What is fibrosis?

Fibrosis, or scar formation, is a pathological condition characterized by excessive production and accumulation of collagen, loss of tissue architecture, and organ failure in response to uncontrolled wound healing.

Several cellular populations have been implicated, including **bone marrow-derived circulating fibrocytes**, **endothelial cells**, **resident fibroblasts**, **epithelial cells**, **myofibroblasts** and recently, perivascular cells called **pericytes**.

ECM: mostly collagen and fibronectin

Alexander Birbrair, Tan Zhang, Daniel Clark Files, Sandeep Mannava, Thomas Smith, Zhong-Min Wang, Maria Laura Messi, Akiva Mintz and Osvaldo Delbono. Type-1 pericytes accumulate after tissue injury and produce collagen in an organ-dependent manner. *Stem Cell Research & Therapy*

Myofibroblast

The recognized cellular conductor of fibrosis is the myofibroblast. This activated form of a fibroblast is induced by local conditions, including mechanical stress, growth factors, adhesion proteins, and cytokines. These highly contractile cells classically express α-smooth muscle actin (α-SMA) and **display increased migration and proliferation**.

Under normal physiological events, fibroblasts are activated and become myofibroblasts to promote wound healing; after epithelialization has occurred, they are lost through apoptosis.

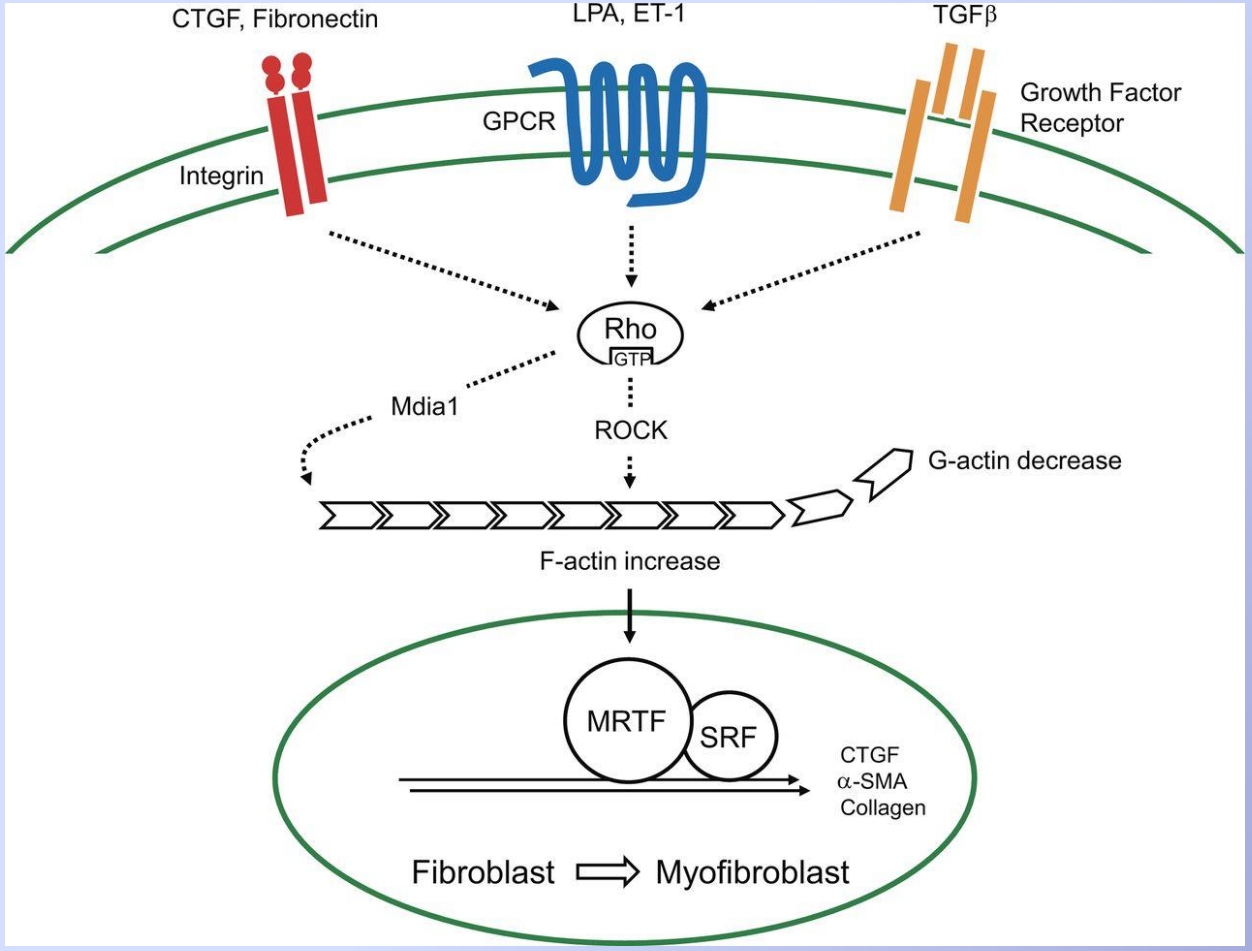
Pei-Suen Tsou, Andrew J. Haak, Dinesh Khanna, Richard R. Neubig
American Journal of Physiology
Cellular Mechanisms of Tissue Fibrosis. 8. Current and future drug targets in fibrosis: focus on Rho GTPase-regulated gene transcription

Genesis of a myofibroblast

- Partial smooth muscle differentiation of a fibroblastic cell
- Activation of a stellate cell (e.g. hepatic Ito cells or pancreatic stellate cells).
- Loss of contractile phenotype (or acquisition of "synthetic phenotype") of a smooth muscle cell.
- Direct myofibroblastic differentiation of a progenitor cell resident in a stromal tissue.
- Homing and recruitment of a circulating mesenchymal precursor which can directly differentiate as above or indirectly differentiate through the other cell types as intermediates.
- Epithelial to mesenchymal transdifferentiation (EMT) of an epithelial cell.

Pei-Suen Tsou, Andrew J. Haak, Dinesh Khanna, Richard R. Neubig
American Journal of Physiology
Cellular Mechanisms of Tissue Fibrosis. 8. Current and future drug targets in fibrosis: focus on Rho GTPase-regulated gene transcription

How does a fibroblast become a myofibroblast?

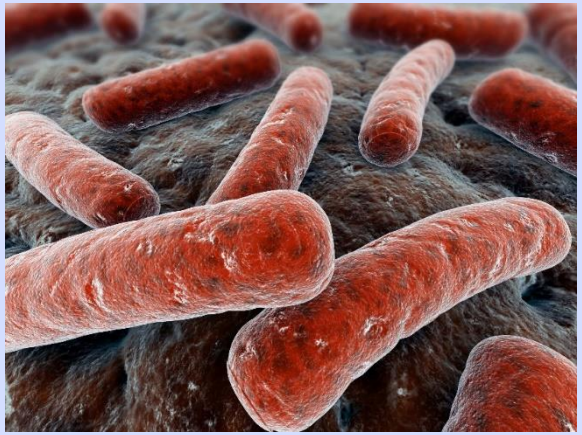


Pei-Suen Tsou, Andrew J. Haak, Dinesh Khanna, Richard R. Neubig
American Journal of Physiology Cellular Mechanisms of Tissue Fibrosis. 8. Current and future drug targets in fibrosis: focus on Rho GTPase-regulated gene transcription

Why fibrosis?

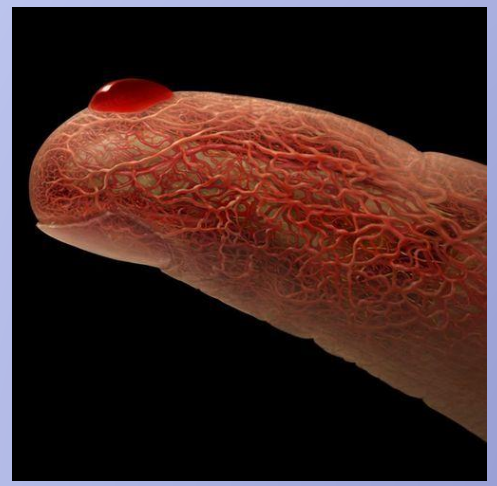
1

HOST DEFENSE AGAINST PATHOGENS



2

WOUND HEALING IN RESPONSE TO EPITHELIAL INJURY



"Fibrosis: ultimate and proximate causes", Victor J. Thannickal, Yong Zhou, Amit Gaggar, and Steven R.Duncan.

Host defense against pathogens

Formation of a fibrotic scar may serve a beneficial role to the host by preventing pathogen invasion and/or spread.

<u>Examples:</u>

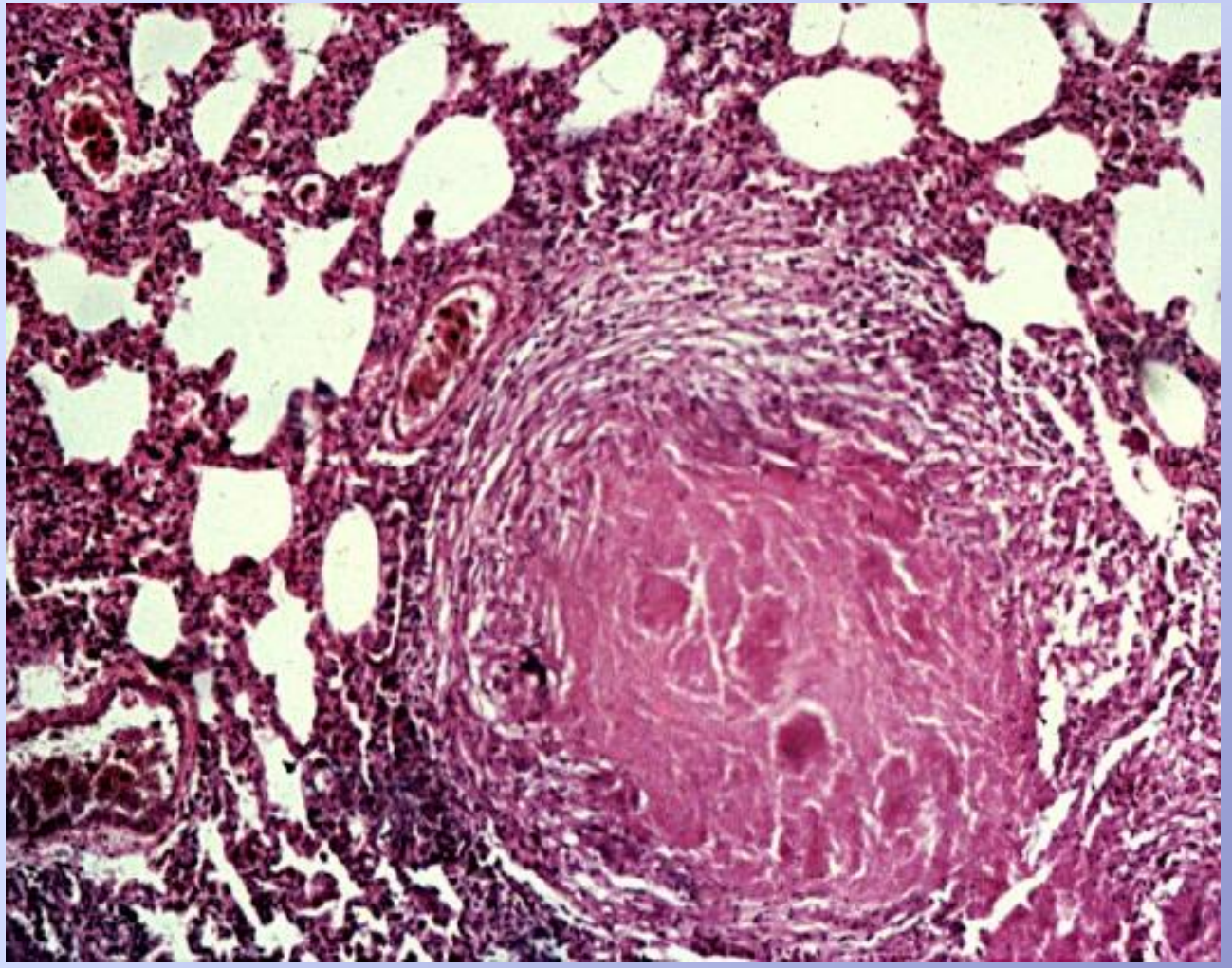
-The thick fibrotic walls surrounding bacterial abscesses

-The fibrotic rim around granulomas that contain mycobacterial pathogens

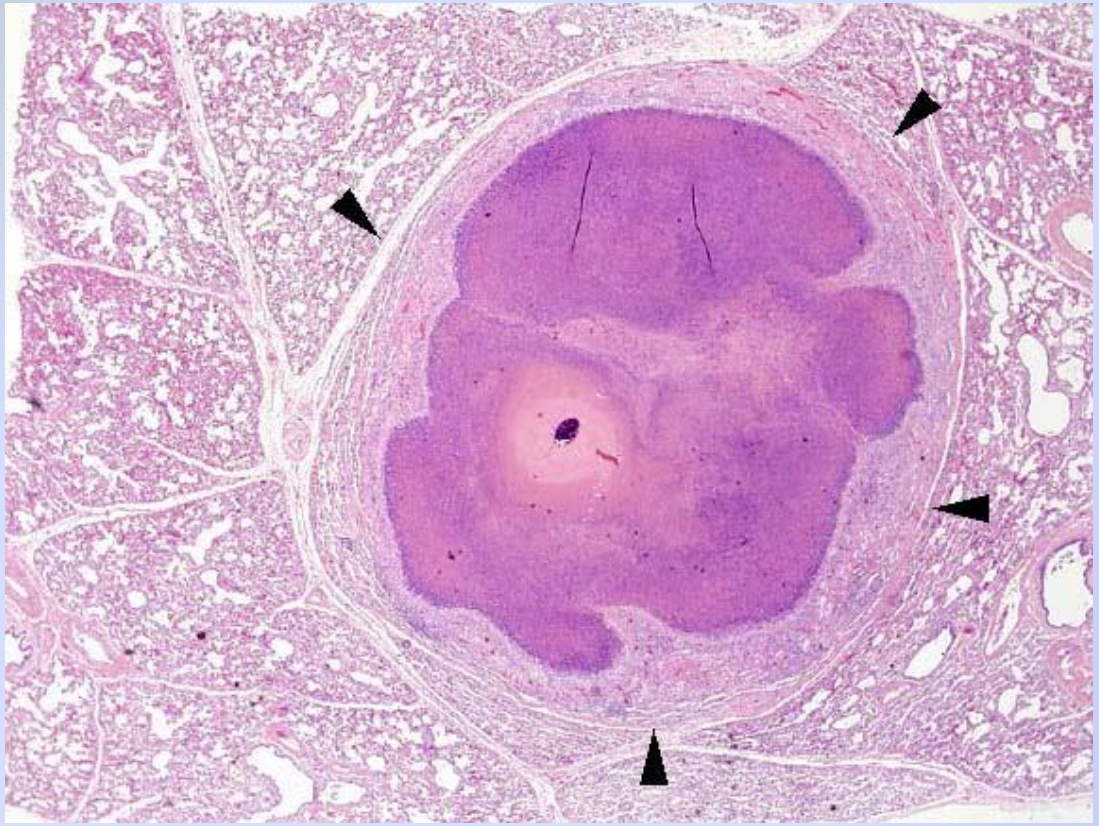
"Fibrosis: ultimate and proximate causes", Victor J. Thannickal, Yong Zhou, Amit Gaggar, and Steven R.Duncan.

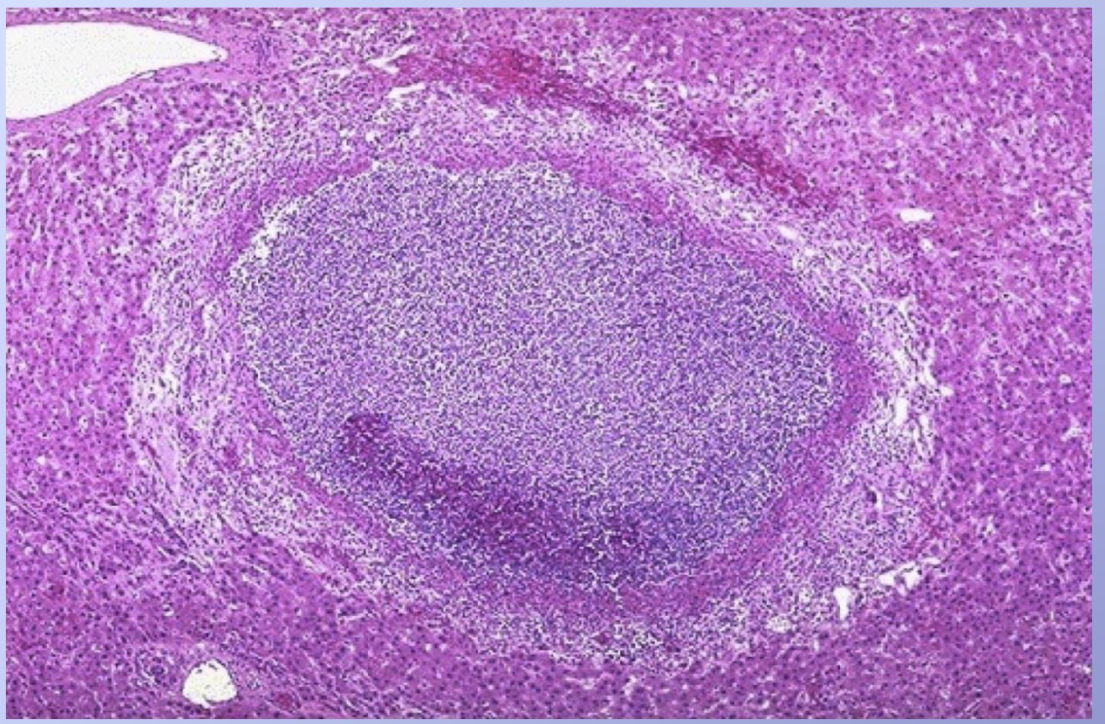
TB: an example

In this example, the excessive virulence of a particular microbe – Mycobacterium Tuberculosis- may not allow killing and eradication of the invading pathogen, and the survival of the host depends on containment of the pathogen by preventing its spread or dissemination.



Bacterial abscesses





Wound healing in response to epithelial injury

1) prevention of excessive blood loss

2) barrier function against the entry of microbes

3) formation of a provisional matrix to facilitate regeneration damaged epithelium

"Fibrosis: ultimate and proximate causes", Victor J. Thannickal, Yong Zhou, Amit Gaggar, and Steven R.Duncan.

FIBROSIS PATHOGENESIS

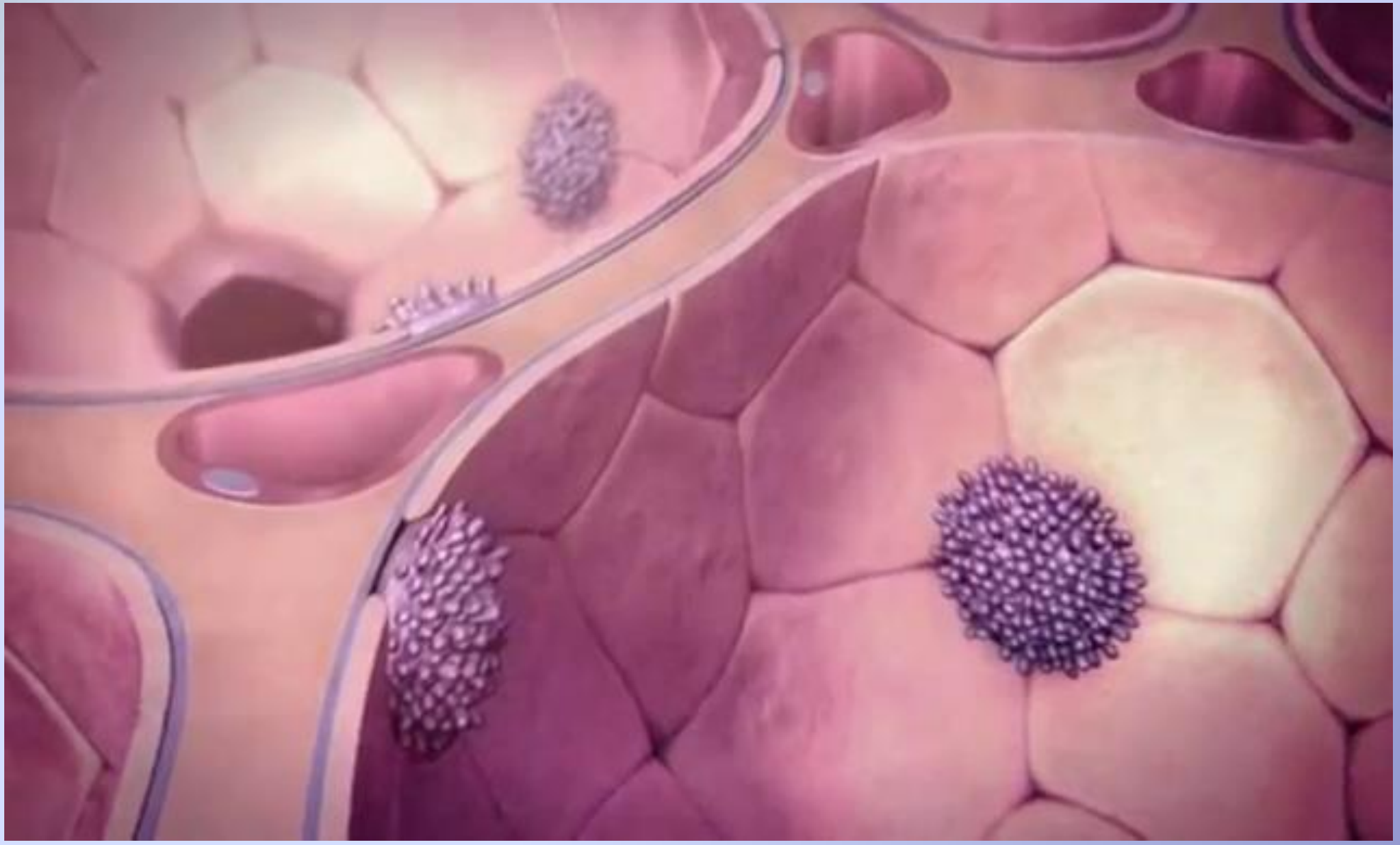
1) Microbial pathogens es. Trypanosoma cruzi, HCV
2) Non microbial pathogens es. silice, asbesto
3) Autoimmune diseases. TC CD8+, TC CD4+, autoantibodies, NK cells, cytokines es. Sistemic sclerosis

4) Loss of epithelial integrity +

Iperactivation of fibrotic pathways → **Idiopathic Pulmonary Fibrosis**

Victor J. Thannickal et al. Fibrosis: ultimate and proximate causes. *The Journal of Clinical Investigation*

Normal lung

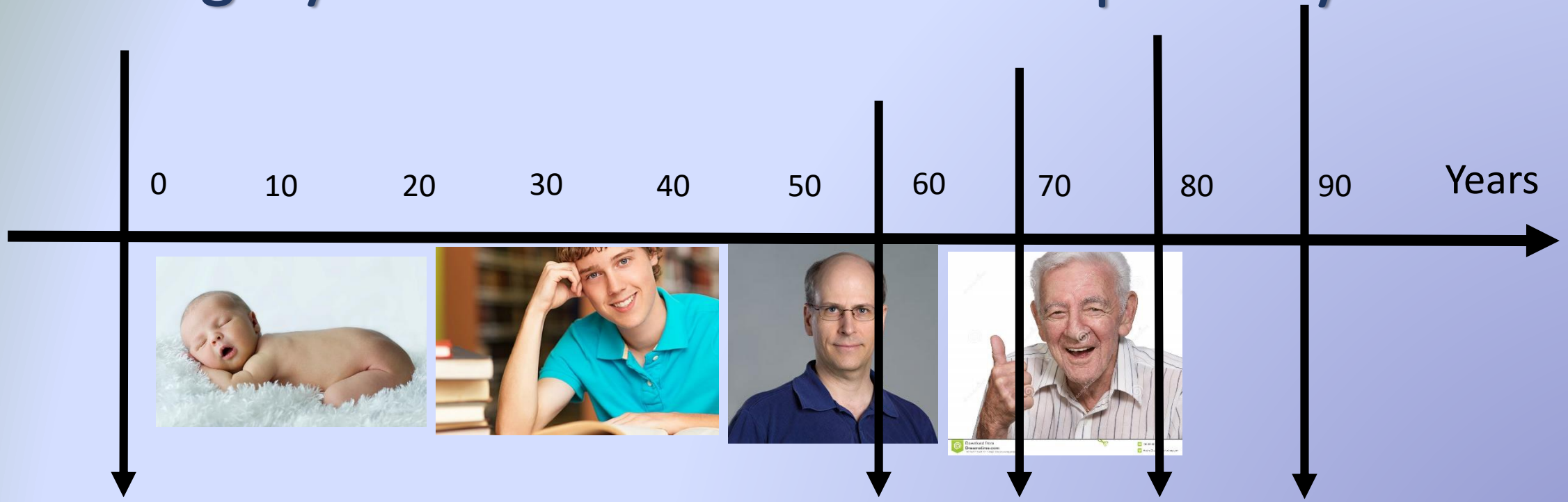


Loss of epithelial integrity

Iperactivation of fibrotic pathways

Loss of epithelial integrity

Iperactivation of fibrotic pathways



Genetic predisposition

Somatic mutations

Loss of epithelial integrity: evidences

GENOME WIDE STUDIES

- DSP gene (desmoplakin) polymorphisms
- Catenin cadherin-associated protein alfa3 polymorphisms
- MUC5B rs35705950_T allele

EXPERIMENTS

- CD151 deficiency

Moises Selman et al. Revealing the Pathogenic and Aging-related Mechanisms of the Enigmatic Idiopathic Pulmonary Fibrosis. Pulmonary Perspective.

Iperactivation of fibrotic pathways: evidences

- It would explain the three clinical forms of IPF:

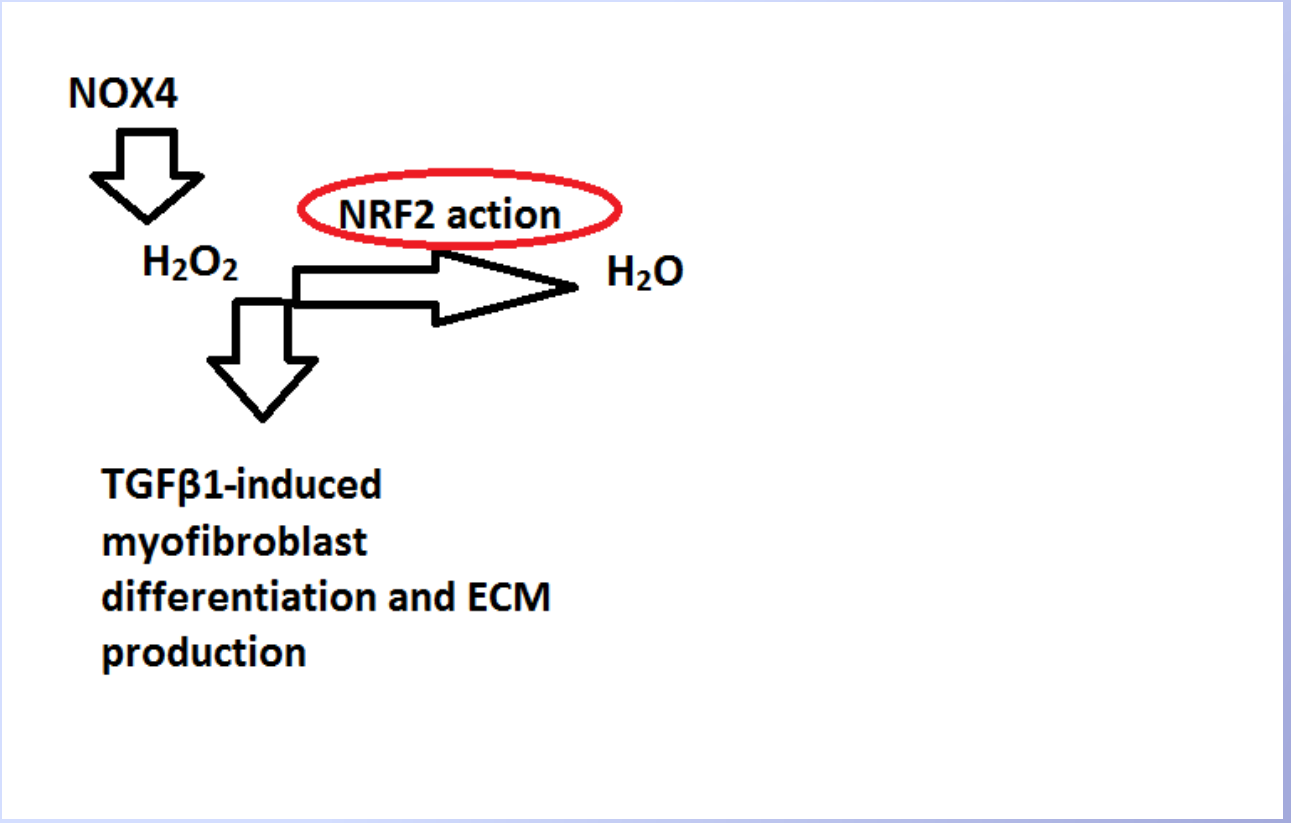
  -stable

  -slowly progressive

  -rapidly progressive
- Consistent with IPF main risk factors pathogenesis, since aging and tobacco smoking may promote DNA mutations.
- Consistent with histological findings: fibroblastic foci

Iperactivation of fibrotic pathways: evidences

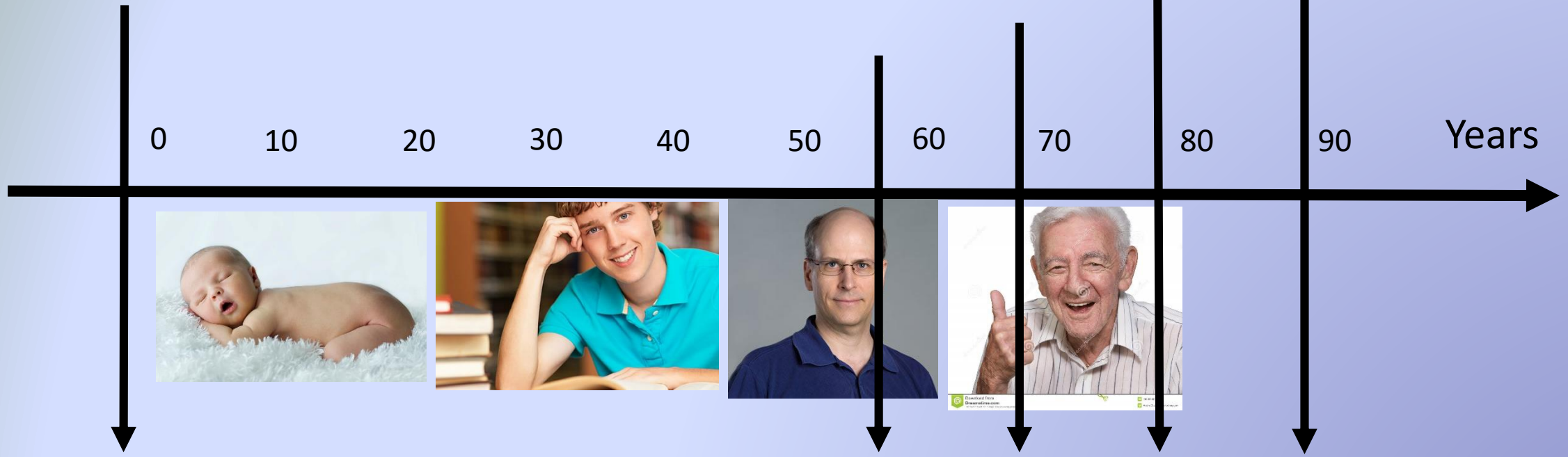
NOX4/NRF2 imbalance



Victor J. Thannickal et al. Fibrosis: ultimate and proximate causes. *The Journal of Clinical Investigation*

Loss of epithelial integrity

Iperactivation of fibrotic pathways



Genetic predisposition

Somatic mutations

FIBROSIS: AN EVOLUTIONARY PERSPECTIVE

1

Why fibrosis has been chosen instead of regeneration?

- **Bioenergetic investment in complete regeneration of a limb/organ was too great** for complex organisms

- **To limit the attendant risk of oncogenic transformation** of a relatively small number of tissue-resident stem.

"Fibrosis: ultimate and proximate causes", Victor J. Thannickal, Yong Zhou, Amit Gaggar, and Steven R.Duncan.

2 Why would aging be conserved throughout evolution?

- **Mutational theory**: Aging is NOT a beneficial factor for evolution.

The mechanism of action involves random, detrimental germline mutations of a kind that happen to show their effect only late in life. Unlike most detrimental mutations, these would not be efficiently weeded out by natural selection. Hence they would 'accumulate' and, perhaps, cause all the decline and damage that we associate with aging.

Medawar, P.B. (1952). An Unsolved Problem of Biology (PDF). London: H.K. Lewis. Edney, E.B. and Gill, R.W. 1968.
*Edney EB, Gill RW (October 1968). "Evolution of senescence and specific longevity". Nature **220** (5164):.*

Why would aging be conserved throughout evolution?

- **Disposable soma theory:** Aging IS a beneficial factor for evolution.

Kirkwood's idea was that organisms only have a limited amount of energy that has to be divided between reproductive activities and the maintenance of the non-reproductive aspects of the organism (soma). It is not preferable for a species to utilize energy for maintenance of the soma that would lead to survival beyond the period of fecundity.

Kirkwood TB. *Evolution of ageing*. 1977. *Nature* 170(5635) 201-4

3 Why are pathology-causing genes such as NOX4 conserved?

- **Antagonistic Pleiotropy:**

If a particular gene mediates beneficial effects in early life but exerts detrimental effects after reproductive age, there will be evolutionary pressure to conserve that gene despite its potential disease-causing effects with aging.

"Fibrosis: ultimate and proximate causes", Victor J. Thannickal, Yong Zhou, Amit Gaggar, and Steven R.Duncan.

NOX4

This explain the role of the **NOX4** (ROS-generating enzyme NADPH oxidase 4), which mediates the myofibroblast differentiation and normal wound healing in young subjects, but promotes persistent fibrosis with aging.
One explanation for the pleiotropic nature of NOX4 action is the lack of a counter-regulatory response involving NFR2 in aged animals; this NOX4/NFR2 imbalance leads to persistent fibrosis associated with the acquisition of a senescent and apoptosis-resistant myofibroblast phenotype in aged mice, whereas young mice demonstrate the capacity for fibrosis reversibility.

Finally, the **identification of antagonistically pleiotropic genes may be particularly attractive for therapeutic targeting in chronic diseases of aging, including organ fibrosis**

"Fibrosis: ultimate and proximate causes", Victor J. Thannickal, Yong Zhou, Amit Gaggar, and Steven R.Duncan.

BIBLIOGRAPHY

Alexander Birbrair, Tan Zhang, Daniel Clark Files, Sandeep Mannava, Thomas Smith, Zhong-
Min Wang, Maria Laura Messi, Akiva Mintz and Osvaldo Delbono. Type-1 pericytes accumulate after tissue injury and produce collagen in an organ-dependent manner. *Stem Cell Research & Therapy*

"Fibrosis: ultimate and proximate causes", Victor J. Thannickal, Yong Zhou, Amit Gaggar, and Steven R.Duncan.

Moises Selman et al. Revealing the Pathogenic and Aging-related Mechanisms of the Enigmatic Idiopathic Pulmonary Fibrosis. Pulmonary Perspective.

Medawar, P.B. (1952). An Unsolved Problem of Biology (PDF). London: H.K. Lewis. Edney, E.B. and Gill, R.W. 1968.

Edney EB, Gill RW (October 1968). "Evolution of senescence and specific longevity". Nature **220** (5164):

Accietto Antonella
Benassi Luca
Dapoto Fabrizio