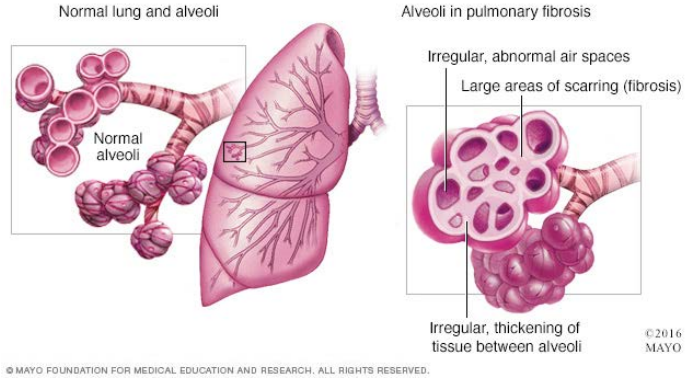
Idiopathic Pulmonary Fibrosis (IPF)

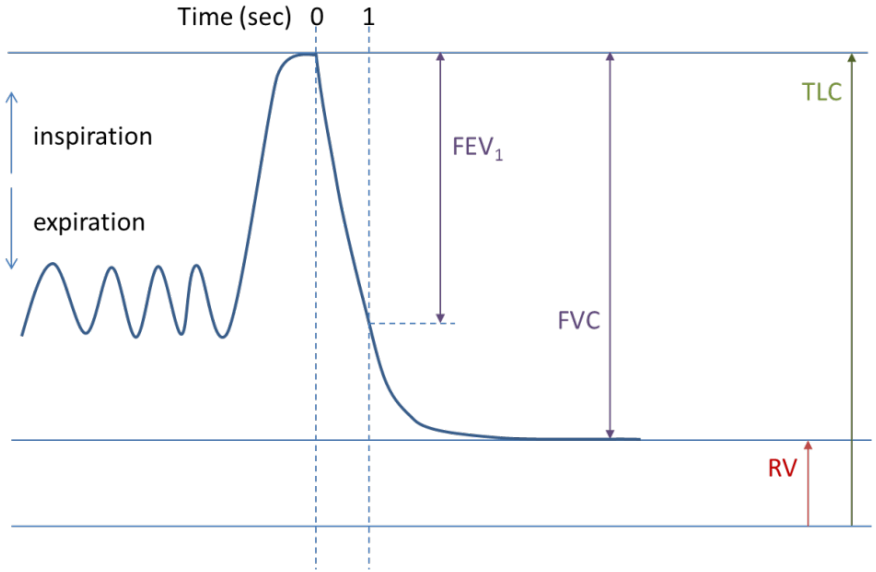
By: Sa Kong

What is Pulmonary Fibrosis?



- Chronic lung disease
  - Currently no cure
  - Life expectancy of patients is usually less than 5 years
  - Scarring of lung tissues causing it to become stiff and thickened
- Symptoms:
  - Difficulty breathing
  - Weight loss
  - Fatigue

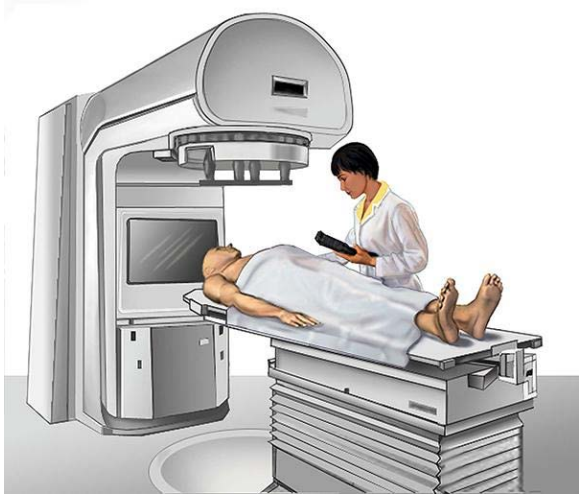
Categorization



- 4 stages of disease
  - Mild
  - Early
  - Severe
  - Advanced
- GAP Index Evaluation
  - Places patients in the above stages based on these criterias
    - Age
    - Recent respiratory hospitalization
    - Baseline Forced Vital Capacity (FVC)
    - 24 Week change in FVC

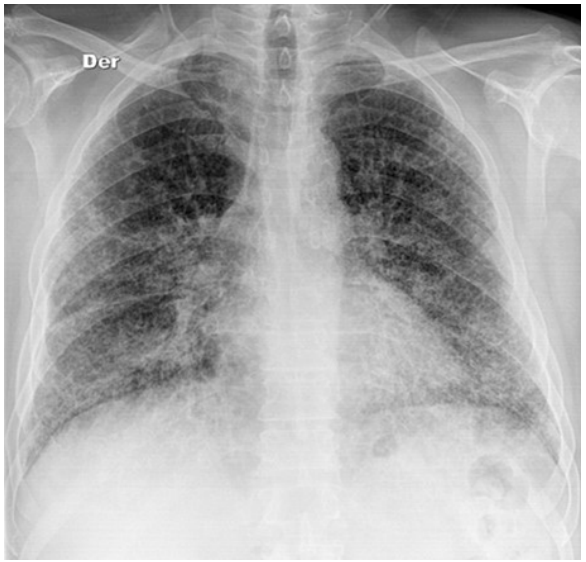
Risk Factors

- Age
  - More likely to occur in middle-aged and older adults
- Smoking
  - More likely to occur in those who smoke
- Occupational and Environmental Factors
  - Exposure to pollutants and toxins
- Cancer Treatments
  - Radiation therapy in the chest area
  - Certain chemotherapy drugs
    - Methotrexate
    - Cyclophosphamide



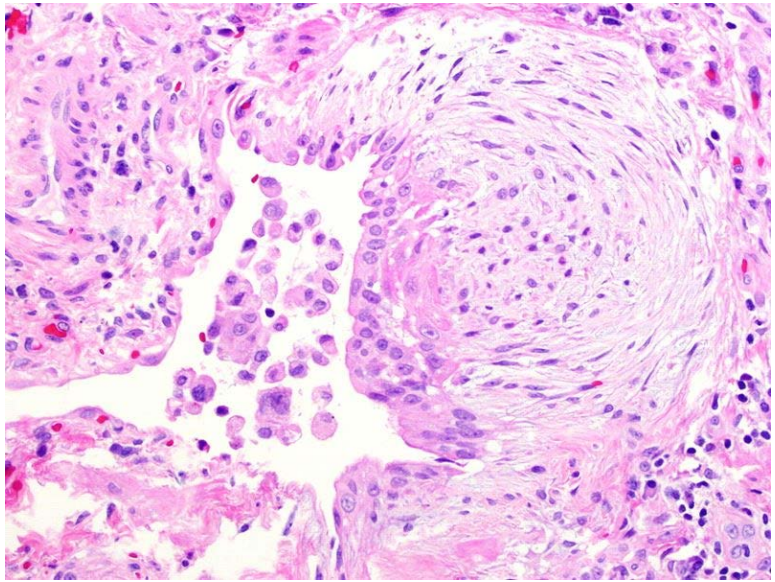
Idiopathic Pulmonary Fibrosis

- When the cause of pulmonary fibrosis can not be pinpointed
  - The disease is called idiopathic pulmonary fibrosis



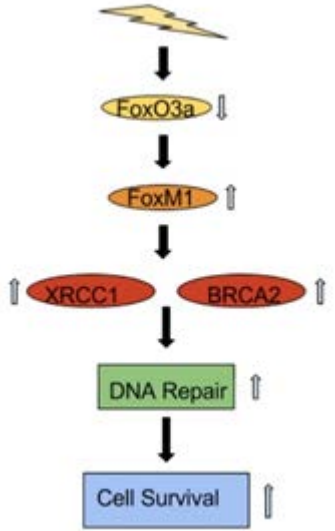
On a cellular level

- Overproduction of type I collagen
- Aberrant proliferation of IPF fibroblasts
  - Resistance to apoptosis
  - Higher cell viability
  - Altered cell signaling pathway

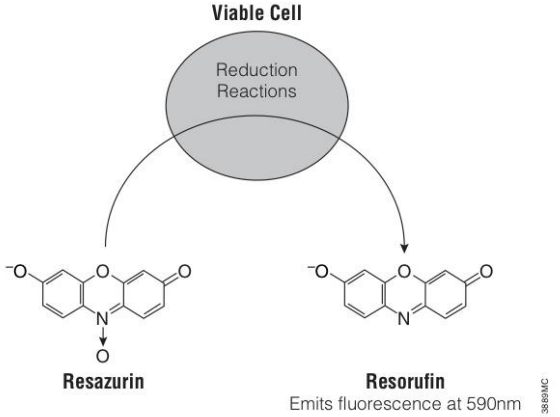


Proposed mechanism of Radiation Induced IPF

- Radiation causes decrease in the expression level of FoxO3a
  - FoxO3a is a transcription factor
- Downregulation in FoxO3a causes upregulation in FoxM1
- Increase in FoxM1 causes higher expression levels of DNA repair proteins
  - DNA damage repair proteins: BRCA2, Rad51, XRCC1
- Increase in DNA repair proteins leads to greater DNA repair activity
  - Allows the IPF fibroblasts to proliferate aberrantly
  - DNA damage accumulates in healthy fibroblasts
    - Signals for apoptosis
    - Decrease of this signaling in IPF



Cell Viability



- Control and IPF fibroblasts will be plated on polymerized collagen
- Both will then be irradiated at 9 Gy
- Cell viability will be checked 3 days after radiation
    - Performed using CellTiter-Blue cell viability assay
        - Reagent resazurin reduced to resorufin
        - The conversion generates fluorescent product
        - Fluorescence proportional to number of viable cells
    - IPF fibroblasts should have higher fluorescence than control fibroblasts

Western Blot

- Both IPF and control fibroblasts will be plated on polymerized collagen then irradiated
- Lysates will be collected at different time points after radiation to observe how radiation alters protein expression as a result of time progression.

Predicted results

Control Fibroblasts (as compared to IPF)

- Higher levels of FoxO3a
- Lower levels of FoxM1
- Lower levels of Brca2, Rad51, XRCC1

IPF Fibroblasts (as compared to control)

- Lower levels of FoxO3a
- Higher levels of FoxM1
- Higher levels of Brca2, Rad51, XRCC1

Future applications

- Pathway may be targeted in future drug development
- By finding a way to stop IPF fibroblasts proliferation
    - Potentially stop disease progression
- As IPF currently has no cure, studying its pathways will provide us with a better understanding of how the disease works and how we can stop it.

Sources

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Additional Sources

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