DIRECT CONTRIBUTION OF EPITHELIUM TO ORGAN FIBROSIS

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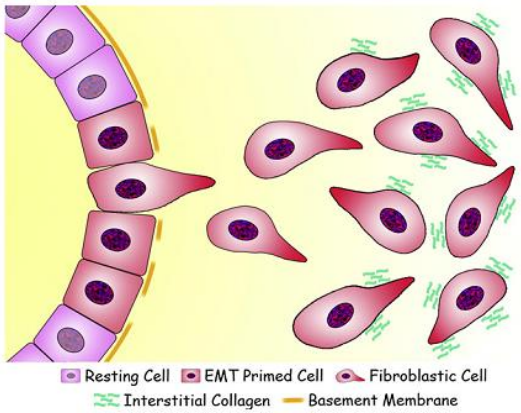
- Fibrosis of epithelial **parenchymal organs** and **end-stage** organ failure represent the final common pathway of many **chronic diseases**
- Fibrosis is a complex response initiated to **protect the host** from an injurious event
- It leads to **serious organ damage** when it becomes **independent** from the initiating stimulus
- It involves massive deposition of matrix by an expanded pool of fibrogenic cells, disruption of the normal tissue architecture, and parenchymal destruction

- **Fibroblasts**, the effector cells of matrix production
- These cells are present in a large number in sites with
  - Ongoing inflammation
  - Reparative reaction
  - Fibrosis

- Three-step model of fibrosis
  - **injury-damaged** epithelial cells release activating cytokines that attract inflammatory cells to the site
  - infiltrating inflammatory cells secrete additional cytokines that further damage the epithelial parenchymal tissue and stimulate fibroblasts to proliferate and to produce matrix proteins
  - fibrogenesis depends on a self-stimulating mechanism and **continues** even after the primary noxious stimulus and inflammation have subsided

- **Where from FIBROBLASTS come**
  - proliferation of pre-existing stromal fibroblasts
  - probably recruitment of bone marrow–derived fibrogenic cells
  - emerging evidence seems to indicate that an important number of matrix-producing fibroblasts arises through a mechanism of epithelial-mesenchymal transition



Progress in pathology
Direct contribution of epithelium to organ fibrosis: epithelial-mesenchymal transition
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- Through this process,
  - epithelial cells would lose intercellular cohesion
  - translocate from the epithelial compartment into the interstitium where, gaining a full mesenchymal phenotype,
  - they could participate in the synthesis of the fibrotic matrix

- **Epithelial-mesenchymal transition** is induced by the integrated actions of many stimuli including
  - Transforming growth factor-β and
  - matrix-generated signals that are also known to be implicated in
    - inflammation
    - repair responses
    - fibrosis

- The **consequences of epithelial-mesenchymal transition** in chronic fibrosing diseases could be two-fold
  - One, supplementing new mesenchymal cells, it might feed the expanding pool of interstitial fibroblasts responsible for the matrix accumulation
  - Two, it could cause loss of epithelial cells, thus, contributing to the parenchymal destruction seen in advanced fibrosis.

- **Markers** of epithelium undergoing epithelial-mesenchymal transition include
  - loss of E-cadherin and cytokeratin
  - de novo expression of fibroblast specific protein **1/S100A4**, **vimentin**, and **α-smooth muscle actin**
  - Loss of basement membrane components
  - production of interstitial-type matrix molecules such as **fibronectin** and **type I/III collagen**.

- Evidence of **epithelial-mesenchymal transition** has been reported in the **kidney**, **lung**, **liver**, **eye**, and **serosal membranes**
- the detection of epithelial-mesenchymal transition in biopsy specimens could be useful and represent a new biomarker of progression in chronic fibrosing diseases.
- a number of studies suggest an **exacerbating** role of **T cells** in fibrosis,
- **Angiotensin II** induces the expression of pro-fibrotic factors such as **connective tissue growth factor** (CTGF)
- **M2 macrophage** invade the fibrotic tissue that secrete many molecules including **IFNg**, which is **anti-fibrotic**

- **Bone morphogenic proteins**, **BMP7 prevents fibrosis** by promoting epithelial regeneration
- **PGE2**, has well established anti-inflammatory activities, may **suppress fibrosis** by inhibiting the proliferation, migration, and differentiation of fibroblasts
- degradation of pathological fibrillar collagen by MMPs (**Matrix metallo-proteinases**) is a key event in the resolution of fibrosis
- **Leukotrienes** (LTs) not only induce fibroblast migration, proliferation, and matrix protein synthesis, but also promote fibrosis through the stimulation and activation of TGFβ
- **thrombin**, factor VII, and factor Xa activate protease-activated receptor-1 (**PAR-1**) on **fibroblasts** and induce their proliferation.

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