Conclusions: Preliminary results suggest that Phi29-based whole genome amplification introduces structural biases that may be related to the composition of the underlying DNA sequence. Some of the reproducible biases induced by Phi29-based WGA may be compensated for by amplifying both samples in pair-wise copy number comparisons.

PD2-2-8  Molecular Pathology, Tue, 16:00 - 17:30

The impact of epidermal growth factor receptor gene status on carcinogenesis of small adenocarcinoma of the lung

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Background: Adenocarcinoma is the most frequent histological subtypes of lung cancers and atypical adenomatous hyperplasia (AAH) is considered as a preneoplastic lesion of adenocarcinoma. According to a hypothesis of multistep carcinogenesis, lung adenocarcinoma develops AAH to invasive adenocarcinoma through bronchioloalveolar carcinoma (BAC). Noguchi classified small peripheral lung adenocarcinoma measured 2 cm or less in the greatest diameter into 6 types. Among them, type A, B and C have BAC components. EGFR mutations are frequently detected in never smokers and adenocarcinomas, especially those with BAC features. We investigate EGFR mutations, EGFR gene copy number, and KRAS mutations in AAH and Noguchi’s type A-C and analyzed the association among histological subsets and genetic and clinicopathological factors to clarify the role of genetic alterations on carcinogenesis of adenocarcinoma with BAC component.

Methods: Sixties lesions measured 2cm or less in greatest dimension which were obtained from 48 patients by surgery were studied: 4 AAH, 19 Noguchi’s type A, 15 type B and 22 type C. EGFR mutations were examined using a mutant-enriched PCR assay for exon 19 deletions and L858R exon 21 mutation, and KRAS mutations were examined using a PCR assay for codon 12 point mutations. EGFR copy number was detected by a fluorescence in situ hybridization (FISH) assay.

Results: One lesion of AAHs had EGFR mutations (25%), but there were no KRAS mutations and high EGFR copy number status in AAHs. EGFR alterations had a tendency to increase the positive alteration according to the advance of histological classification, and high EGFR copy number status was significant frequently detected in Noguchi’s type C than AAH-B group including AAH, Noguchi’s type A and B in univariate analysis (Type C versus AAH-B: 31.8% versus 5.3%, P=0.0091). KRAS mutations were detected in 5 lesions (8.3%) among total 60 lesions without statistical correlation with other factors. Multivariate analysis revealed that Noguchi’s type C significantly correlated with larger tumor size (OR=3.61, 95%CI: 1.12-11.6, P=0.031) and high EGFR copy number status (OR=5.94, 95%CI: 1.25-28.3, P=0.025) than AAH-B group.

Conclusions: EGFR mutations occur in the AAH lesion and may influence the carcinogenesis of lung adenocarcinoma. By contrast, increased EGFR copy number may be a late event of tumor development and play a role in the progression of lung adenocarcinoma.

PD2-3-1 Molecular Targets and Prognostic Factors, Tue, 16:00 - 17:30

Prognostic significance and origin of plasma KRAS mutations in patients with non-small cell lung cancer (NSCLC)

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Background: KRAS codon 12 mutations occur in about 30% of non-small cell lung cancer (NSCLC) tissue and are associated with adenocarcinoma histology, poor survival and resistance to erlotinib or gefitinib. In this study, we evaluated the reliability and clinical significance of plasma KRAS mutations in NSCLC patients.

Patients and Methods: 180 Swiss patients with NSCLC were screened for KRAS mutations in plasma and matched peripheral blood mononuclear cells (PBMC) using a combined restriction fragment-length polymorphism and polymerase chain reaction (RFLP-PCR) assay. Survival analysis was performed using the Kaplan-Meier method and the Cox multivariate model. KRAS mutations were validated in a second laboratory by DNA sequencing, using matched plasma, serum, PBMC and tumor tissue.

Results: Baseline characteristics: 69% male, 69% smokers, 86% stage IIIB/IV and 44% adenocarcinoma. Median age at diagnosis was 61 years and median survival was 12 months. Chemotherapy was given to 78% of the patients, 27% had surgical resection and 12% radiation. Mutation screening revealed KRAS mutations in 16/180 (9%) plasma and 0/180 (0%) PBMC samples. Plasma KRAS mutations (P = 0.014), tumor stage (P < 0.001) and surgical resection (P < 0.001) were independent predictors of prognosis in the multivariate model.

Conclusions: Plasma KRAS mutations were associated with poor survival and concordant with tumor KRAS mutations. Further studies are warranted to test if plasma KRAS mutations predict resistance to erlotinib or gefitinib in NSCLC patients.

PD2-3-2 Molecular Targets and Prognostic Factors, Tue, 16:00 - 17:30

Amplification Of Epidermal Growth Factor Receptor Gene And Its Prognostic Implication In Surgically Resected Adenocarcinoma Of The Lung

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Background: An increased copy number for the epidermal growth factor receptor (EGFR) gene has been suggested to be a valid marker to predict response of EGFR inhibitors in the advanced stage of lung cancer. However, no clear evidence has been demonstrated as to whether