and survival in lung cancer patients. The SNP, which arose in Africa, modulates the splicing of MRPL43, leading to a linear decrease in the major isoform and a switch in the balance of oxidative phosphorylation and glycolysis. Our work identifies a new pathway of potential relevance to lung cancer and provides new insight into the role of mitochondrial ribosomes in cancer.

High expression of endoplasmic reticulum oxidoreductin (ERO) 1L is associated with resistance to cisplatin

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Various conditions such as low oxygen and low nutrition cause accumulation of unfolded or misfolded proteins in the endoplasmic reticulum (ER), leading to ER stress. To overcome this, cells have resistance mechanisms called unfolded protein response (UPR). When UPR is insufficient, ER-mediated apoptosis occurs. Recent reports have shown that several diseases including cancers can be caused by ER stress. In cancers, high proliferation rates and the presence of mutated gene products lead to accumulation of unfolded and misfolded proteins in the ER and adaptation to ER stress is essential for survival of cancer cells.

As preliminary analysis, we used publicly available expression profiles (GSE10245 and normal tissue data sets) and analyzed expression levels of 84 ER stress pathway genes. We found ER oxidoreductin 1L (ERO1L) was highly expressed in many types of cancer tissue, while expression was low in normal tissues. In addition, using Oncomine™, we found ERO1L high expression was associated with poor prognosis of non-small cell lung cancer. There are some reports that expression of ERO1L is beneficial to tumor cells, but association with lung cancer has not been reported. Therefore, we sought to determine the role of ERO1L in lung cancer, including response to therapy.

Using quantitative RT-PCR and Western blotting, we identified NCI-H441, HCC2935, and NCI-H2347 as ERO1L high expression cell lines. NCI-H520, NCI-H522, and SK-LU-1 were ERO1L low expression cell lines. We then exposed these cells to cisplatin (CDDP) and determined the half maximal inhibitory concentration (IC50). IC50 values for CDDP was 91, 64, and 21 μM, respectively, in cells with high ERO1L expression. IC50 values for CDDP was 2.6, 4.1, and 22 μM, respectively, in cells with low ERO1L expression. We then exposed cell lines to both CDDP and EN460, an ERO1L inhibitor. When CDDP was combined with low dose EN460 (1/10 of IC50), there was a trend toward decreased IC50 for CDDP. We also evaluated IC50 values for CDDP plus high dose EN460 (1/3 of
IC50), but high dose EN460 didn’t sensitize cells to CDDP. In summary, high ERO1L expression was associated with poor prognosis of non-small cell lung cancer and resistance to CDDP therapy, which may be ameliorated with addition of EN460. These data suggest that ERO1L may promote lung cancer cell survival and resistance to chemotherapy by reduction of ER stress, and that ERO1L inhibitor may sensitize CDDP-resistant cancer cells to CDDP.

Intratumoral CCL21 and checkpoint blockade cooperatively inhibit NSCLC tumor growth in vivo to a greater extent than either monotherapy alone

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Recent studies reveal responses in approximately 20% of non-small cell lung cancer (NSCLC) patients treated with inhibitors of the PD-1/PD-L1 checkpoint. This includes robust and durable responses in previously treated patients with progressive locally advanced or metastatic NSCLC. However, a large percentage of patients do not respond to checkpoint inhibitors delivered as single agents. Studies demonstrate that tumor-infiltrating CD8+ T cells are requisite for antitumor responses to antibody-mediated therapies that block PD-1 or PD-L1. One potential approach to extend the effectiveness of checkpoint inhibitors to additional NSCLC patients is to enhance T cell responses by in situ vaccination that takes advantage of the full repertoire of available tumor antigens. In preclinical and clinical trials, we discovered that CCL21 has antitumor properties and CCL21-DC has the capacity to induce both local T cell recruitment and systemic immune responses. We hypothesized that in situ vaccination with CCL21-DC could serve as a tool to restore tumor T cell infiltration, tumor antigen presentation, and T cell responsiveness, thereby sensitizing non-responsive NSCLC tumors to checkpoint blockade. To test this hypothesis, we first evaluated CCL21-DC as a monotherapy in the well-characterized syngeneic KRASG12D murine model of lung cancer. We observed decreased tumor growth, increased tumor-infiltrating lymphocyte (TIL) cytolytic activity against the autologous tumor, and increased IFNγ/TNFα in the tumor, as well as systemically in the spleen. Using the same LKR13 murine model, we observed that anti-PD-1 monotherapy also inhibited tumor growth, increased TIL cytolytic activity against the autologous tumor, and increased IFNγ/TNFα in the tumor, as well as systemically in the spleen. To determine if TIL activity from the CCL21-DC treatment group could be enhanced by PD-1 blockade, we performed an in vitro cytolytic assay. TIL from the CCL21-DC group had significantly greater cytolytic activity against the autologous tumor in the presence of PD-1 antibody relative to control antibody. We next evaluated intratumoral CCL21 and intraperitoneal anti-PD-1 administered in combination to LKR13 tumor-bearing mice. Both monotherapies reduced final tumor volume approximately three-fold, and the combination proved more efficacious than either agent alone. We obtained similar results utilizing the syngeneic 3LL murine lung cancer model. Both monotherapies significantly reduced tumor growth, such that the final 3LL tumor volume at the time of necropsy was approximately half that of the control group, and the combination of checkpoint blockade and CCL21 augmented the antitumor activity nearly two-fold more. Collectively, these data support the hypothesis that intratumoral administration of CCL21-DC and checkpoint blockade therapy cooperatively inhibit NSCLC tumor growth to a greater extent than either monotherapy alone. We anticipate that the capacity of in situ vaccination to drive both DC and T cell effector infiltration of NSCLC tumors will play an important role in increasing the number of patients responding to immunotherapy in the future.

Diagnostic and predictive quantitative-imaging features in lung cancer screening

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Background: Although the National Lung Screening Trial (NLST) found a 20% reduction for lung cancer mortality among participants screened with low-dose computed tomography (LDCT) compared to standard chest radiography, there are many limitations of LDCT screening. First, LDCT screening identifies large numbers of indeterminate pulmonary nodules (IPNs) of which only a fraction develop into cancer. At present non-invasive approaches do not exist to determine whether these IPNs are cancerous or benign. Next, if a nodule is detected, clinical guidelines provide for the evaluation and follow-up of nodules, but do not provide clinical decision tools to predict risk and probability of cancer development. Cumulatively, these limitations of LDCT screening critically require development of non-invasive, accurate quantitative imaging-based classifier models that i) can be reduce false positives by differentiating