News Release

Title

Discovery of novel blood biomarker predicting the risk of acute exacerbation and disease progression: serum mitochondria DNA in idiopathic pulmonary fibrosis

Key Points

• Patients with idiopathic pulmonary fibrosis (IPF), an incurable, fatal lung disease of unknown origin, often suffer from an acute exacerbation, an unpredictable worsening of the disease that is highly deadly.

• A study lead by Nagoya University in collaboration with Tosei General Hospital and Yale School of Medicine that included 70 patients with IPF revealed that increased concentrations of mitochondrial DNA (mtDNA) in the sera obtained at the time diagnosis was associated with earlier development of acute exacerbation, higher risk of disease progression within a year, and worse overall prognosis.

• These findings demonstrated the potential of circulating mtDNA as a novel biomarker predictive of acute exacerbation and disease progression of IPF.

Summary

Dr. Koji Sakamoto (first and corresponding author, Assistant Professor, Department of Respiratory Medicine), Dr. Taiki Furukawa (co-first author, Medical IT Center), and Naozumi Hashimoto (Associate Professor, Department of Respiratory Medicine) at Nagoya University Graduate School of Medicine (Dean: Kenji Kadomatsu, MD, PhD), showed that increased concentrations of circulating mitochondrial DNA (mtDNA) is a novel predictor of disease progression and acute exacerbation (AE) of idiopathic pulmonary fibrosis (IPF).

IPF is a progressive, fatal lung disease of unknown etiology. Some patients experience rapid worsening of lung function while others experience more modest decline. Presently, there are no accepted biomarkers that predict clinical deterioration. The research group quantified concentrations of mtDNA in the sera obtained from 70 IPF patients at the time of diagnosis and identified a relationship with various clinically

significant parameters, such as prognosis. The results revealed that increased serum mtDNA was significantly associated with greater risk of AE and disease progression in one year, as defined by the composite outcome of >10% percent predicted forced vital capacity (%FVC), AE, and death. The present study also confirmed the association between serum mtDNA concentrations and mortality.

Overall, these findings support the potential of circulating mtDNA as a novel biomarker of poor clinical outcomes in IPF, namely disease progression, development of AE, and mortality. Because the predictive performance of serum mtDNA was comparable to that of established biomarkers such as KL-6 and SP-D, further study of mtDNA could lead to new clinical discoveries into this enigmatic disease.

Research Background

IPF is an irreversible and progressive fibrotic lung disease unknown cause. Currently, the prevalence in the Japanese population is about 10 per 100,000/year with an incidence of 2.23 per 100,000/year. There is no curative treatment available against this devastating disease. Moreover, the disease course is highly variable as some patients inexplicably develop an AE, an unpredictable and potentially lethal complication manifested as rapid worsening of respiratory status. AE is estimated to be the leading cause of death for IPF patients, and the development of a biomarker to herald its development is an unmet clinical need.

Mitochondria are a small organelle inside the cells that produce the energy to meet the metabolic demands of the cell – frequently known as the “powerhouse of the cells.” Recent studies have implicated mitochondrial dysfunction in the pathology of IPF; cells will release their mtDNA under stress to stimulate an immune response. Recent work has shown that mtDNA released into the circulation can be measured as a biomarker of these processes that reflects disease activity.

Research Results

The research group retrospectively collected preserved blood samples and clinical information in a cohort of IPF patients that included 70 subjects with a median age of 66 and 56 males (80.0%). Median follow-up time was 52 months, during which time 17 patients experienced AE-IPF (25.7%). For these patients, serum mtDNA concentrations were determined by quantitative PCR.

The median concentration of mtDNA in the serum was 801 copies/μl. When subjects

were stratified by this value, those with high serum mtDNA concentrations (≥801 copies/μl) exhibited higher incidence of AE, greater annual decline in %FVC, and mortality.

They conducted time-dependent receiver operating characteristic (ROC) curve analysis (Figure 1). It revealed that a serum mtDNA concentration of 1371.5 copies/μl can reliably stratify subjects at risk for developing an AE within one year (sensitivity of 85.4%, specificity of 80.6%, area under the curve (AUC): 0.90). To further confirm its predictive role for AE-IPF, they then conducted a competing risk analysis with mortality as a competing risk factor. A substantially higher risk for developing AE (median incidence time 5.8 vs 24.3 months, Figure 2) was observed in patients with elevated serum mtDNA levels. These results demonstrated that elevated circulating mtDNA levels predict early development of AE-IPF.

The team also compared the predictive capacity of mtDNA and other serum biomarkers for disease progression within one year. In this analysis, disease progression was defined as > 10% absolute decline in %FVC, AE, or death within one year. Circulating mtDNA concentrations was a stronger predictor of disease progression (Figure 3) than KL-6 or SP-D, both of which are widely used in clinical practice in Japan.

Finally, the team used the same cutoff value (1371.5 copies/μl) and confirmed prior reports showing that elevated concentrations of circulating mtDNA is associated with increased mortality (median survival: 76.6 months versus 36.2 months, p=0.005 by log-rank test).

Overall, the research team provided robust evidence supporting circulating mtDNA as a biomarker of poor clinical outcomes in IPF. They found that elevated serum mtDNA levels were associated with the development of disease progression, AE, and worse survival.

Research Summary and Future Perspective

In the present study, the research team elucidated the potential of serum mtDNA as a biomarker predicting the disease progression and development of AE in IPF. Their future research plan includes (1) a validation of their findings in a prospective, multicenter cohort, (2) assessment of serum mtDNA in response to anti-fibrotic therapies, and (3) Perform in vitro studies to characterize the cellular mechanisms of mtDNA in AE-IPF in vivo.

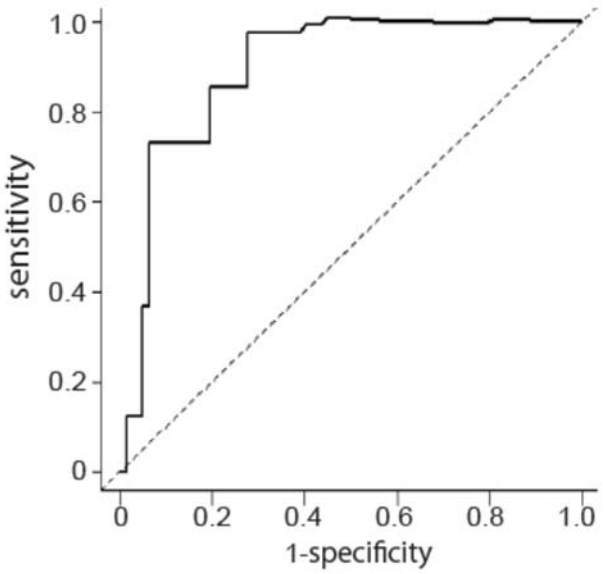

Figure 1: Time dependent ROC curve assessing predictive value of mtDNA for acute exacerbation

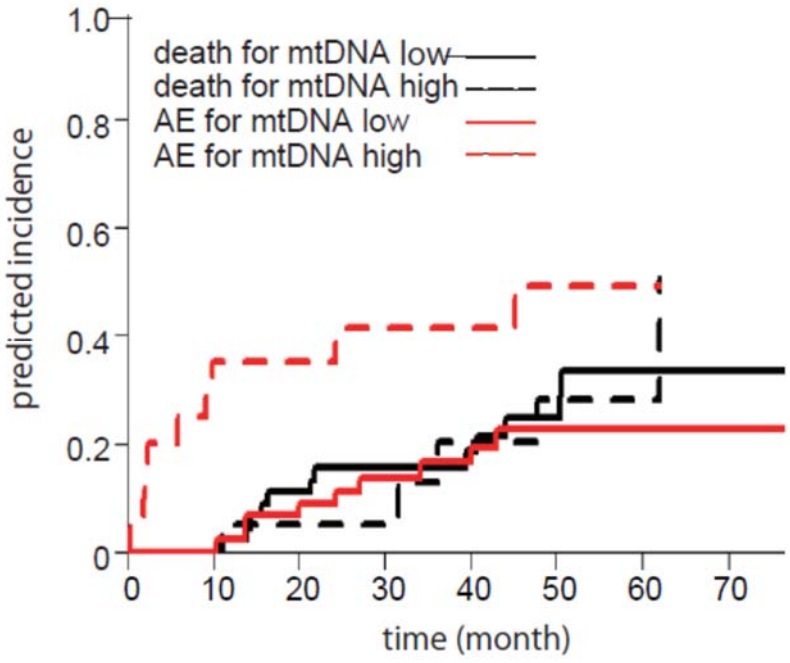

Figure 2: Cumulative incidence curves of acute exacerbation (red) and competing all-cause mortality (black) stratified by serum mtDNA level.

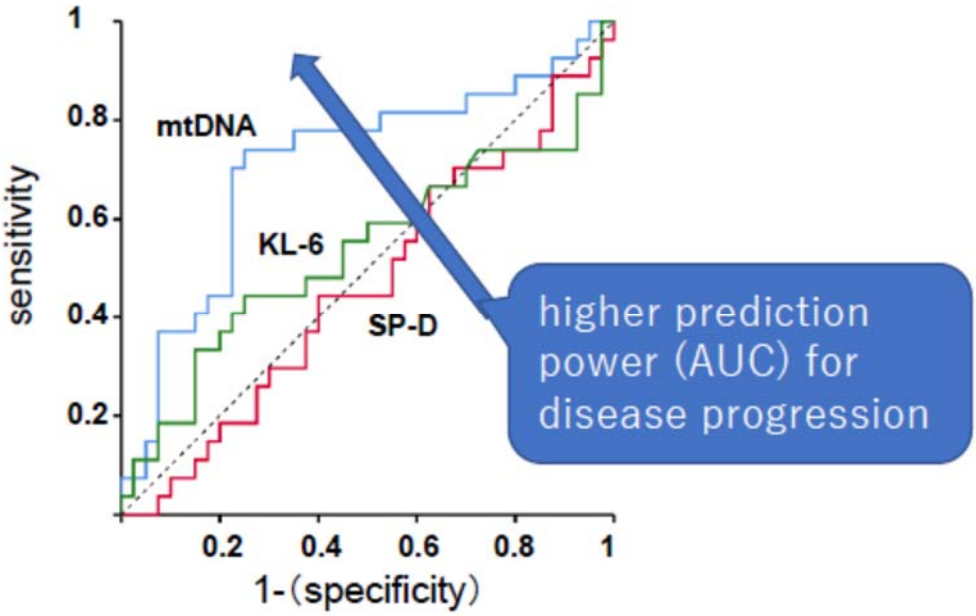

Figure 3: ROC curves for evaluating serum biomarkers as predicting composite outcome (>10% absolute decline of %FVC, acute exacerbation, or death) within a year.

Publication

Serum mitochondrial DNA predicts the risk of acute exacerbation and progression of IPF
Koji Sakamoto[1*], Taiki Furukawa[2*], Yasuhiko Yamano[3], Kensuke Kataoka[3], Ryo Teramachi[1], Anjali Walia[4], Atsushi Suzuki[1], Masahide Inoue[1], Yoshio Nakahara[1], Changwan Ryu[4], Naozumi Hashimoto[1], Yasuhiro Kondoh[3]
[1]Department of Respiratory Medicine, Nagoya University Graduate School of Medicine
[2]Department of Medical IT Center, Nagoya University Hospital, Nagoya, Japan
[3]Department of Respiratory and Allergy, Tosei General Hospital, Seto, Japan
[4]Section of Pulmonary, Critical Care, and Sleep Medicine, Yale University School of Medicine, New Haven, Connecticut
*These authors contributed equally to this work.
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