246. Genetic and molecular background in pulmonary fibrosis

P1994
Mutations in SFTPC, SFTPA2 and TERT explain 60% of familial pulmonary fibrosis and correlate to specific disease phenotypes

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Idiopathic Pulmonary Fibrosis (IPF) is a fatal lung disease, histologically characterized by diffuse interstitial remodeling and patchy inflammation. A significant percentage of IPF patients have a familial form of the disease. Separate reports have identified mutations in Surfactant Protein-C (SFTPC), Surfactant Protein-A2 (SFTPA2), Telomerase Reverse Transcriptase (TERT) or Telomerase RNA component (TERC) in these families.

We determined the frequency of mutations in SFTPC, SFTPA2, TERT and TERC in 20 patients with Familial Pulmonary Fibrosis (FPF).

Heterozygous non-tolerated sequence changes were detected in 12 out of 20 patients, consisting of 5 SFTPC, 2 SFTPA2 and 5 TERT mutations. Mutations segregated with disease in each family and haplotype analysis showed that identical mutations had arisen independently. Families with SFTPC and SFTPA2 mutations always had evidence of parent-offspring disease transmission, while in families with TERT mutation sibs were affected. Pediatric pulmonary disease occurred only in families with SFTPC mutations. Carriers of an SFTPA2 mutation also suffered from lung cancer. Families with a TERT mutation usually presented as typical IPF and did not show clear symptoms associated with other known syndromes of telomere shortening.

This is the first report of a cohort of IPF families that is completely sequenced for candidate genes. We could identify a mutation in 60% of patients with FPF. These mutations correlated with a specific disease phenotype. The function of each of the mutated genes is very different, but all indicate towards a central role for the alveolar type II cell in disease pathogenesis.
P1995

Association between polymorphisms in the P53 and P21 genes and IPF
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Introduction: Idiopathic pulmonary fibrosis (IPF) is devastating and progressive lung disease. Its aetiology remains unclear but is thought to involve damage to the epithelium and abnormal repair. Alveolar epithelial cells near areas of remodelling show an increased expression of proinflammatory mediators. The purpose of this study was to investigate the role of genes involved in cell cycle control in IPF.

Materials and methods: We included 353 controls and 77 IPF patients and determined genotypes for five polymorphisms in the P53 gene and four polymorphisms in CDKN1A, the gene encoding p21. In PBMC from 16 healthy controls mRNA expression of P53 and p21 was determined.

Results: The rs12951053 and rs1402273 polymorphisms in the p53 gene were significantly associated with survival in IPF patients. Carriers of the minor allele had a 4-year survival of only 22% versus 57% in the non-carrier group (p=0.006). All four polymorphisms in CDKN1A were significantly predisposed to IPF. The rs2395655G allele was associated with an increased risk of developing IPF. In addition, the rs2395655G allele was associated with a rapid decline in lung function. The rs733590 polymorphism was significantly associated with p21 mRNA expression levels.

Conclusion: This study reports the novel finding that polymorphisms in the p53 gene are associated with survival and polymorphisms in the p21 gene predispose to IPF. This suggests cell cycle defects are involved in the pathology of IPF. Variations in the p53 and p21 genes may impair the response to cell damage and increase the loss of alveolar epithelial cells.


P1996

Genetic variability in the IL1RN gene and the balance between IL-1Ra and IL-1β in IPF
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Introduction: Idiopathic pulmonary fibrosis (IPF) is a rapidly progressive interstitial lung disease of unknown etiology. Interleukin (IL)-1β plays an important role in inflammation and has been associated with fibrotic remodelling. We investigate the balance between IL-1β and interleukin-1 receptor antagonist (IL-1Ra) in bronchoalveolar lavage fluid (BALf) and serum as well as the influence of genetic variability in the IL1B and IL1RN gene on disease susceptibility and cytokine levels.

Materials and methods: In 77 IPF patients and 349 healthy controls, single nucleotide polymorphisms (SNPs) in the IL1RN and IL1B gene were determined. Serum and BALf IL-1Ra and IL-1β levels were measured using a multiplex suspension bead array system and were correlated with genotypes.

Results: In BALf a significantly increased IL-1Ra/IL-1β ratio was found in IPF patients compared to healthy controls. In the IL1RN gene, one SNP was associated with both the susceptibility to IPF and reduced IL-1Ra/IL-1β ratios in BALf.

Conclusion: Our results show that genetic variability in the IL1RN gene plays a role in the pathogenesis of IPF and that this role may be more important than until recently thought. IPF patients appear to have a decreased level of IL-1Ra, which might contribute to a pro-inflammatory and pro-fibrotic environment in their lungs.

P1997

The relationship of IL-4 cytokine gene polymorphisms, HRCT and histopathological score in patients with idiopathic pulmonary fibrosis
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Introduction: Idiopathic pulmonary fibrosis (IPF) is a serious disease with unknown etiology, where an influence of cytokine gene polymorphisms is presumed. We compared HRCT and histopathological score (IS) and histopathological score with IL-4, and IL-4RA gene polymorphisms in IPF patients.

Subjects and methods: IPF was diagnosed in 46 patients according to ATS/ERS consensus statement. 43 patients had evaluable HRCT investigations, 14 patients had surgical lung biopsy. HRCT scans were evaluated using IS and AS scales by Gay et al. The histopathological evaluation of lung biopsies comprised: myofibroblast foci (MF), inflammation, eosinophils, granulomas and Ascrict criteria for fibrosis grading. The IL-4 (-1098) (-590) (-33) and IL-4 RA +1902 gene polymorphisms were characterized utilizing a PCR-SSP method.

Results: AS was higher in IL-4 haplotypes 1 TTC and TTC carriers (p=0.0423). Ascrict score was more advanced in IL-4 haplotype 2 GCC (p=0.013) and MF counts were higher in TTC carriers (p=0.0736). IL-4 RA +1902 A1 G and IL-4 -590 A1 T correlated with higher AS (p=0.0535, p=0.0123). Ashcroft score was higher in IL-4 -1098 A2 G and IL-4 -33 A1 T carriers (p=0.0443, p=0.0915).

Conclusions: We assume that IL-4 and IL-4RA polymorphisms might influence HRCT and histopathological phenotypes of IPF. The correlation of all genotypically relevant IL-4 genes polymorphisms (especially IL-4 -33 T) with AS could mean, that new alveolar lesions with continuing fibroses are more pronounced in these polymorphisms carriers. The positive correlation of IL-4 -33 A1 T with Ascrict score might support a hypothesis of fibrogenetic role of IL-4 in IPF.

P1998

Familial idiopathic pulmonary fibrosis and “genetic anticipation”
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Background: Telomere dysfunction can be associated to “genetic anticipation”, earlier age of onset and more rapid progression of disease in succeeding generations, well known in Dyskeratosis Congena, due to heterozygous TERC/TERT mutations (essential components of telomerase), which have been reported in 8-15% of families with Idiopathic Pulmonary Fibrosis (IPF) and 1-3% of non familial IPF.

Aims and objectives: Retropective study to assess whether a form of genetic anticipation can be found in families with IPF and to establish clinical features and outcome of familial IPF in comparison to non familial IPF.

Methods: We reviewed all files of patients with familial IPF seen at our department (17 families consisting of a total of 37 individuals) and compared age at diagnosis, clinical progression, frequency of acute exacerbations and survival outcomes with a database of 162 patients with non familial IPF. We are sequencing TERT and TERC genes in patients with familial IPF.

Results: Among the familial IPF patients, 5 had their father or mother affected, in all these cases the son/daughter was diagnosed earlier than the parents (mean age 56.4 years vs 72.4), and had a more rapid progression (all patients had at least one disease progression during follow-up); mean age of diagnosis of siblings and non familial IPF patients was 60.9 years and 65.4 years respectively.

Conclusions: We hypothesize a form of genetic anticipation in families with IPF with the latest generations being most severely affected. We are sequencing TERT and TERC genes in these patients to demonstrate that genetic anticipation in Familial IPF is associated to the inheritance of shorter-than-normal telomeres in association with the defective telomerase activity.

P1999

Association of single nucleotide polymorphisms in 4 genes (VDR, COL1A1, CALCR and BGLAP) with susceptibility to steroid osteoporosis in patients with idiopathic pulmonary fibrosis (IPF)
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Steroid osteoporosis is a serious medical and economic problem. At the same time, osteoporosis is a polydiscogenic problem. Aim: To assess effectiveness of steroid osteoporosis prevention by antiresorptive agents (ARA - Bisphosphonates, Calcitomin) in patients with IPF with different genetic predisposition to osteoporosis.

Subjects: 114 patients with IPF, 19 males, 95 females, age 56.7±10.6 years, treated with Corticosteroids (CS).

Methods: Bone mineral density (BMD) measuring by DEXA, patients’ questionnaires and genotyping were used. Genomic DNA was isolated from peripheral leukocytes. We investigated 5 SNPs by PCR-RFLP analysis in 4 genes: vitamin D receptor, collagen type alpha1, calciotnin receptor and osteocalcin.

Results: Severity of BMD loss and bone fractures occurrence strongly correlated with CS cumulative dose (p=0.010 and p=0.001, respectively). Multiple regression analysis showed significant influence of only VDR-FokI on BMD (p=0.009), and BGLAP was about significant (p=0.081). Environmental factors, firstly ARA intake, seems to have stronger influence on BMD than genes (adjusted R²=0.065).

VDR 601796 rs1544410 BslI 0.382
VDR 601796 rs2238571 FokI 0.408
COL1A1 1205015 rs800012 Van/111 0.175
CALCR 114131 rs800197 AluI 0.276
BGLAP 112280 rs800247 HinfII 0.180

Conclusion: ARA administration is necessary for all patients with IPF, irrespec-
tive of genotype. VDR-FokI analysis is useful to reveal subjects with increased risk of osteoporosis. BGLAP analysis is useful in order to show higher BMD loss prevention. Further efforts are required to clarify weight of BGLAP.
P2000
The genetic polymorphism of metalloproteinases MMP2, 7, 9 and MMP inhibitor TIMP2 in sarcoidosis
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Background: Increased activity of metalloproteinases may play a role in the initiation and propagation of inflammation in sarcoidosis. It may also be one of the factors responsible for the development of lung fibrosis. The aim was to verify whether polymorphisms of MMP2, C737T, MMP7 A181G, MMP9 T1702A and tissue inhibitor of metalloproteinase (TIMP2) G2418C predispose to sarcoidosis.

Material and methods: 139 patients with sarcoidosis and 100 healthy subjects were included. MMPS and TIMP2 mRNA were measured in peripheral blood lysate using real time RT-PCR. DNA for genetic polymorphism was extracted from peripheral blood by GTC method. Protein concentrations in peripheral blood lysate were measured by ELISA, and MMP2 and 9 activities in BAL fluid were estimated by gel zymography.

Results: TT genotype of MMP9 T1702A was more frequent in sarcoidosis (p=0.0001). The presence of the risk allele was shown using both methods. The significance of differences in MMP7 and TIMP2 polymorphisms. MMP2, 7, 9 and TIMP2 mRNA, as well as concentrations of these molecules were elevated (p<0.0001). There was no relation to radiological stages, lung function test parameters, activity markers and the presence/absence of Löfgren syndrome. There were no differences in the distribution of MMP2, MMP7 and TIMP2 polymorphisms. MMP2, 7, 9 and TIMP2 mRNAs, as well as concentrations of these molecules were elevated (p<0.0001 for each). Gel zymography did not show differences in MMP2 and MMP9 activity in BAL fluid between different genotypes.

Conclusions: The TT homozygotes of MMP9 T1702A genotype may be predisposed to sarcoidosis. Elevated mRNAs of all these molecules suggest their inducibility.

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P2001
Dose-dependent pro- or anti-fibrotic effects of calciuminhibitors in bronchoalveolar lung allogeneic stem cell transplantation
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Background: Bronchiolitis obliterans (BO) is a common complication after allogeneic SCT. It has no beneficial effect during the fibroproliferative phase of BO following SCT.

Methods: Primary cultures of human lung fibroblasts were grown from surgical lung biopsies obtained from 8 patients with BO after SCT. Fibroblasts were stimulated with increasing concentrations of each drug, and cell proliferation was measured by an MTS assay. The biological effects of ET-1 were monitored by ET immunoreactivity. The biological effects of ET-1 are mediated through two distinct receptors, ET-A and ET-B.

Results: In fibroblasts derived from patients with BO after SCT low concentrations of CsA (0.01 mg/l, 0.1 mg/l) and FK506 (0.001 mg/l, 0.01 mg/l) significantly inhibited cell proliferation and ET-1 immunoreactivity. The biological effects of ET-1 were monitored by ET immunoreactivity. The biological effects of ET-1 are mediated through two distinct receptors, ET-A and ET-B.

Conclusions: Our data suggest that calciuminhibitors such as CsA and FK506 have no beneficial effect during the fibroproliferative phase of BO following allogeneic SCT.

Methods: We aimed at analyzing membrane-bound Fasl expression on alveolar macrophages (AM) and lymphocytes (AL) as well as soluble Fasl (sFasl) levels in bronchoalveolar lavage (BAL) from ILDs patients: pulmonary sarcoidosis (PS), hypersensitivity pneumonitis (HP), silicosis, asbestosis, idiopathic pulmonary fibrosis (IPF), nonspecific interstitial pneumonia (NSIP), and healthy subjects (n=89,12,7,8,23,6,17, resp.).

Results: In IPF significantly increased percentage of AM FasL+ and CD8+ FasL+ cells as well as sFasL, levels in BAL were found. Increased sFasL levels were also observed in HP, NSIP and asbestosis were characterized by higher AM FasL+ levels. The expression of both receptors was equally expressed, whereas in control fibroblasts expression of both receptors was lower compared to IPF cells. Stimulation with TGF-beta1 caused a further increase of ET-A and ET-B receptor expression in fibroblasts.

Conclusions: The concurrent comparative BAL analysis for Fasl expression indicates that Fasl+ AM and AL (especially Tc cells) comprise an important element in the pathogenesis of fibrotic process, mostly in IPF. Fasl might play a crucial role in other fibrosis-complicated ILDs, like NSIP and asbestosis.

P2003
Heme oxygenase−1 induced by quercetin attenuates TGF−β-stimulated collagen production in fibroblasts
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Quercetin is a flavonoid with a wide variety of cytoprotective and modulatory functions. Heme oxygenase−1 (HO−1) is an inducible enzyme. Its reaction product, carbon monoxide (CO), confers cellular protection in a number of conditions and diseases associated with oxidative or inflammatory injury. Furthermore, quercetin was reported to be a potent inducer of HO−1 in several cell types. We hypothesized that quercetin suppresses the production of collagen in fibroblasts via the induction of HO−1. Here, we showed that quercetin induced HO−1 and growth factor-β (TGF-β) inhibited collagen induction in NH373T cells and in normal human lung fibroblasts. This suppressive effect of quercetin was mediated by quercetin-induced HO-1. The suppression of collagen production was confirmed by the reaction product of HO-1, CO, but not by bilirubin. Furthermore, the translocation of the nuclear factor E2-related factor−2 (Nrf2), an important transcription factor that regulates the expression of HO-1 from the cytoplasm to the nucleus, was demonstrated in NH373T cells by exposure to quercetin.

Methods: Our data demonstrate for the first time a difference in the pattern of initiation and propagation of inflammation in sarcoidosis. It may also be one of the factors responsible for the development of lung fibrosis. The aim was to verify whether polymorphisms of MMP2, C737T, MMP7 A181G, MMP9 T1702A and tissue inhibitor of metalloproteinase (TIMP2) G2418C predispose to sarcoidosis.

Results: In fibroblasts derived from patients with BO after SCT low concentrations of CsA (0.01 mg/l, 0.1 mg/l) and FK506 (0.001 mg/l, 0.01 mg/l) significantly inhibited cell proliferation and ET-1 immunoreactivity. The biological effects of ET-1 are mediated through two distinct receptors, ET-A and ET-B.

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Results: In IPF significantly increased percentage of AM FasL+ and CD8+ FasL+ cells as well as sFasL, levels in BAL were found. Increased sFasL levels were also observed in HP, NSIP and asbestosis were characterized by higher AM FasL+ levels. The expression of both receptors was equally expressed, whereas in control fibroblasts expression of both receptors was lower compared to IPF cells. Stimulation with TGF-beta1 caused a further increase of ET-A and ET-B receptor expression in fibroblasts.

Conclusions: The concurrent comparative BAL analysis for Fasl expression indicates that Fasl+ AM and AL (especially Tc cells) comprise an important element in the pathogenesis of fibrotic process, mostly in IPF. Fasl might play a crucial role in other fibrosis-complicated ILDs, like NSIP and asbestosis.

P2004
Different expression pattern of endothelin receptors in primary human lung fibroblasts derived from idiopathic pulmonary fibrosis compared to healthy controls
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Background: Endothelin-1 (ET-1) has a considerable fibrogenic activity and it has been implicated in the pathogenesis of pulmonary fibrosis. Increased levels of ET-1 have been demonstrated in serum and bronchoalveolar lavage fluid of patients with idiopathic pulmonary fibrosis (IPF), and lung tissue of IPF patients show increased ET-1 immunoreactivity. The biological effects of ET-1 are mediated through two receptors – ET-A and ET-B. However, disease specific patterns of ET receptor expression in fibrotic and normal primary human lung fibroblasts had not been demonstrated yet.

Methods: Primary human lung fibroblasts were isolated and propagated from lung parenchyma derived from patients with IPF (n=4) as well as from parenchyma derived from healthy controls (n=8). Isolated cells were grown to confluence. After transforming growth factor beta1 (TGF-beta1) stimulation total protein was harvested and immuno blot analysis was performed.

Results: In fibroblasts derived from patients with IPF the ET-A and ET-B receptors were equally expressed, whereas in control fibroblasts expression of both receptors was lower compared to IPF cells. Stimulation with TGF-beta1 caused a further increase of ET-A and ET-B receptor expression by IPF fibroblasts, but no such increase was observed in control fibroblasts.

Conclusion: Our data demonstrate for the first time a difference in the pattern of...
ET receptor expression between IPF and normal lung, and a disease-specific reaction upon stimulation with TGF-beta1. Our observations may have implications for our understanding of the roles of ET-1 and TGF-beta1 in the pathogenesis of IPF.

P2005
Role of phosphatidylinositol-3-kinase (PI3K) in TGF-β-induced proliferation and differentiation of human lung fibroblasts into myofibroblasts
Enrico Cornaggia Trussello, Evolina Pagano, Elisa Gila, Maria Jemmolo, Nunzio Crimi, Carlo Vancheri. Clinical and Molecular Biomedicine, University of Catania, Catania, Italy

Molecular mechanisms and pathogenesis of idiopathic pulmonary fibrosis (IPF) remain unclear yet TGF-β-induced differentiation and proliferation of fibroblasts/myofibroblasts are recognized as primary events. We investigated the role of PI3K/Akt pathway in TGF-β-induced proliferation of human lung fibroblasts and their differentiation into myofibroblasts. Moreover, we evaluated the expression of all PI3K class I p110 isoforms (α, β, δ and γ). By using selective inhibitors, we also dissected the functional role of these isoforms.

Ex-vivo human lung fibroblasts were stimulated with TGF-β in the presence or absence of PI3Ks pan-inhibitor LY294002 as well as of selective inhibitors. Cell proliferation was evaluated by cell counts and WST-1 proliferation assay. Western blot analysis and the Sircol assay were used for assessing a-Smooth Actin (SMA) expression and collagen production, respectively. RNA messenger and protein levels of p110 isoforms were evaluated by QRT-PCR and western blot analysis, respectively.

Here we show that LY294002 was able to abrogate the TGF-β-induced increase in cell proliferation, α-SMA expression and collagen production besides to inhibit Akt phosphorylation, thus demonstrating the central role of PI3K/Akt pathway in TGF-β-induced lung fibroblast proliferation and differentiation. Moreover, we show that PI3K p110 and p100 are functionally expressed in human lung fibroblasts, in addition to the ubiquitously expressed p100 and p110. Finally, we demonstrate that TGF-β nuclear translocation of p110 and p100 in the fibroblastic process. Overall, these results suggest that specific class I PI3K isoforms can be pharmacological targets in IPF.

P2006
Inhibition of TGF-β1-induced extracellular matrix production in primary human pulmonary fibroblasts by rapamycin
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Fibroblasts proliferation and extracellular matrix (ECM) accumulation play a key role in the development and the progression of pulmonary fibrosis. Rapamycin has been showed to decrease extracellular matrix in normal mesangial cells and human lung fibroblasts. This study is to examine the role of rapamycin on transforming growth factor β1 (TGF-β1)-induced lung fibrosis and to determine the related mTOR signaling pathways in primary human pulmonary fibroblasts. Primary human pulmonary fibroblasts were isolated from healthy lung transplantation donors. Growth arrested, synchronized cells were treated with TGF-β1 (10ng/ml) and various concentrations rapamycin (0.01, 0.1, 1, 10ng/ml) for 24h. mTOR, p-mTOR, S6K and p-S6K were assessed by Western blot analysis, type III collagen and fibronectin secretion detected by Elisa assay, type III collagen and fibronectin mRNA level determined by Realtime-PCR assay. TGF-β1 (10ng/ml) increased type III collagen, fibronectin secretion and mRNA level obviously compared to controls (p<0.05), rapamycin reduced the enhanced production of type III collagen, fibronectin mRNA and protein induced by TGF-β1 accompanying inhibition of S6K and mTOR phosphorylation. These data demonstrated that rapamycin inhibited TGF-β1-induced type III collagen/fibronectin mRNA and protein may be through mTOR/p70S6k pathway, rapamycin maybe have potential effect for being used in the treatment of pulmonary fibrosis.

P2007
Familial cases of idiopathic pulmonary fibrosis: Clinical observation
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Background: Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, often fatal interstitial lung disease of unknown etiology. Familial idiopathic pulmonary fibrosis (FIPF) is defined when two or more affected individuals are identified in one family. FIPF accounts for 0.5-2.2% of all IPF cases.

Results: We found 10 FIPF patients in 5 families among totally observed 475 IPF cases. There were 3 pairs of siblings (2 males and 4 females) and 2 pairs of mother and daughter. Fifteen FIPF was diagnosed according to ATS/ERS criteria, histologically proven in 9 of 10 subjects. The mean age of IPF manifestation appears to be low: 37±5.3 years. All patients were treated by systemic corticosteroids, 4 of 10 - in combination with cytotoxic agents: 2 of 10 (mother and daughter in one family) have rather favorable course of IPF and are alive. The rest 8 cases had rapid severe progression of disease. Among them two patients are still alive, but demonstrate severe deterioration of their conditions, 6 - died within five years since first symptoms of disease occurred. The cause of death was progressive respiratory failure in 4 cases, respiratory failure with pneumonia in one case and lung cancer in another case.

Conclusion: 2.1% of our cohort of IPF patients has familial history of pulmonary fibrosis. Although rare, such cases represent an important subgroup in which genetic susceptibility to lung fibrosis plays a significant role. FIPF appears to be genetically indistinguishable from non-familial forms, but characterized by younger age of onset, resistance to treatment, progressive course and unfavorable prognosis. Multimodal metabolic analysis could improve our understanding of the pathogenic mechanisms of IPF.

P2008
Paraquat-induced epithelial-mesenchymal transition: Role of Rac1b/Akt
Twi
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Objective: To examine whether paraquat (PQ), a well-known reactive oxygen species (ROS) producer, could induce epithelial-mesenchymal transition (EMT) which involving in ROS-mediated pulmonary fibrosis and possible mechanisms.

Method: Human alveolar epithelial (A549) cells were cultured and exposed to sub- lethal doses of PQ, specific signaling pathway inhibitors and siRNAs for ROS signaling pathway. Intracellular ROS was measured with DCFH-DA. Protein and RNA was evaluated by Western blot and real-time PCR, respectively.

Results: Intracellular ROS increased after various concentration paraquat stimulus for 5 minutes (p<0.05), while only PQ at the concentration of 20μM (PQ20) induced EMT manifested as increased fibroinectin, decreased E-cadherin and a fibroblast-like cell appearance. mRNA of Twist, a key transcriptional factor for EMT, increased after PQ20 stimulus for 30minutes (p<0.05), accompanied with a dramatic increase of nuclear translocation of p110 and p100 in the fibroblastic process.

Overall, these results suggest that specific class I PI3K isoforms can be pharmacological targets in IPF.

P2009
The prevalence of neoplastic transformation in idiopathic pulmonary fibrosis (IPF) lungs. A report from a transplanted IPF population
Elisabetta Balestro1, Emanuela Rossi 1, Francesca Lunardi 2, Nazarena Nannini 2, Monica Loy1, Federico Rea1, Marina Saetta1, Fiorella Calabrese2. 1Department of Cardiac, Thoracic and Vascular Science, University of Padua Medical School, Padua, Italy; 2Department of Diagnostic Medical Sciences and Special Therapies, University of Padua Medical School, Padua, Italy

Idiopathic pulmonary fibrosis (IPF) is known to be associated with increased risk of lung cancer being about 3 times higher than the general population. The prevalence of lung cancer in patients with IPF is currently unknown. In this study, we aimed to determine the prevalence of lung cancer in patients with IPF and to identify clinical predictors of lung cancer development.

Methods: We reviewed the medical records of all lung transplant recipients who underwent IPF at our center between 2000 and 2010. The study population included 374 IPF patients (F:M=17:37). Although all lungs showed metaplasia, the score of squamous (p>0.001), cuboidal (p=0.018) and bronchial (p=0.008) metaplasia was significantly higher in the “cancer” group. The reviewers were blinded to the diagnosis of IPF and to the presence of lung cancer.

Results: Nine cases of lung cancer were identified among 374 IPF patients (2.4%). The prevalence of IPF with lung cancer was 2.4%. The prevalence of lung cancer was significantly higher in the “cancer” group (p=0.003). In multivariate analysis, the presence of bronchial metaplasia was an independent predictor of lung cancer (p=0.04).

Conclusion: The prevalence of lung cancer is 2.4% in IPF patients. The prevalence of lung cancer is significantly higher in the “cancer” group. The presence of bronchial metaplasia is an independent predictor of lung cancer.

P2010
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