Using Agent-Based Modeling to Study Interstitial Lung Disease

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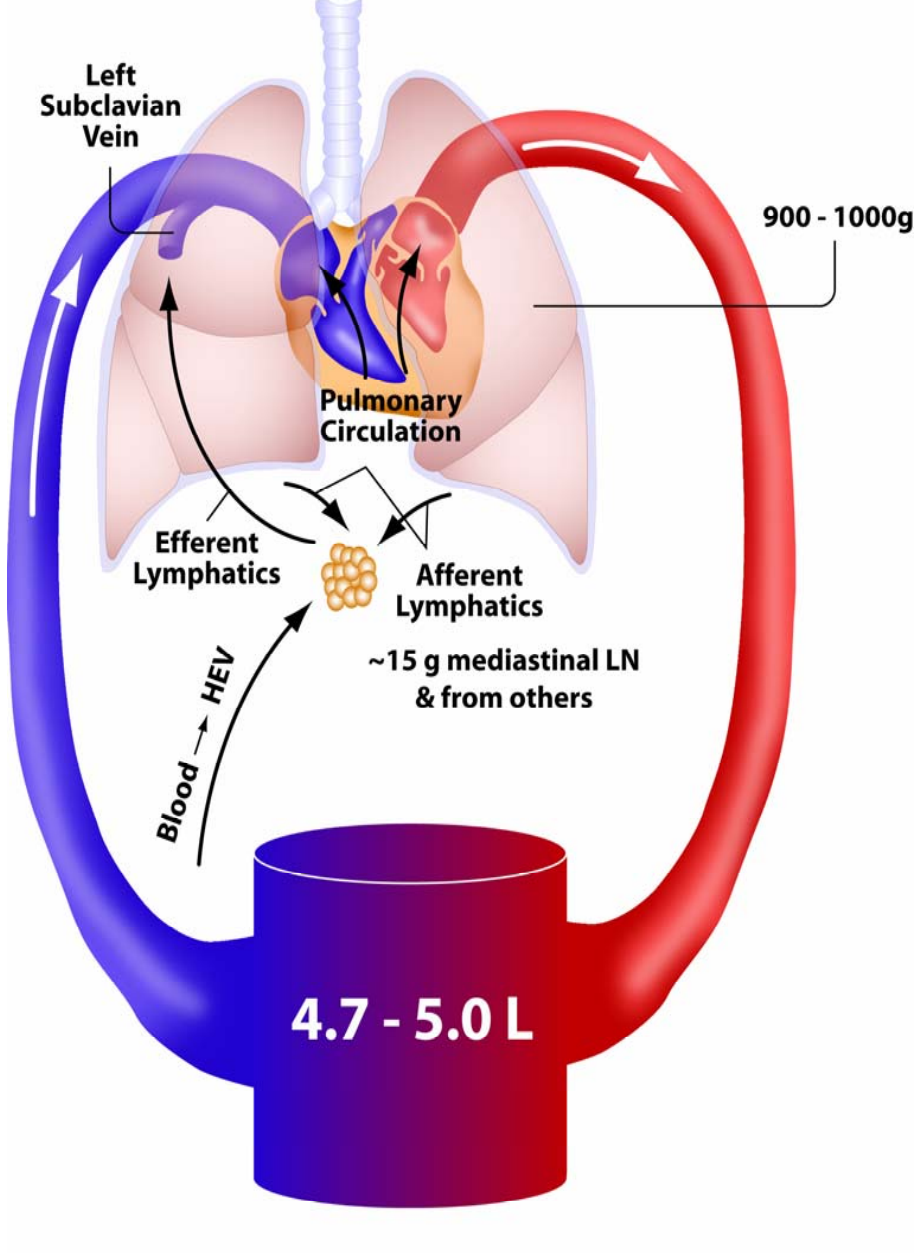
What is represented in the model:

1. lungs

2. lymph nodes

3. blood

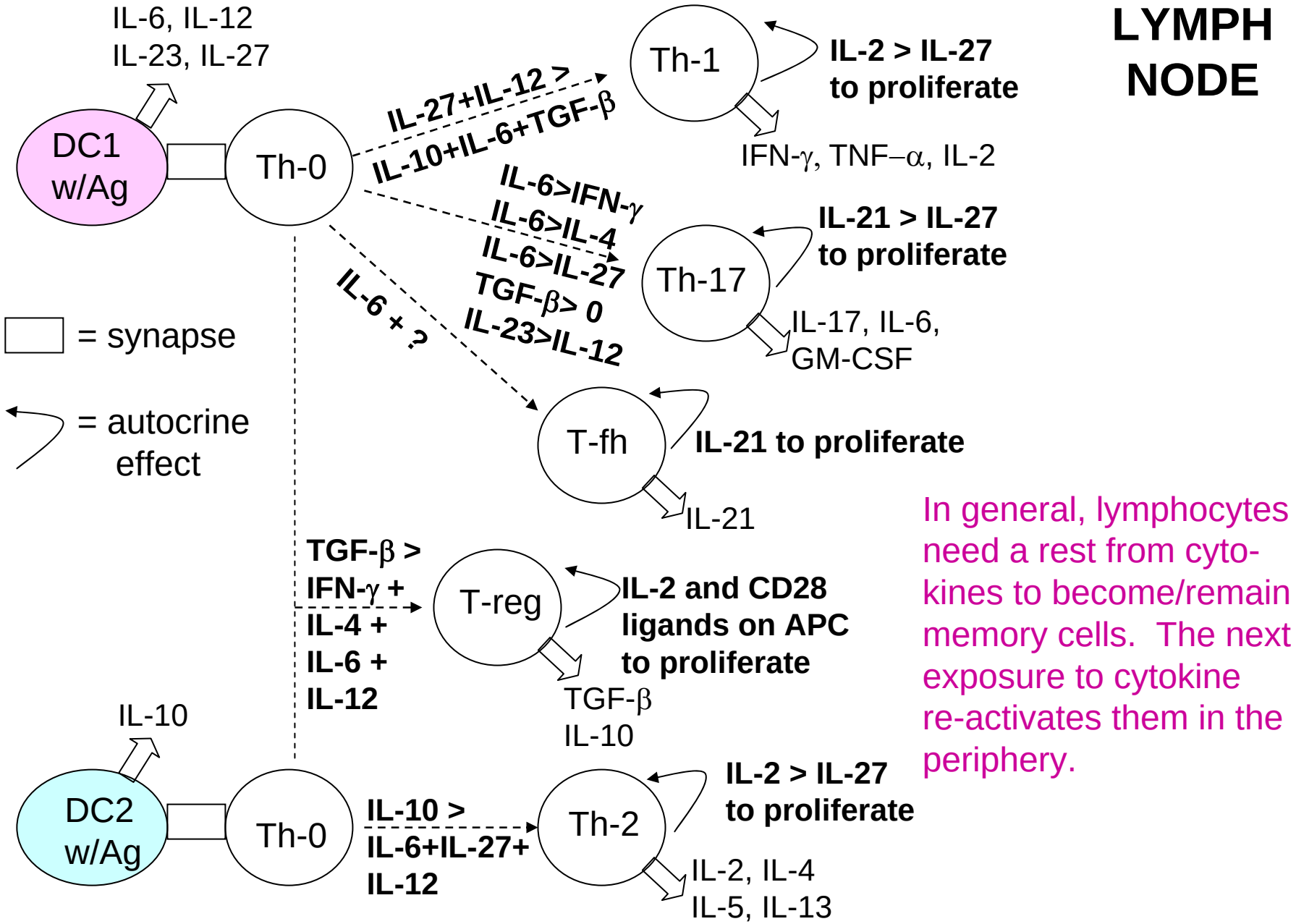


Lung	Blood	LN & Spleen
1 L	: 5 L	: 0.215 L

Agent Types

- Parenchymal Cells — *impart tissue function*
- Dendritic Cells — *tissue surveillance, antigen presentation*
- Macrophages — *scavenging, killing pathogens*
- Granulocytes — *phagocytosis, killing pathogens*
- Natural Killer Cells — *kill stressed cells*
- CTLs — *CD8+ T lymphocytes, cell mediated immunity*
- T Cells — *CD4+ T lymphocytes (T_H1, T_H2, T_H17, Treg, T_{HF})*
- B Cells — *lymphocytes, humoral immunity (Antibodies)*
- Portals — *blood vessels, lymphatic ducts*

LYMPH NODE



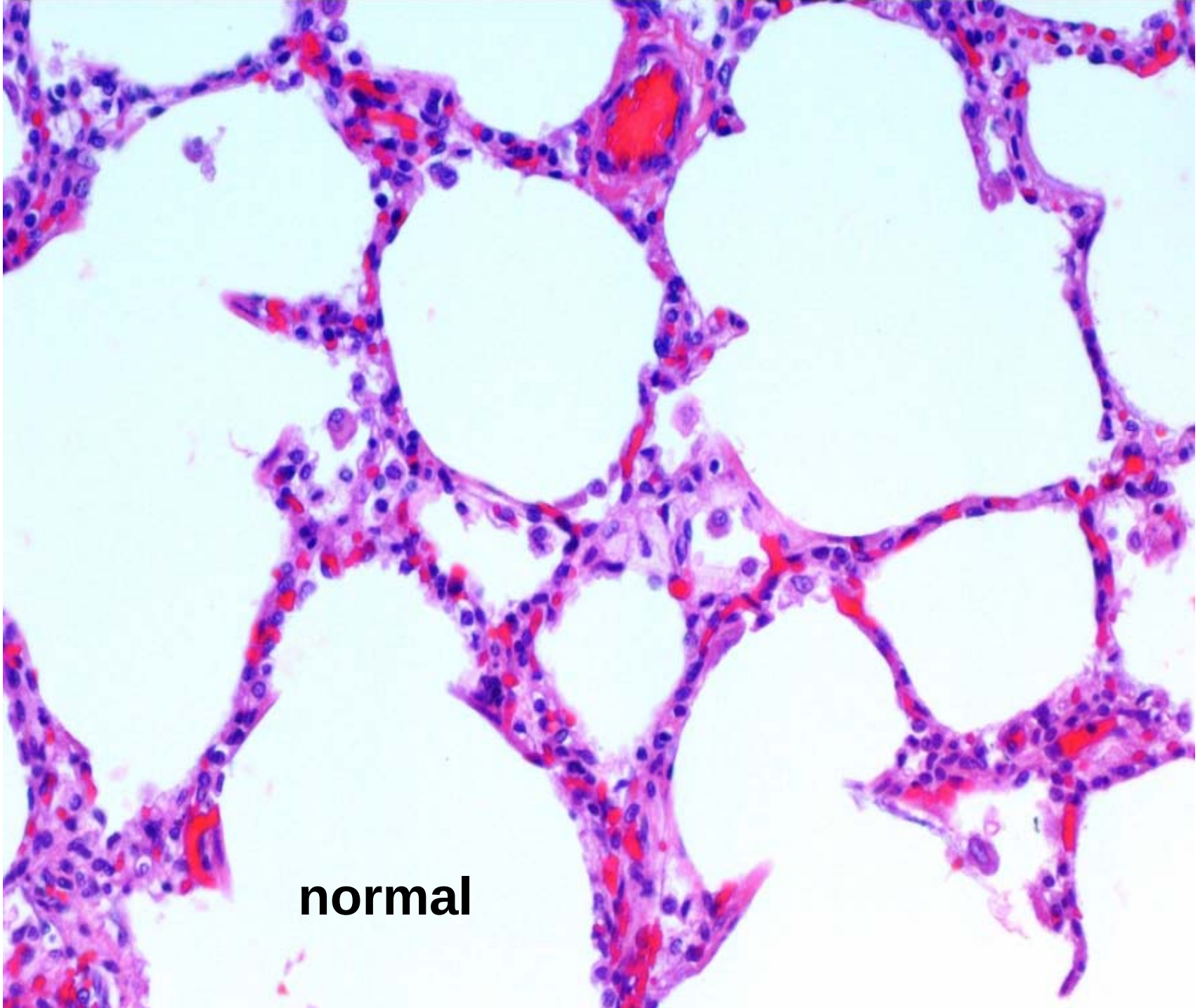
In general, lymphocytes need a rest from cyto-kines to become/remain memory cells. The next exposure to cytokine re-activates them in the periphery.

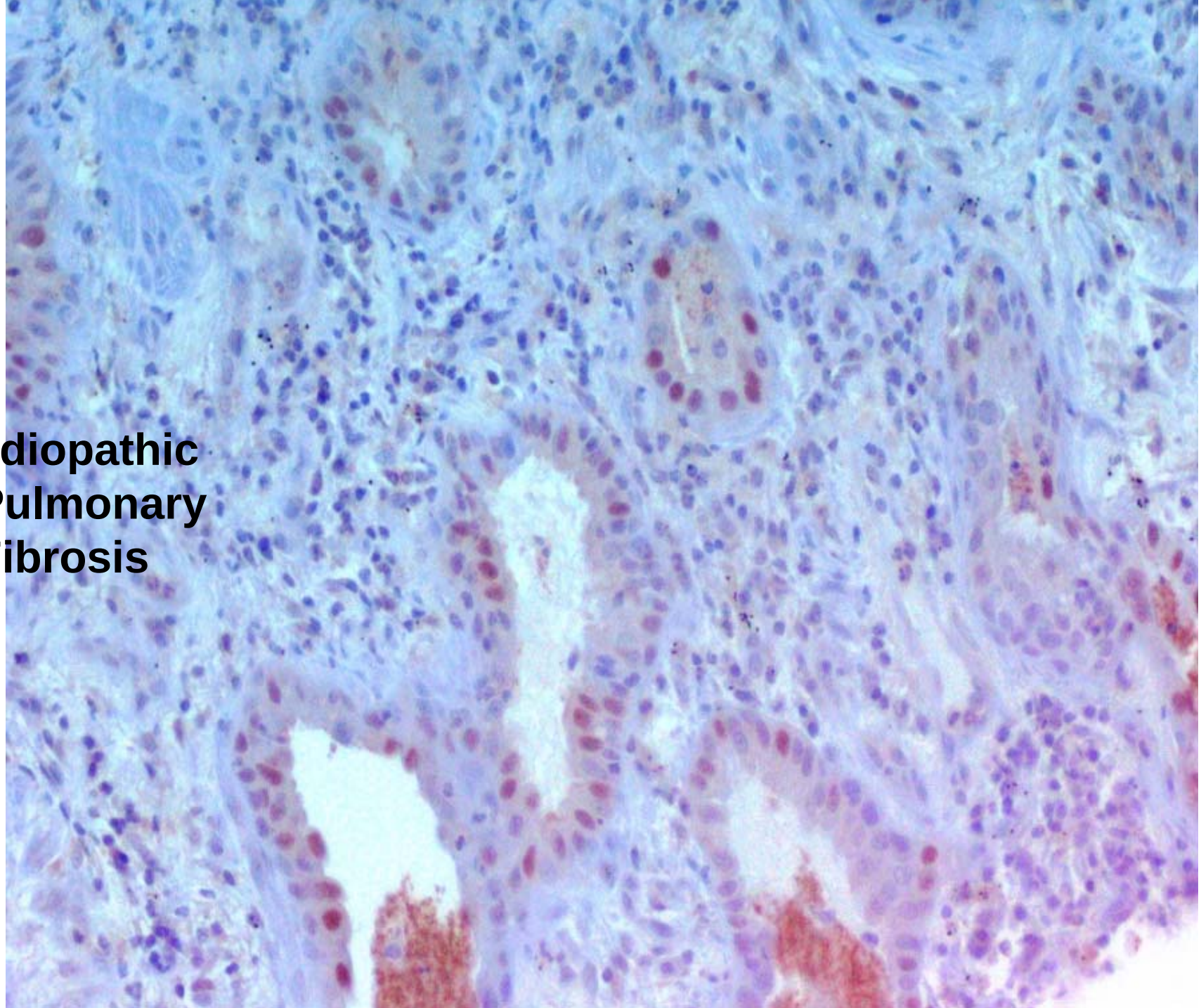
A review of some biologically demonstrated DC, Th and cytokine interactions

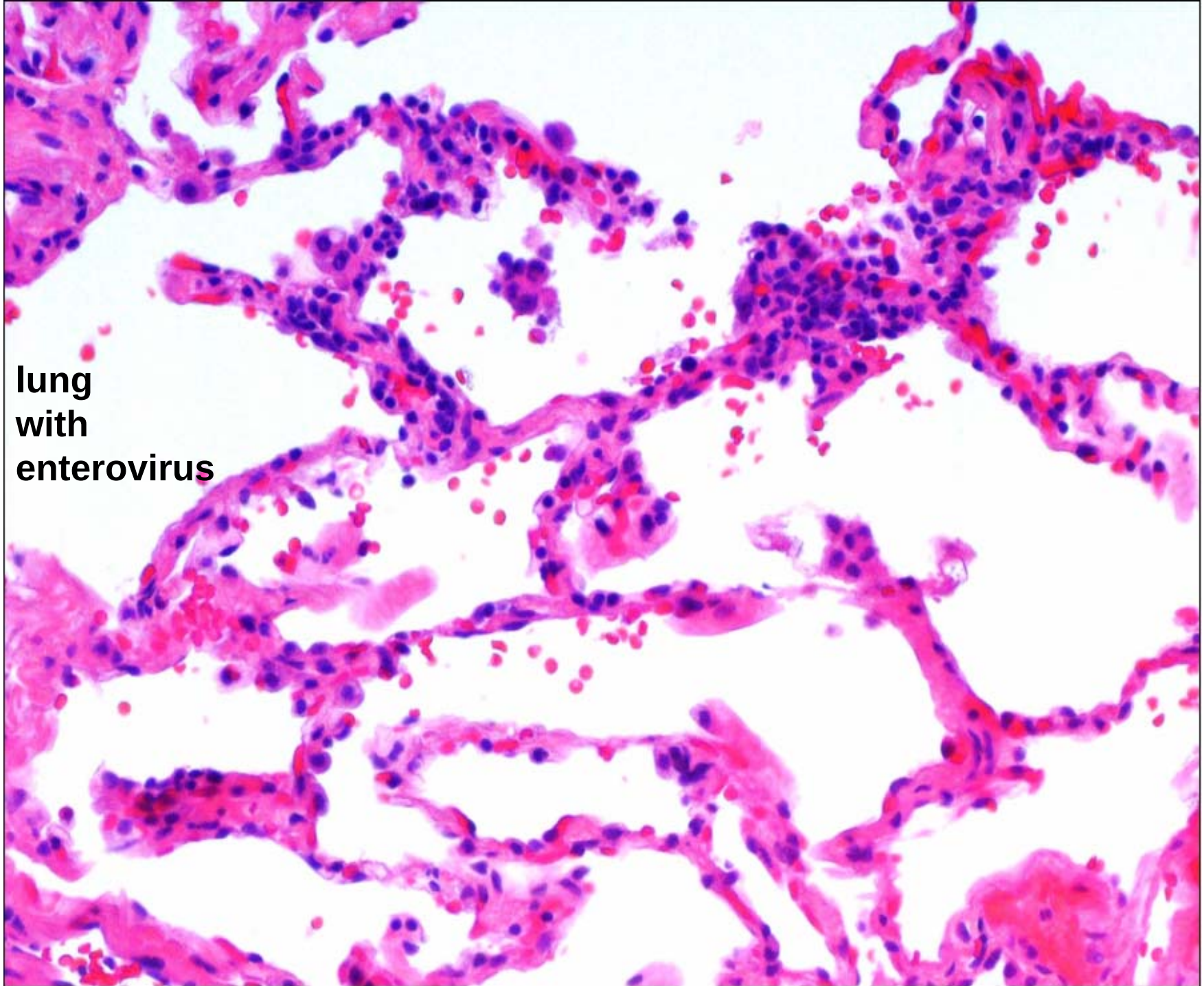
Interstitial Lung Disease

(thickening of the tissue between the air sacs that makes breathing difficult)

- Idiopathic vs. known cause
- Temporal heterogeneity vs. homogeneity
- Treatable vs. incurable
- Inflammatory vs. not
- Infection vs. no infection
- Auto-immune vs. not
- Hereditary vs. not
- All forms have different pathological patterns


normal


Idiopathic
Pulmonary
Fibrosis


lung
with
enterovirus

Signals (cytokines, chemokines, molecules, small organisms)

signal	represents	signal	represents	signal	represents
PK1	stress signal, i.e. HSPs, Uric Acid, HMGB1, chemokines	Ab1	IgG2a	CK1	IFN-γ, TNF-α, IL-2
Apoptotic debris	apoptotic cells	Ab2	IgG1, IgE	CK2	IL-4, IL-13, IL-5, IL-2
Necrotic debris	debris/leakage from necrotic cells	Ab5	IgM	CK17	IL-17
Virus	generic, influenza-like	Comp.	activated complement	MK1	IL-12, IL-1, IL-8, chemokines
Bacteria	*Streptococcus pneumoniae*	G	ROI, de-granulation products	MK2	IL-10, chemokines
L-TGF-β	latent-TGF-β	Air		MK6	IL-6
TGF-β	TGF-β	Fiber	Collagen, fibrin	MK23	IL-23
CTGF	connective tissue growth factor	ANG-II	angiotensin-II	MK27	IL-27
EGF	epidermal growth factor	PDGF	platelet products	GMCSF	GM-CSF
IGF-2	insulin-like growth factor	MMP/ TIMP	protease/ anti-protease	CK21	IL-21

New Agent Sub-types:

ParenchymalAgent

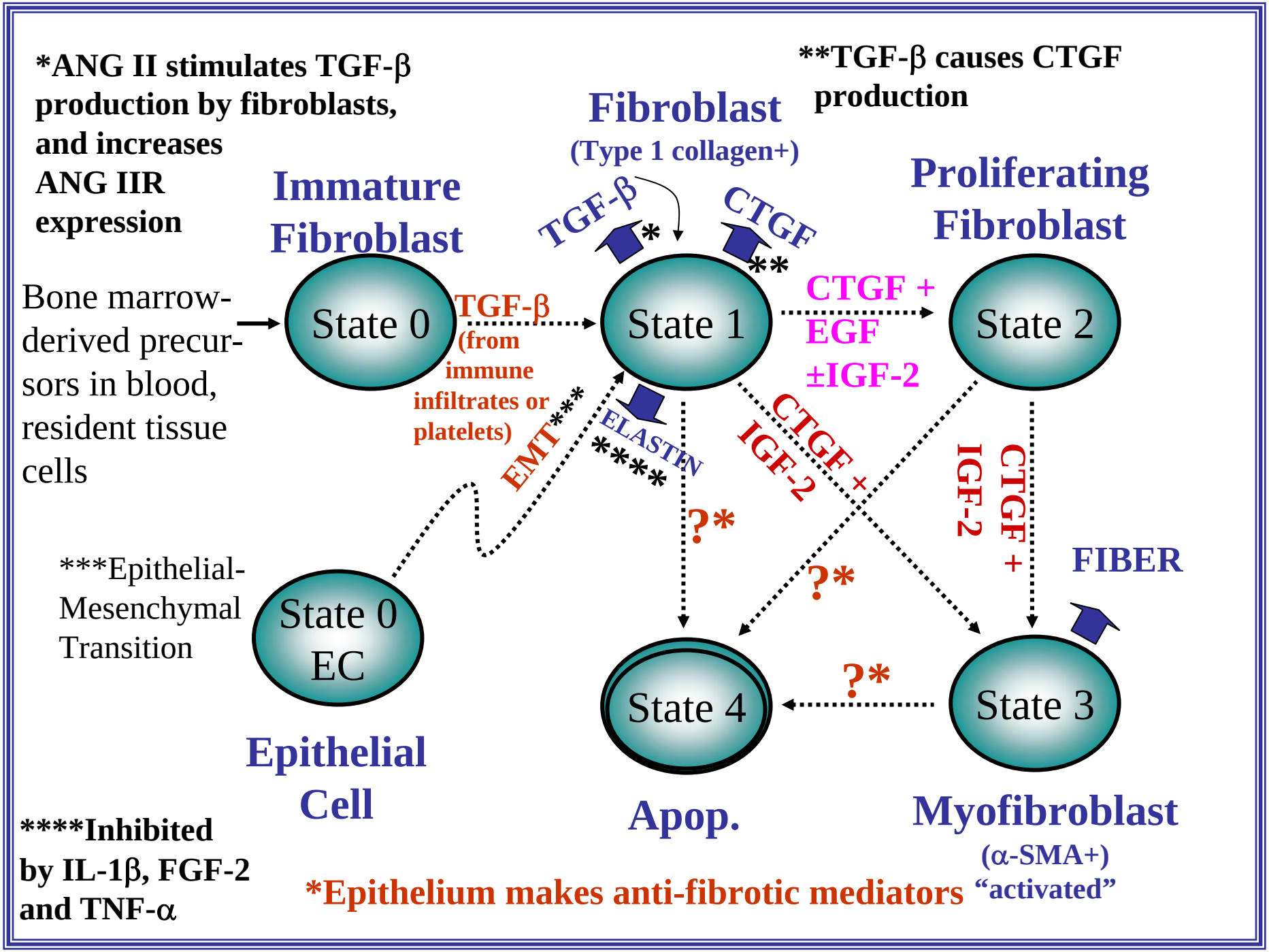
- Epithelial type I*
- Epithelial type II*
- Endothelial*
- Fibroblast (Myofibroblast)

- RBC Agents
- Platelets

StructuralAgent

- Interstitial space
- Alveolar air space

*These are attached to a basement membrane


*ANG II stimulates TGF-β production by fibroblasts, and increases ANG IIR expression
**TGF-β causes CTGF production
Fibroblast
(Type 1 collagen+)
Immature Fibroblast
Proliferating Fibroblast
Bone marrow-derived precur-sors in blood, resident tissue cells
State 0
TGF-β
(from immune infiltrates or platelets)
State 1
CTGF +
EGF
±IGF-2
State 2
TGF-β*
CTGF**
EMT***
ELASTIN****
?*
CTGF + IGF-2
IGF-2 + CTGF
FIBER
***Epithelial-Mesenchymal Transition
State 0 EC
Epithelial Cell
State 4
Apop.
State 3
Myofibroblast
(α-SMA+)
"activated"
****Inhibited by IL-1β, FGF-2 and TNF-α
*Epithelium makes anti-fibrotic mediators

Pulmonary Fibrosis Etiology Questions:

- What causes the injury in pulmonary fibrosis?
  -epithelial VS. endothelial injury
  -viral (re-activation)
  -complement activation
    α-endothelial auto-antibodies, humoral autoimmunity
  -failure to quench reactive oxygen species

- What type of perturbation leads to patterns that resemble those of IPF?
  -there are cell type(s) with defects in apoptosis

Goals:

- Identify potential mechanisms for idiopathic pulmonary fibrosis by matching outcome patterns of the simulation and human specimen photomicrographs.
- Targetable potential mechanisms will be further investigated by traditional laboratory methods in an animal model of disease.
- Ultimately, identify targets for pharmacological abrogation of pulmonary fibrosis disease mechanisms.

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The End

Difficulties?