diffuse plasma staining), they could be converted into semi-quantitative numerical values (e.g., 0/1/2/3) based on their ordinal nature. This conversion allowed for a reassessment of relationships between different expression levels using Pearson correlation and between expression levels and categorical variables using pairwise t-tests adjusted for multiple testing with the Bonferroni correction. Additionally, when comparing different expression levels, a simpler categorization of "none" versus "any" was applied, and a Fisher's exact test was used to determine whether the different types of expressions were independent. For specific analyses, tumor tissue cores were treated independently, even if obtained from the same patient. For each patient, we examined pairs of samples from the tumor and the adjacent nontumor environment to map their mutational status and expression levels. The samples from the three tumor sites were compared to the same normal sample. Survival curves for different patient groups were estimated using Kaplan-Meier plots. The differences between the groups were analyzed using the log-rank test. OS was defined as the time in months from the surgical intervention to the last available follow-up or the date of death from any cause.

R version 4.4.1 was used for all statistical analyses, and a p-value of less than 0.05 was considered statistically significant.

3.2. LNEN- study

Four Central European centers participated in the second LNEN study: the National Koranyi Institute of Pulmonology, Budapest, Hungary, the National Institute of Oncology, Budapest, Hungary; the Medical University of Graz, Austria; and Palacky University, Olomouc, Czech Republic. A total of 141 patients who underwent surgical resection for LNEN between 1997 and 2021 were examined. The distribution of patients based on LNEN subtypes was as follows: 66 patients had SCLC, 49 LCNEC, and 26 AC. Only whole tissue samples were processed to avoid bias due to intratumoral heterogeneity. The tissue samples were analyzed for the expression of four TIM markers, namely T cell immunoglobulin and mucin domain 3 (TIM3), V-domain immunoglobulin suppressor of T cell activation (VISTA), Glucocorticoid induced tumor necrosis factor receptor (GITR), and Tumor necrosis factor receptor superfamily, member 4 (OX40L). Due to the limited quantity of samples, only VISTA expression was measured in 21 cases of SCLC. To evaluate the quality and reliability of older FFPE blocks (over 15 years) from SCLC patients, these samples were stained with

commonly used diagnostic antibodies against CD56 and Ki-67. The level of immune infiltration was assessed by examining CD3 expression. Immunohistochemistry staining was performed following the recommended protocols using the Ventana BenchMark Ultra IHC/ISH System. The expression levels were visualized using the Liquid DAB and Substrate Chromogen System, and the sections were subsequently counterstained with hematoxylin. To ensure the reliability of the staining protocol, human tonsils were utilized as positive tissue controls. All slides were digitally scanned, and the sections were thoroughly examined and evaluated with CaseViewer 2.4.

To ensure accurate biomarker evaluation, marker expression was assessed in at least 20 random tumor areas by two pathologists, with a third consulted in cases of >20% discrepancy, and tumor cells were evaluated separately from immune cells.

The proportion of positively stained tumor and immune cells was manually quantified relative to total cell counts, due to concerns about the reliability of software-based evaluations, even with routinely used antibodies.

All statistical analyses were performed with R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). Fisher's exact tests and Kruskal-Wallis rank sum tests were used to

assess associations between histological subtypes and clinicopathological characteristics, specifically for categorical and continuous variables. The Bonferroni method was applied to adjust for multiple comparisons. Marker expression levels and clinicopathological parameters were compared using Wilcoxon signed-rank tests, with Bonferroni correction applied. Hierarchical clustering of samples based on expression levels was performed using the Complex Heatmap R package (version 2.10.0). The distance matrix was calculated using the Manhattan distance measure, and dendrograms were created using the ward.D clustering method. During the statistical analysis of the obtained results, Pearson correlation coefficients (R) were calculated between expression levels, and the Bonferroni method was used to correct p-values for multiple comparisons. To identify key markers distinguishing LNEN subtypes and assess their prognostic value, we performed principal component analysis and categorized into "low" (i.e., median or below-median) and "high" (i.e., above-median) expressing groups, followed by univariate Kaplan-Meier and multivariate Cox regression analyses to evaluate their impact on overall survival.

4. Results

4.1. KRAS- study

Pathological evaluation of tumor cores revealed a single dominant morphological component in 71% of cases. 47% of samples showed an acinar pattern, followed by solid (26%), lepidic (22%), and papillary architectures (5%). We found that KRAS G12C, G12D, and G12V were the most common mutations in our cohort, found in 33%, 25%, and 24% of all patients, and in 38%, 23%, and 24% of the samples, respectively. It is important to note that while the mutational landscape concerning KRAS mutations was mostly homogeneous across different TMA cores from the same tumor, there were 19 cases where the dominant mutational subtype varied between tumor punctures. Moreover, 14 LADC samples completely lacked any KRAS mutations despite the initial diagnosis of KRAS mutant LADC established by direct sequencing.

The KRAS mutational status did not show a statistically significant association with the morphological growth patterns. The KRAS G12A mutation was absent in lepidic LADCs. In contrast, the micropapillary LADC samples did not contain wild-type KRAS genes or multi-hit (i.e., simultaneous multiple types of) KRAS alterations. Furthermore, the evaluation of mucin secretion revealed that 33.3% of tumors do not express

mucin at all. Intracellular mucin secretion was found in 11.5% of cases, while extracellular and mixed mucin secretion was observed in 43.7% and 11.5% of the examined LADCs, respectively.

Patients with KRAS wild-type or mutationally heterogeneous tumors showed a trend toward better overall survival, although the differences were not statistically significant.

The morphological growth patterns of the examined LADCs did not appear to influence the distribution of NLRP3 when the surgically resected specimens were categorized according to the predefined NLRP3 expression subgroups. However, when NLRP3 expression was evaluated on a semi-quantitative scale, solid LADCs demonstrated significantly higher levels of NLRP3 compared to acinar samples ($p=0.001$). Although the PD-L1 group showed no correlation with tumor morphology, when evaluating PD-L1 expression on a continuous scale, we observed that PD-L1 expression was significantly higher in tumor tissue cores with solid morphology than in those with acinar (means: 14.6% vs. 4.4%, t-test adjusted p-value: 0.007) or lepidic growth patterns (means: 14.6% vs. 1.6%, t-test adjusted p-value: 0.002). A weak but significant positive correlation was found between NLRP3 and CD3 expression, with NLRP3 positive tumors exhibiting greater T-cell

infiltration. Similarly, CD163 macrophage density was higher in NLRP3 expressing tumors, indicating an association between NLRP3 and immune cell presence.

KRAS mutations were unexpectedly detected in 24.1% of non-tumorous lung tissues, with some showing the same G12D subtype as their paired tumor samples, and a few even exhibiting mutations despite wild-type tumor status. NLRP3 expression was rarely present in non-tumorous tissues and showed no clear correlation with tumor NLRP3 levels. While CD3 and CD163 expression levels in tumor and adjacent normal tissues showed some consistency, only CD163 demonstrated a weak but significant positive correlation.

4.2. LNEN- study

In our LNEN cohort, SCLC and LCNEC were predominantly found in active smokers with central and peripheral tumor locations respectively, while AC occurred mainly in never-smokers, highlighting distinct clinicopathological patterns relevant to survival analysis.

Several clinicopathological factors significantly influenced survival, and although distinct expression patterns of immunotherapeutic markers (OX40L, GITR, TIM3) were

observed among LNEN subtypes, hierarchical clustering based on these markers did not align with histological classification. Tumor cell analysis revealed that grade 2 LNENs had higher GITR and TIM3 expression than grade 3 tumors, and GITR levels were elevated in never-smokers compared to current smokers, likely reflecting individual smoking patterns.

To better understand the immune landscape of LNEN subtypes, we analyzed CD3 expression and found that immune cell infiltration was significantly lower in ACs compared to LCNEC and SCLC, and lowest in centrally located or non-necrotic tumors. Although ACs showed reduced VISTA and GITR expression in immune cells and SCLCs had lower TIM3 levels, clustering based on immune cell markers alone could not distinguish LNEN subtypes.

Significant positive correlations were found among tumor and immune cell expressions of OX40L, TIM3, and GITR, indicating coordinated regulation of these immunotherapeutic markers within the tumor microenvironment.

No significant associations were found between CD3 expression and the levels of VISTA, OX40L, GITR, or TIM3, although a positive trend was noted between immune cell GITR and VISTA expression.

Principal component analysis showed that while PC1 did not separate LNEN subtypes, PC2 and PC3 effectively distinguished ACs from LCNECs and SCLCs based on immune and tumor cell marker expression. ACs had high TIM3 and GITR expression in tumor cells but low GITR in immune cells, whereas SCLCs showed high GITR and low TIM3 in immune cells, and LCNECs exhibited high GITR and TIM3 levels in immune cells. Patients were divided into low- and high-expression groups for each immune marker, revealing that high TIM3 expression in immune cells was significantly associated with better overall survival, while low GITR expression showed a similar trend. Multivariate analysis identified diabetes, tumor grade, and histological subtype as independent prognostic factors, with immune cell TIM3 and GITR expression showing borderline prognostic significance.

5. Conclusions

Our study revealed significant differences in the clinical behavior of LADC subtypes, with KRAS G12C being the most prevalent mutation. In several cases, different regions of the same tumor showed distinct mutational profiles, indicating considerable intratumoral heterogeneity. Elevated NLRP3 expression was linked to increased immune activity; however, no significant correlation was found between NLRP3 levels and specific KRAS variants. These findings suggest that targeting the NLRP3 inflammasome could represent a novel therapeutic strategy for LADC.

Our second analysis focused on the immunophenotypic variability of LNENs. By evaluating VISTA, OX40L, GITR, and TIM3 expression, we identified distinct immune marker patterns among LNEN subtypes. TIM3 was highly expressed in AC, while GITR was predominant in SCLC and LCNEC. Immune cell infiltration patterns also varied, with lower immune marker levels in AC suggesting a more immunosuppressive environment. Importantly, TIM3 expression correlated with improved survival, highlighting its potential as a prognostic marker. These findings support the development of subtype-specific immunotherapeutic strategies targeting TIM3, GITR, and VISTA.

6. Bibliography of the candidate's publications

Cumulative impact factor: 28,854 (8,6 + 20,254)

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