474. New insights in the pathology of lung cancer

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LSC 2012 Abstract – LRIG1 regulates cadherin-dependent contact inhibition directing epithelial homeostasis and preinvasive squamous cell carcinoma development

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Epidermal Growth Factor Receptor (EGFR) pathway activation is a frequent event in human lung cancer with over-expression one of the earliest abnormalities in the bronchial epithelium of smokers and present in all stages of preinvasive cancer. Mutations in EGFR itself are rare and the mechanisms regulating EGFR pathway activation remained elusive. Leucine-rich immunoglobulin repeats-1 (LRIG1), an inhibitor of EGFR activity, is one of 4 genes identified that predict patient survival across solid tumor types.

We hypothesize that tissue homeostasis is maintained via strong endogenous regulation of EGFR signaling by the inhibitor LRIG1 and its loss is the key step in the initiation of preinvasive lung disease.

Our experiments show that deletion of LRIG1 is sufficient to promote murine airway hyperplasia. In vitro, LRIG1 deficient cells display loss of contact inhibition, whereas re-expression of LRIG1 in human lung cancer cell lines impairs growth. We find that LRIG1 forms a ternary complex with EGFR and E-Cadherin at the cell surface. This complex modulates the activity of the EGFR and downstream pathways. We also show that loss of heterozygosity at the LRIG1 locus as well as down-regulation of LRIG1 gene expression are early events in the development of preinvasive human squamous lung cancer.

Our findings imply that lung cancer development is driven by a change in the amplitude of EGFR signaling governed by the loss of contact inhibition.

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LSC 2012 Abstract – Effects of the Hedgehog (Hh) pathway inhibitor GDC-0449 on lung cancer cells and cisplatin resistant lung cancer cells are mediated by lung cancer stem cells (SPs)

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We aimed at investigating if Hh pathway inhibitor GDC-0449 is effective in the lung cancer cell lines HCC (adeno-carcinoma) and H1339 (small cell lung carcinoma) and also the corresponding cisplatin resistant lung cancer cells, and if possible effects of GDC-0449 are mediated via SPs. GDC-0449 inhibited concentration dependently cell growth in both lines, and also cisplatin resistant cells. In HCC and H1339 SPs of 0.57 and 0.46% could be identified, respectively, while in cisplatin resistant cell lines, those were identified as 2.8% and 3.4%, which were significantly higher than the non-cisplatin-resistant lung cancer cell lines. In both cisplatin resistant and non-resistant cells, SP but not non-SP cells were able to repopulate the original tumour population. The Hh receptor smoothened was detectable in SP but not in non-SP cells, showing activation of Hh only in SP. GDC-0449 considerably reduced SP in HCC and H1339 cells, and also in cisplatin resistant HCC and H1339 cells. We demonstrate for the first time that GDC-0449 effectively reduces cell growth in lung cancer cell lines, and remarkable in cisplatin resistant lung cancer cells. This effect is mediated by inhibition of stem cell-like SPs.

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LSC 2012 Abstract – Down-regulated let-7b and mir-126 in tumors and surrounding tissue correlate with high microvessel density and poor survival outcomes in non-small-cell lung cancer patients

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32 squamous lung carcinoma, 18 lung adenocarcinoma and 45 healthy individuals were included. let-7b and miR-126 expression were detected by real-time RT-PCR. 3 tissues of lung cancer patients (tumor, tumor surroundings and healthy lung tissue) were compared.

Expression of anti-angiogenic let-7b and miR-126 were significantly lower in tumor tissue and surroundings compared to both healthy lung tissue of diseased patients and control. There was no difference between tumor and tumor surrounding tissue. High let-7b expression and miR-126 expression were highly associated with both better progression-free and overall survival. High micro-vascular density was negatively associated to let-7b and miR-126 expression and highly associated with poor overcome.

Our results confirm a possible role of those two miRNas in lung cancer angiogenesis and suggest the potential new target angiogenic lung cancer therapy.

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Overcome the EGFR-TKIs resistance with cucurbitacin BE compound by targeting STAT3, ERK1/2 and AKT

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Epidermal growth factor receptor (EGFR) mutant non-small cell lung cancer (NSCLC) is highly sensitive to EGFR tyrosine kinase inhibitors (TKIs) therapy, but acquired resistance eventually develops at about 9-12 months. Overcoming the drug resistance is of great clinical and scientific significance. In this study, We showed that STAT3,ERK1/2 and AKT were persistently activated in the resistant cells with T790M mutation(PC9/ER) and 52 tumor samples from EGFR-TKIs resistant NSCLC patients.The growth inhibition of the triterpenoid compound cucurbitacin BE (Cu BE) was tested in vitro and in vivo against PC9/GR cells. Cu BE can inhibit the growth of PC9 and PC9/GR cells in a dose- and time-dependent manner, resulting in G2/M phase arrest and apoptosis. This was associated with inhibition of activated Stat3,ERK1/2 and AKT, increased level of autophagy(LC3B expression), and down-regulated the expression of caspase 3 and survivin. Moreover, in a nude mouse tumor xenograft model, Cu BE decreased the PC9/GR tumor volume by 46.4% ($P < 0.05$) compared with the mice treated with erlotinib. These data suggest that treatment with CuBE, which can inhibite the activation of STAT3,ERK1/2 and AKT, appears to be an effective strategy for NSCLC patients with EGFR-TKIs resistance.

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Diagnostic yield of ROSE (rapid on-site evaluation) and cell block obtained by endobronchial ultrasonography (EBUS) in patients with lung cancer

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Introduction: The cytological diagnosis of lymph node(LN) metastases depends on many variables such as the number of passes made at each station,access to ROSE or type of sample processing.Our objective was to analyze the diagnostic value of ROSE and cell block(CB) obtained for mediastinal staging by EBUS in lung cancer.
Methods: Selective EBUS sampling was performed to patients with lung cancer and mediastinal disease by chest CT or PET-CT.For each fine needle aspiration(FNA),we collected the results of ROSE,final cytology diagnosis and CB.At least 3 FNA per LN were performed if ROSE did not show malignant cells.
Results: We studied 148 patients from June 2010 to August 2011,of which 49 met the inclusion criteria.87.8% were male with a mean age of 62.7 years(42-78).A total of 130 FNA were performed,being unable to obtain a BC in 23.1% of them.The % of agreement between cytology and CB was 94.9%.BC added 3.1% of new diagnoses.ROSE avoided the need of obtaining 71 FNA,from a total of 134 second and third passes(47%).The % of agreement between ROSE and the final cytology report was 82.6%, presenting a NPV and a PPV of 73% and 100%, respectively.Benignity was confirmed by surgical techniques in all patients with negative EBUS,which represents a NPV of 100% in the studied sample.
Conclusions: 1.CB has a high correlation with cytology(94.9%)but adds few new diagnoses(3.1%).It should be mainly used for immunohistochemical or molecular studies.
2. ROSE avoids 47% of FNA,based on its PPV of 100%.
3. The NPV of cytology after 3 passes with ROSE assessment is 100%.This approach can avoid further confirmatory surgical techniques.

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Prx1 modulates the chemosensitivity of lung cancer to docetaxel through suppression of FOXO1-induced apoptosis

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The level of Prx1, a major 2-Cys peroxiredoxin family member, is frequently elevated in several human cancers, including lung cancer, and this may confer increased resistance to treatment. Although Prx1 suppresses radiation-induced c-Jun NH_2-terminal kinase (JNK) activation and apoptosis in non-small cell lung cancer (NSCLC), the precise mechanism of chemoresistance is not yet clear. In this study, we investigated the role of Prx1 in docetaxel-induced apoptosis in A549 lung cancer cells. We generated shRNA targeting Prx1 in A549 cells to test the sensitivity to docetaxel treatment. The effects of docetaxel on the growth of scrambled- and shPrx1-infected A549 xenograft tumors in nude mice were measured. We found that Prx1 knockdown resulted in enhanced docetaxel-induced cytotoxicity in a dose-dependent fashion. *In vivo*, the growth rate of shPrx1-infected A549 tumors was significantly reduced compared to that of scrambled shRNA-infected A549 tumors. Prx1 knockdown also augmented the inhibitory effects of docetaxel on tumor growth. In addition, Prx1 knockdown increased apoptotic potential through activation of the caspase cascade and suppressed docetaxel-induced phosphorylation of Akt and its substrate forkhead box O1 (FOXO1). Moreover, treatment with the phosphatidylinositol 3-kinase (PI3K) inhibitor LY294002 reduced the phosphorylation of FOXO1 and increased the cytotoxicity of docetaxel in A549 cells. Our findings suggest that Prx1 may modulate the chemosensitivity of lung cancer to docetaxel through suppression of FOXO1-induced apoptosis.

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Overexpression of inhibitor of DNA-binding proteins and angiogenic markers have higher impact on survival of non small cell lung cancer patients

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Background: The inhibitor of DNA binding (Id) proteins have been implicated in oncogenic transformation, progression and in tumor angiogenesis, the last one by regulation of vascular endothelial growth factor (VEGF) expression. Notwithstanding, these mechanisms have not been fully understood. The aim of this study was to evaluate the Ids 1,2,3 and VEGF expression and angiogenesis amount in non small cell lung cancer (NSCLC) and their role on patients' prognosis.
Methods: Immunohistochemistry and morphometry were used to evaluate Ids, VEGF expression and microvessel density (CD34+) in neoplastic and stromal cells from 85 patients with surgically excised NSCLC. The impact of these markers was tested on follow-up until death from recurrence lung cancer.
Results: The Kaplan-Meier survival curve analysis showed that expression of Id-1, CD34 and VEGF were associated with poor prognosis (Log Rank Test, $p<0.001$). A Cox model analysis controlled for histological type, lymph node stage, Ids, VEGF, CD34 and age demonstrated that only Id1, Id3 and vascular density were significantly associated with survival time. A point at the median for Id1, Id3 and vascular density divided patients into 2 groups, each one with distinctive prognosis. Those with higher expression of Id1, Id3 and vascular density had a higher risk of death when compared to those with lower Id-1, Id-3 and vascular density.
Conclusion: In resected NSCLC, Id1, Id3, VGF and vascular density were strongly associated with prognosis. Therefore, Id1 and Id3 seem to contribute on tumor progression and should be considered as prognostic markers in NSCLC.

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Clinicopathological significance and prognostic importance of circulating plasma DNA expression in advanced non-small cell lung cancer and its efficacy as a diagnostic tool

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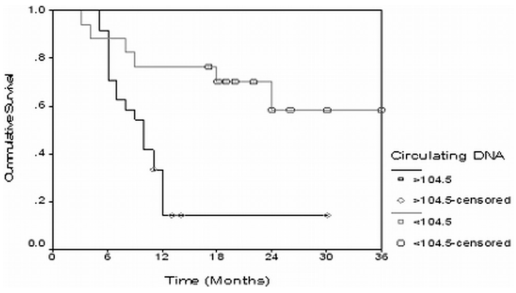
Lung cancer is commonest neoplasm.Thereis continuous need for new prognostic markers. Circulating plasma DNA levels is over-expressed in many cancers, including lung.
Aim of work: To study the expression of circulating DNA in NSCLC and assessment of its utility as a diagnostic marker and impact on therapeutic efficacy.
Methods: Plasma DNA was determined through the use of polymerase chain reaction in 41 patients with advanced NSCLC and 38 age-matched controls. All 41 patients with advanced NSCLC received platinum-based chemotherapy. Circulating plasma DNA levels was correlated with response to therapy, overall survival, and lactate dehydrogenase level.
Results: There was a significant correlation between circulating plasma DNA levels and stage, LDH levels and tumor status. Plasma DNA levels were significantly inversely correlated with treatment response.



Conclusion: Circulating plasma DNA levels is frequently over-expressed in primary NSCLC, and appears to be potentially useful marker for diagnosis, significant predictor of survival and response to therapy. Overall survival according to circulating plasma DNA levels.

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