Fibrotic Pathways from the Basic to Translational Science Perspective

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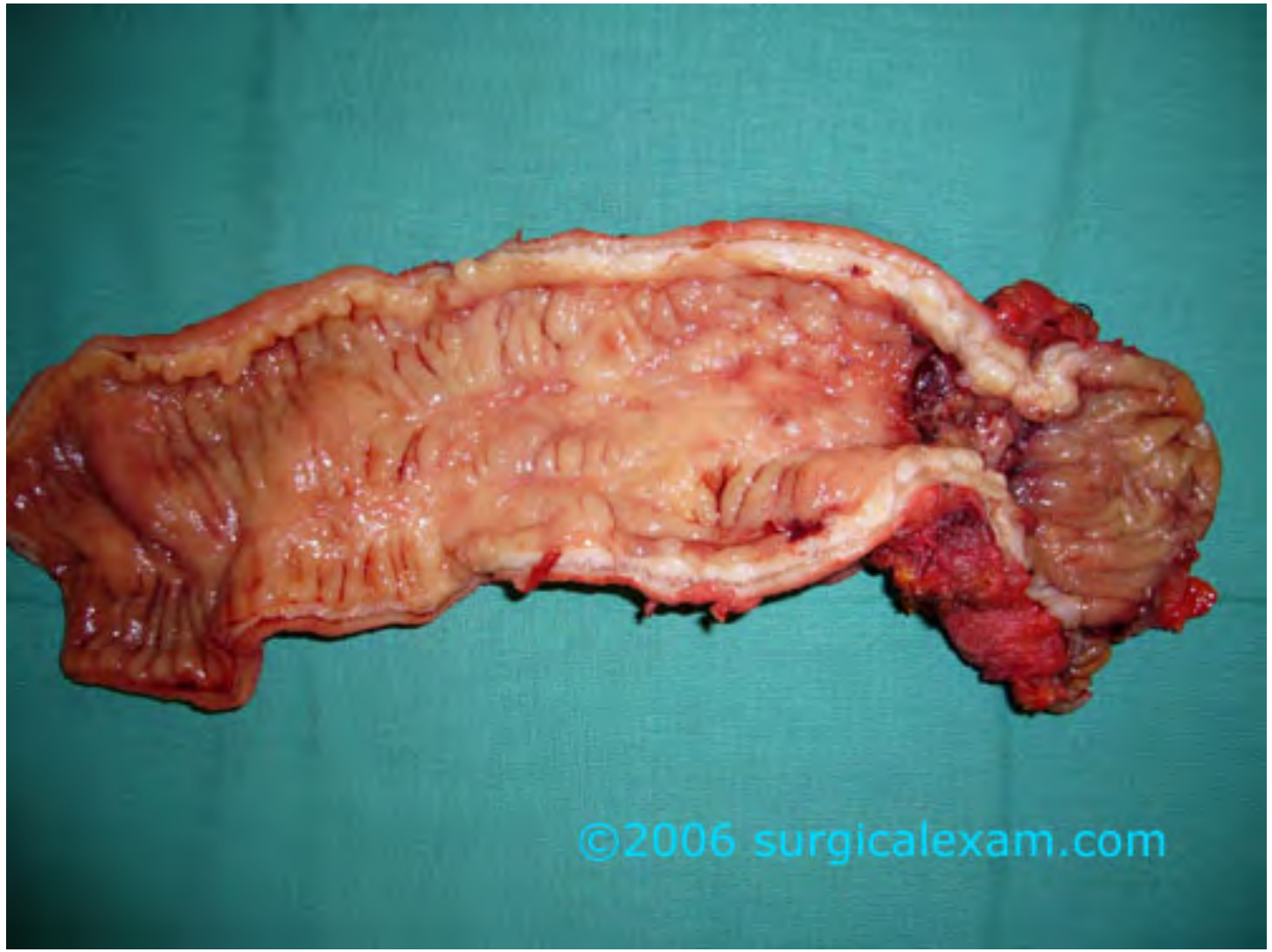
Disclosures

- None

Outline

- What is the current understanding of tissue remodeling in IBD?
  - MMPs
  - Fibrocytes
  - Smooth muscle
- New pathways/targets
- What can we learn from other organ systems?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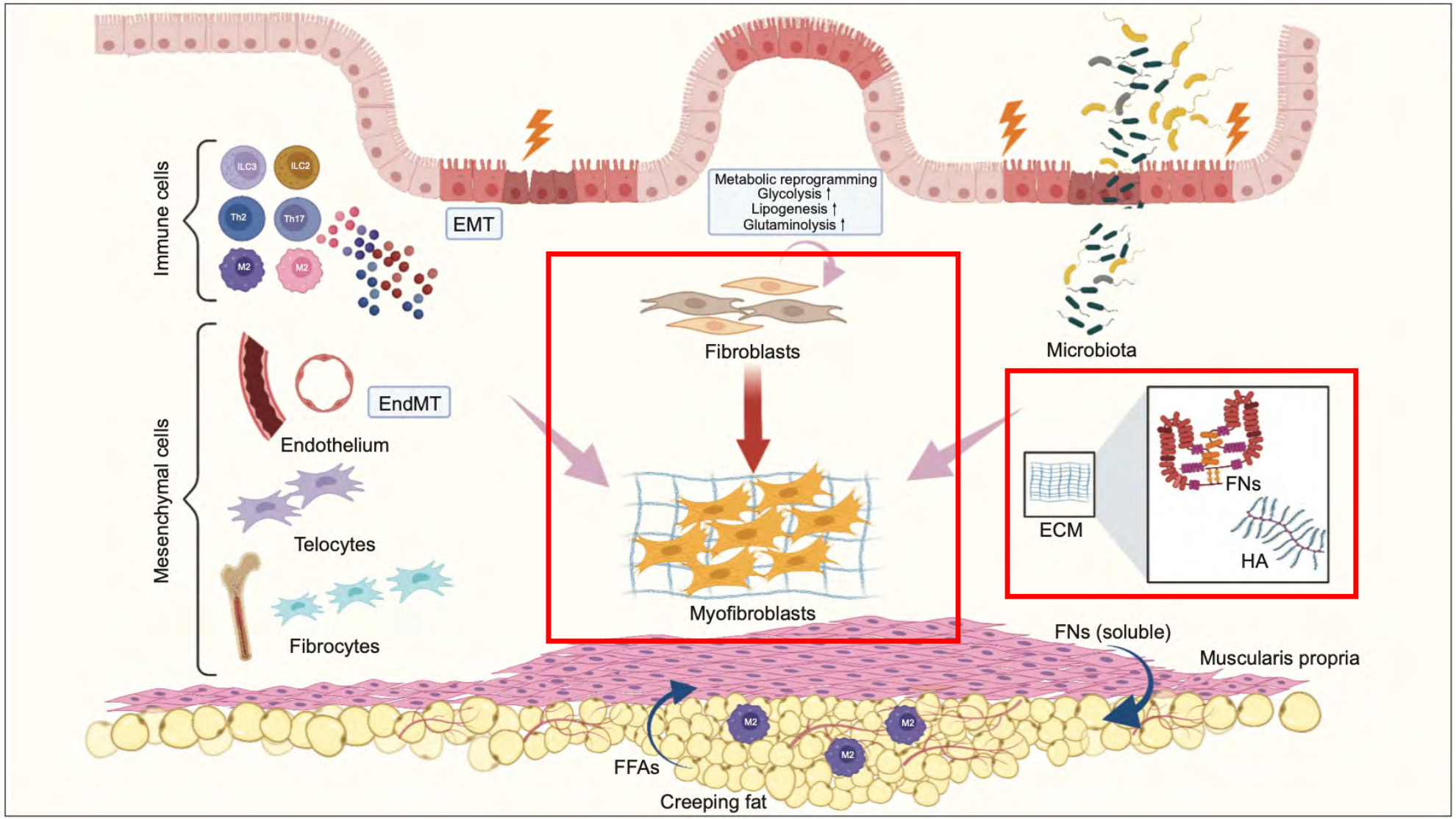
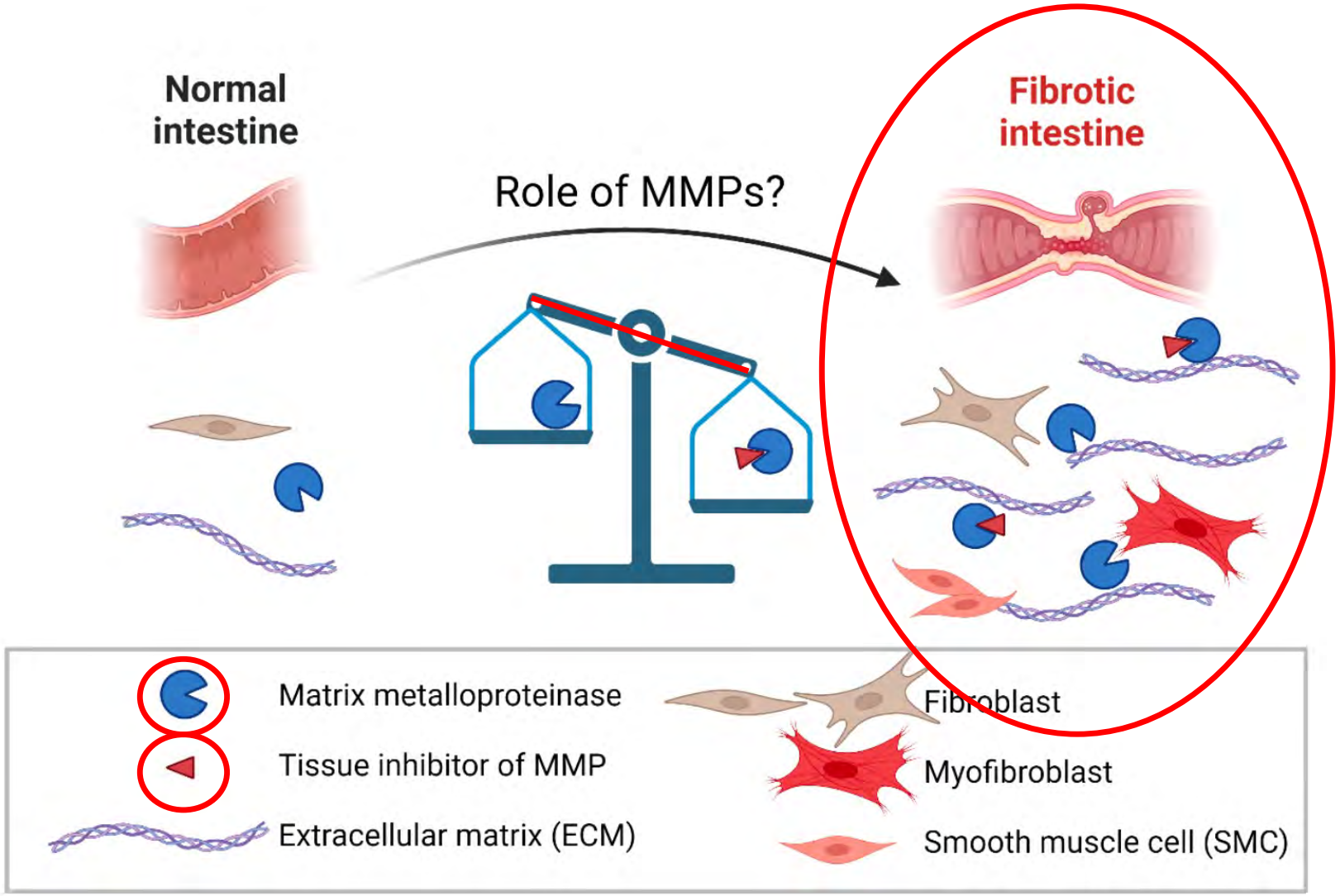
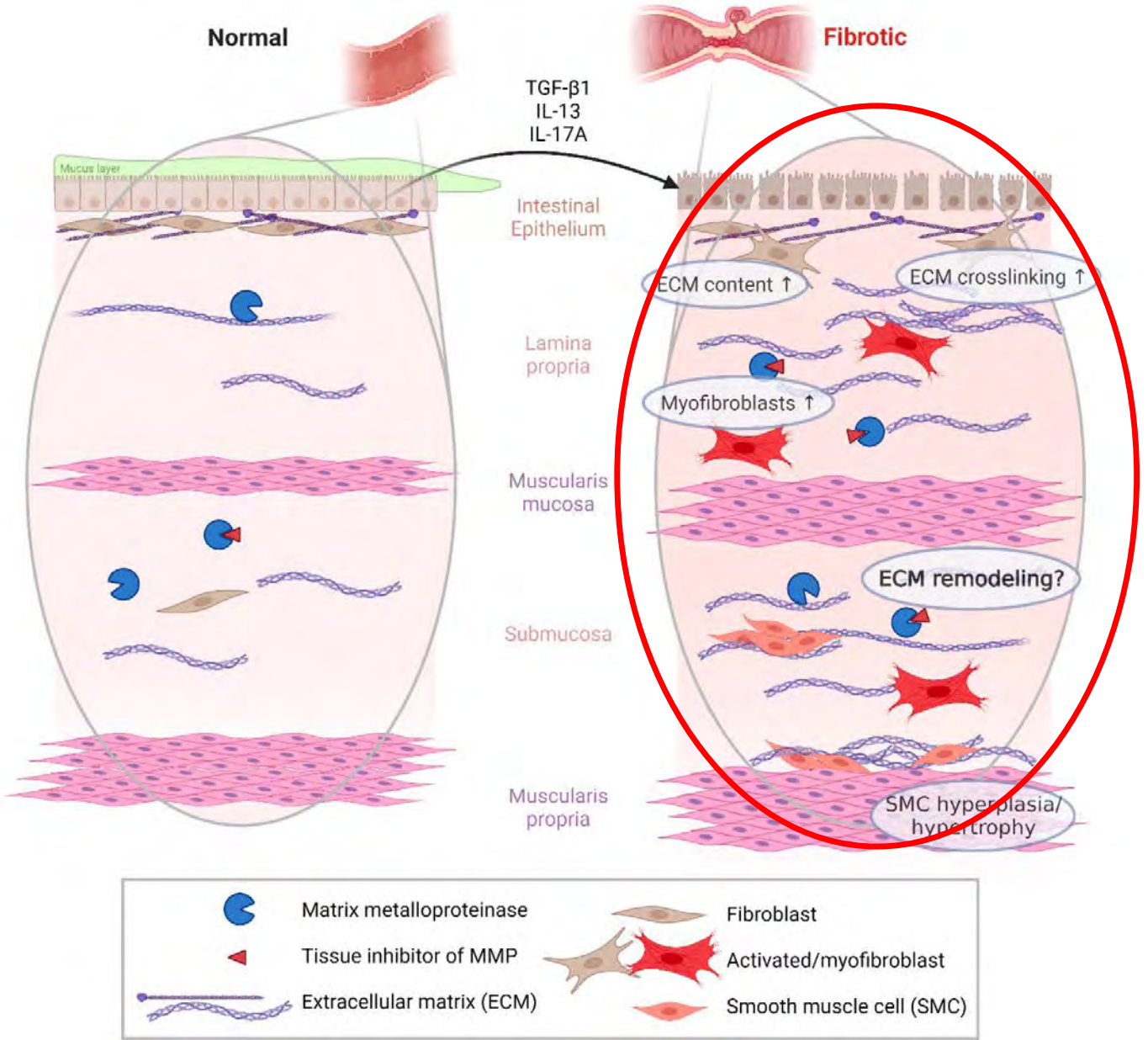

Immune cells
ILC3
ILC2
Th2
Th17
M2
M2
EMT
Metabolic reprogramming
Glycolysis ↑
Lipogenesis ↑
Glutaminolysis ↑
Fibroblasts
Microbiota
Mesenchymal cells
EndMT
Endothelium
Telocytes
Fibrocytes
Myofibroblasts
ECM
FNs
HA
FNs (soluble)
Muscularis propria
M2
M2
M2
FFAs
Creeping fat

Wu et al., 2023



Biel et al., 2023



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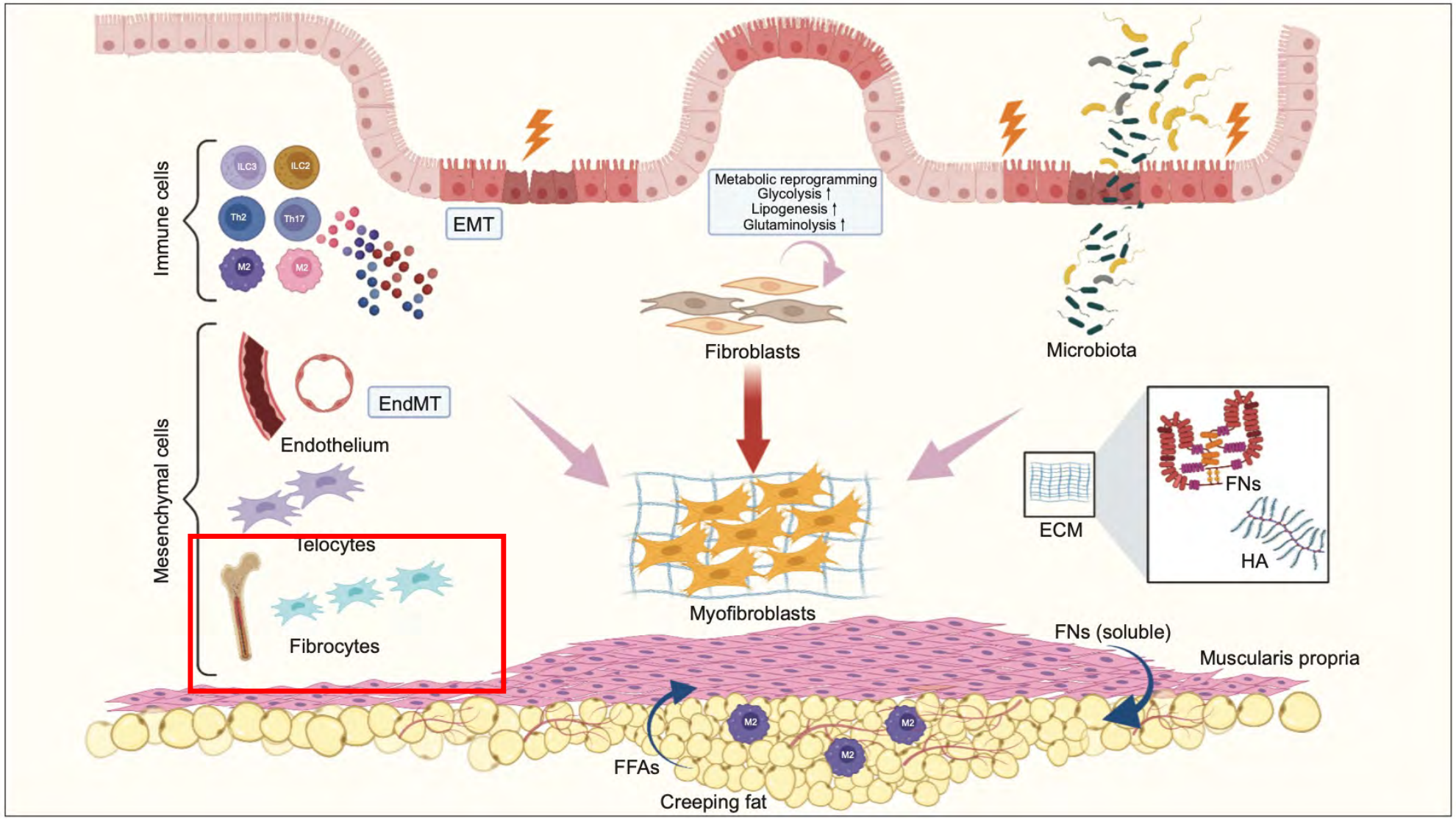
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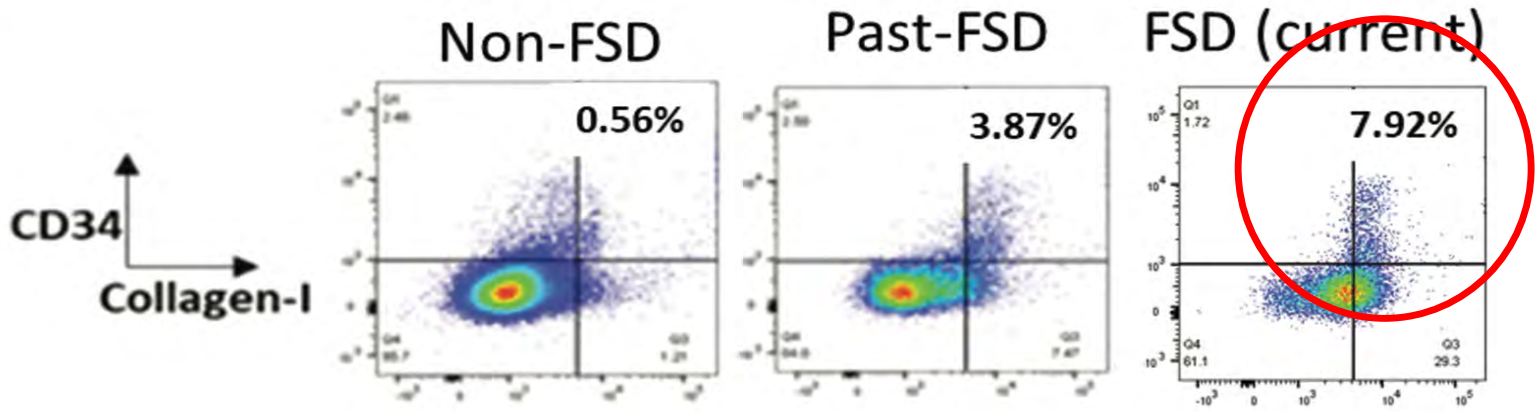
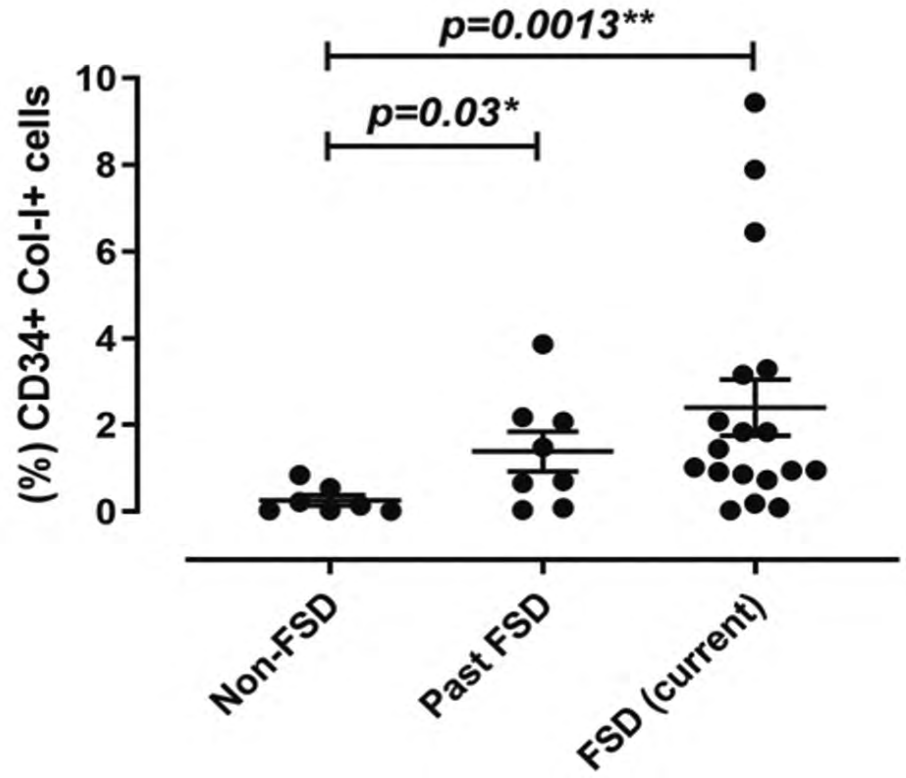
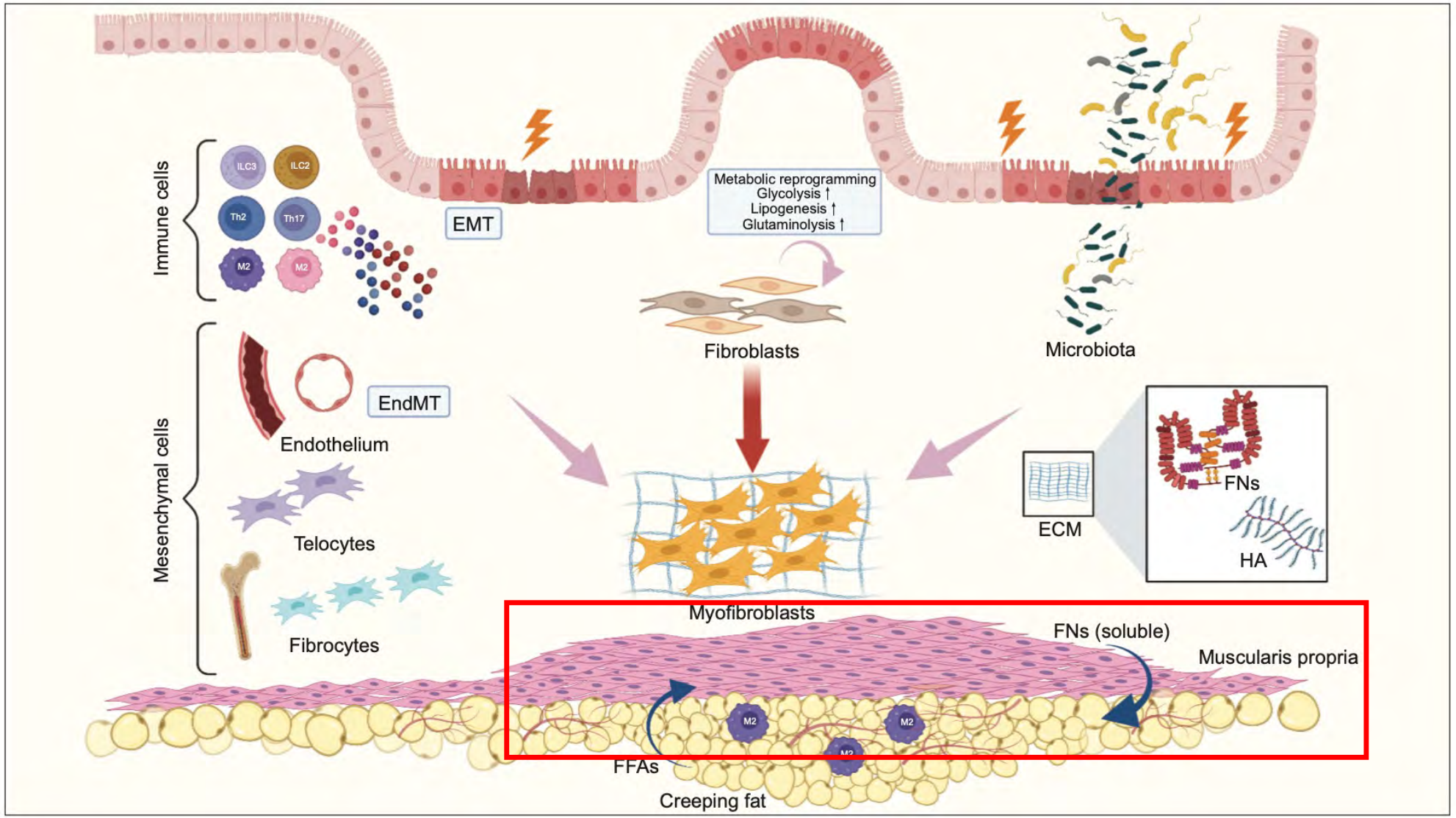

Non-FSD
Past-FSD
FSD (current)
CD34
Collagen-I
0.56%
3.87%
7.92%
Q1
1.72
Q4
61.1
Q3
29.3


p=0.0013**
p=0.03*
(%) CD34+ Col-I+ cells
10
8
6
4
2
0
Non-FSD
Past FSD
FSD (current)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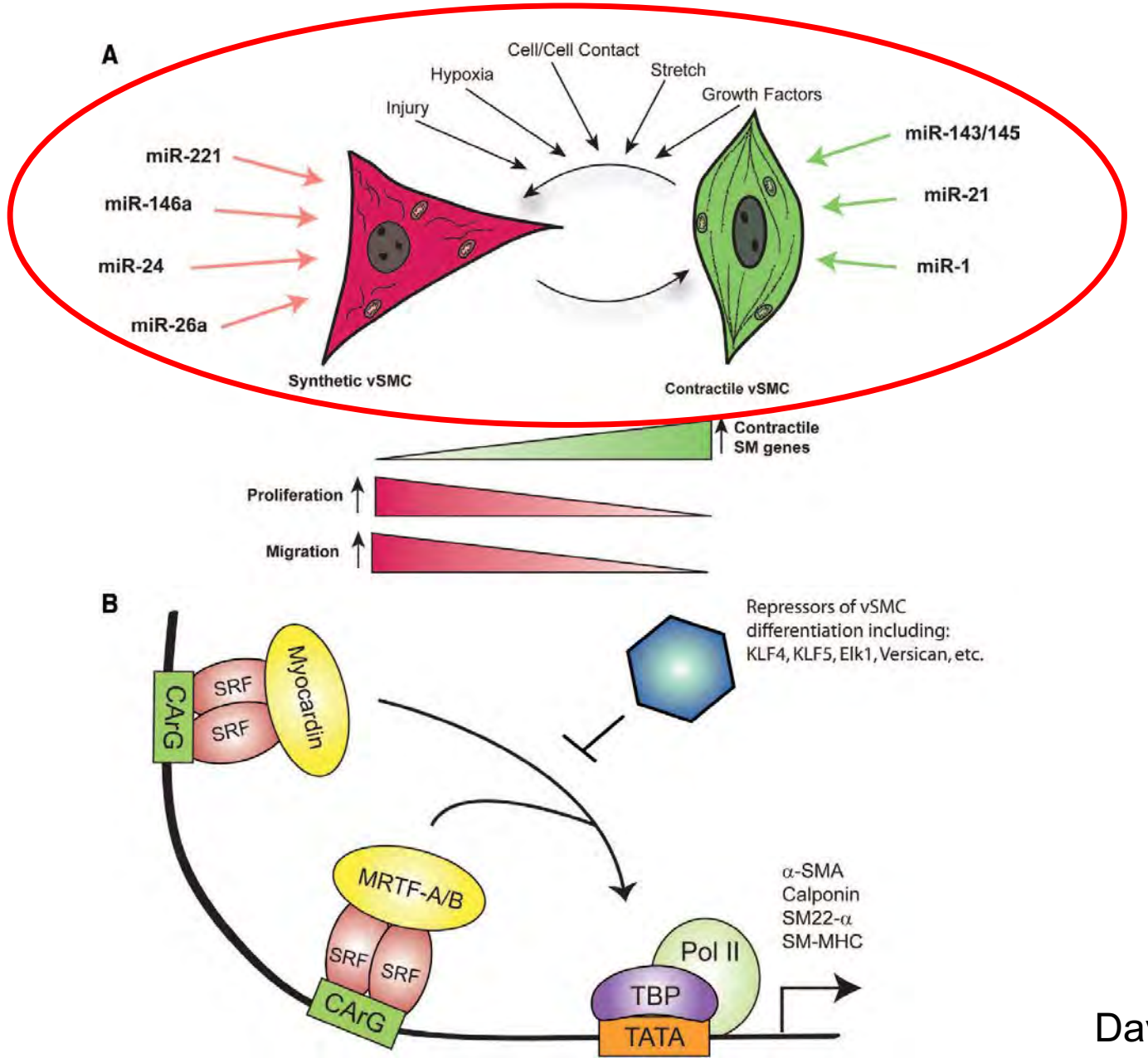
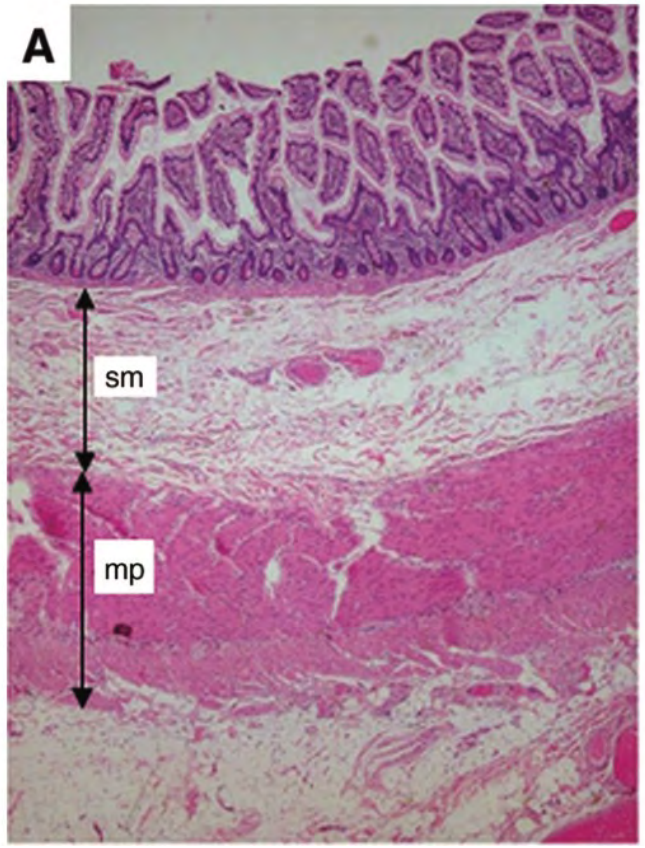
Wu et al., 2023



Davis-Dusenbery et al., 2011

Smooth muscle expansion is a major component of a stricture



Chen et al., 2017

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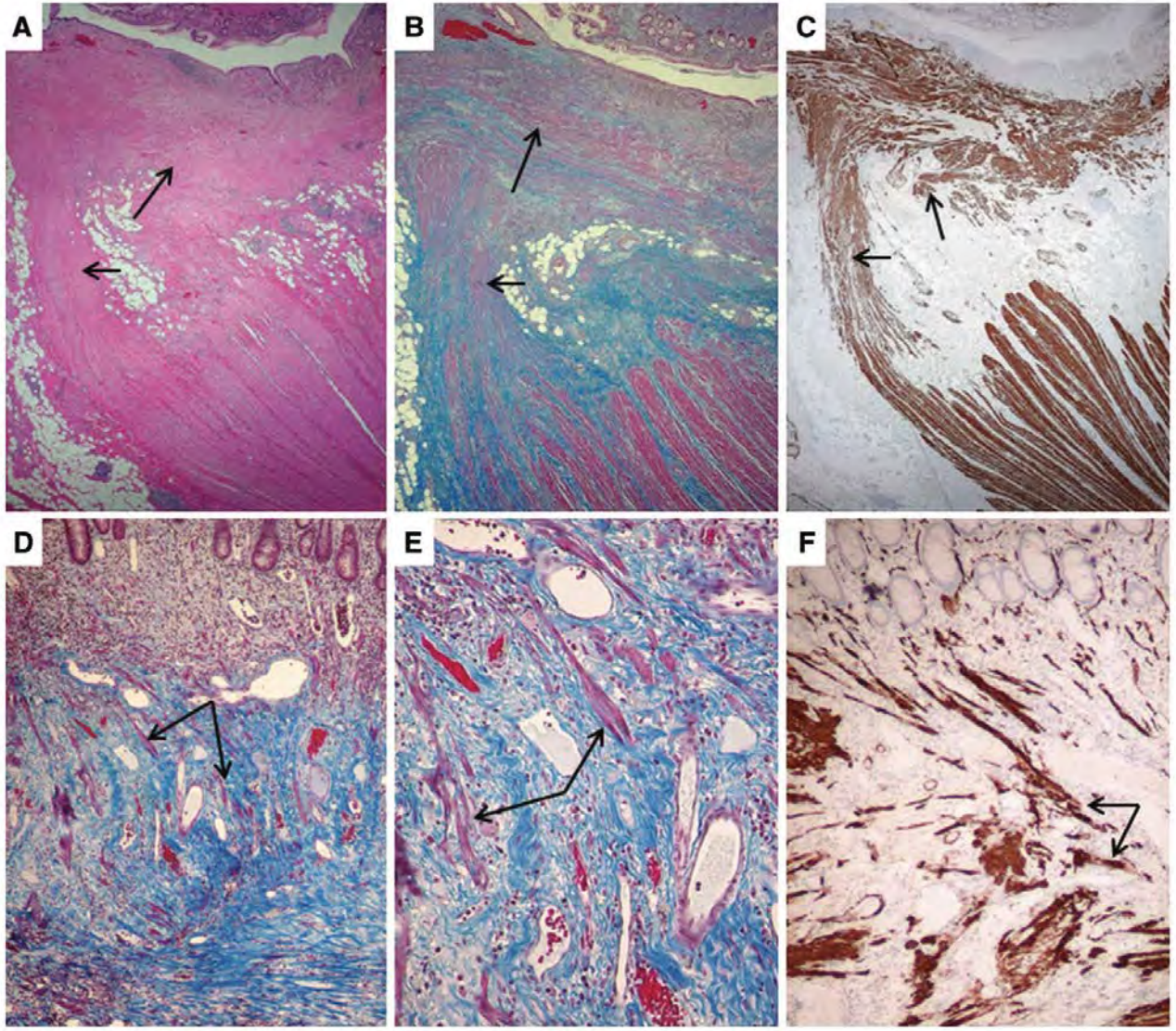
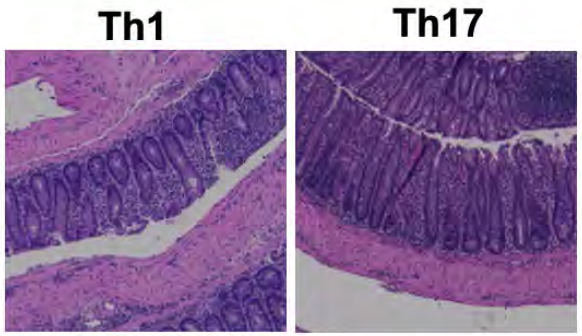


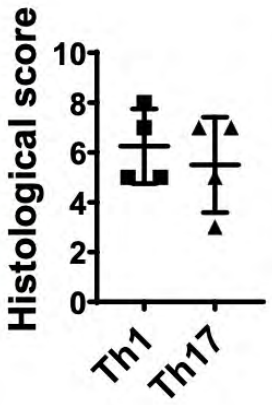
Chen et al., 2017

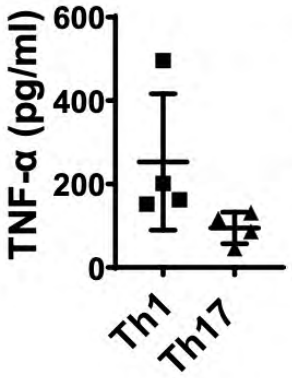
New targets

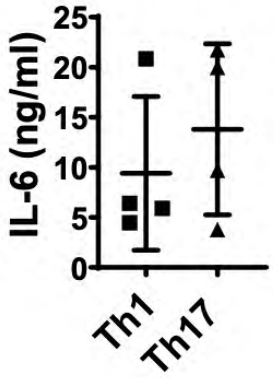
Amphiregulin

Th17 cells drive fibrosis - inflammation-independent



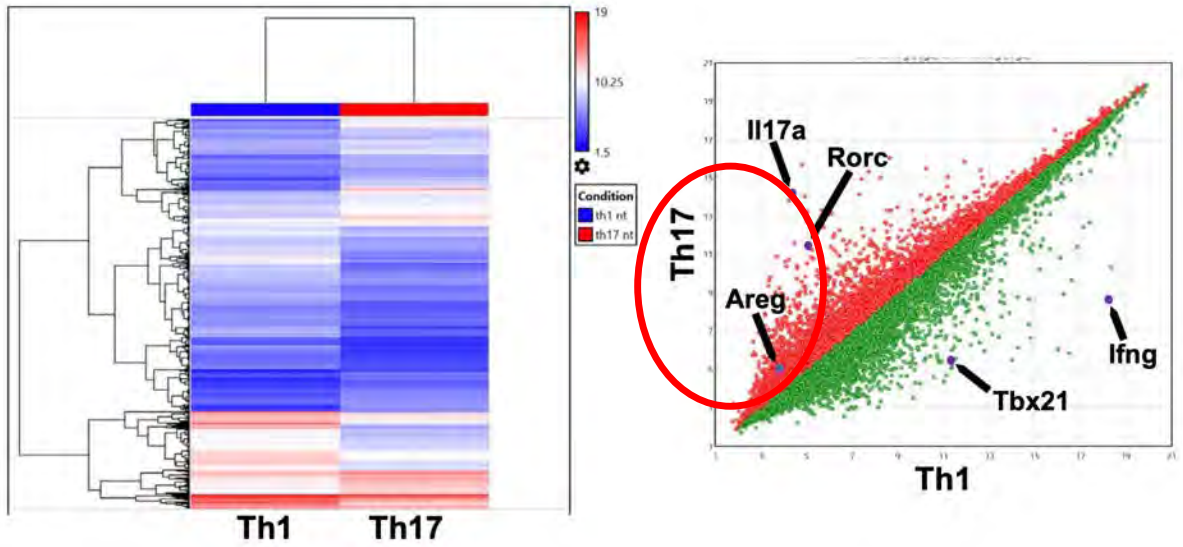






Zhao et al., 2023

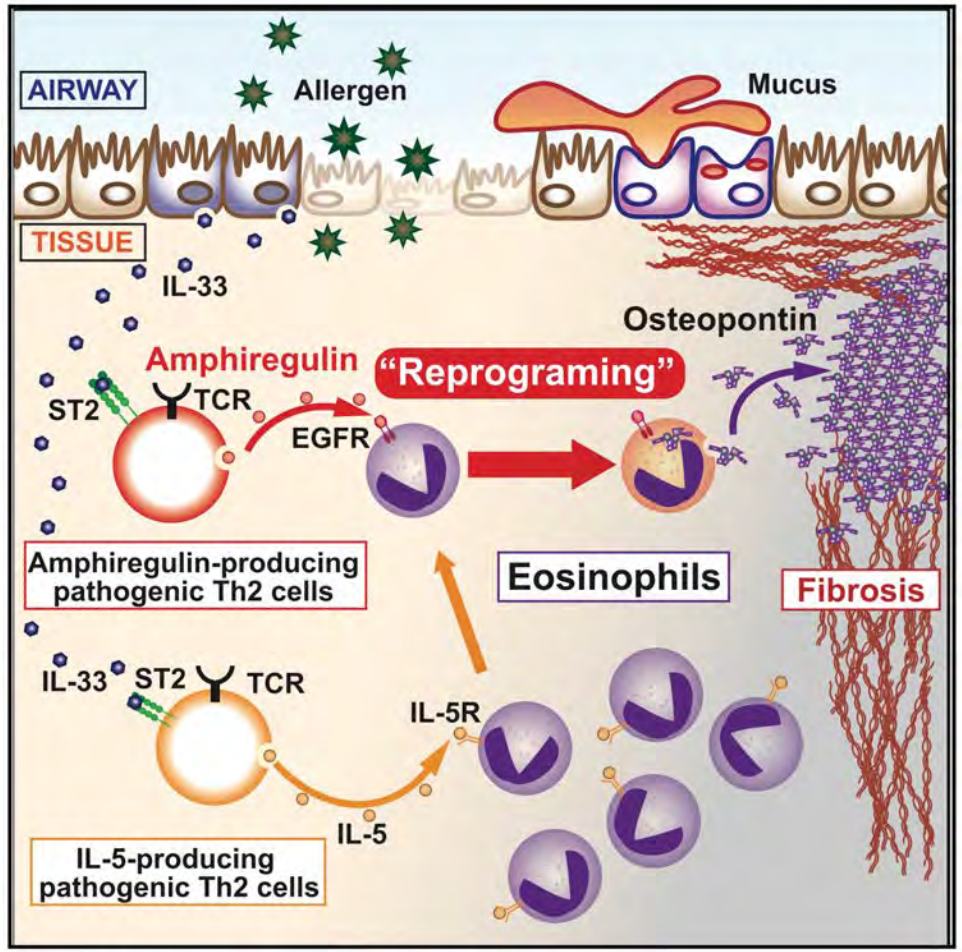
Th17 cells produce amphiregulin



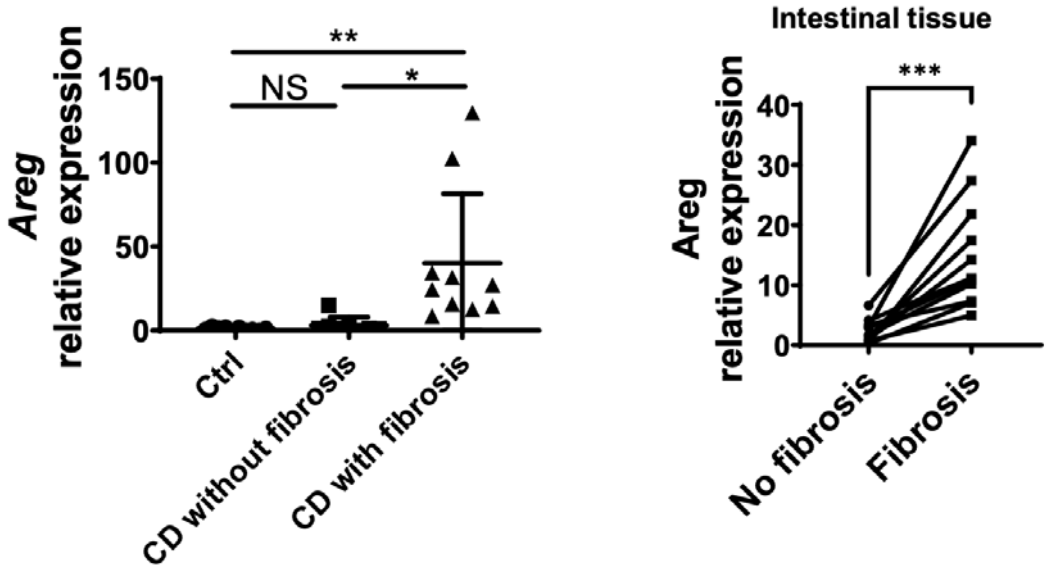
Zhao et al., 2023

Immunity

Amphiregulin-Producing Pathogenic Memory T Helper 2 Cells Instruct Eosinophils to Secrete Osteopontin and Facilitate Airway Fibrosis

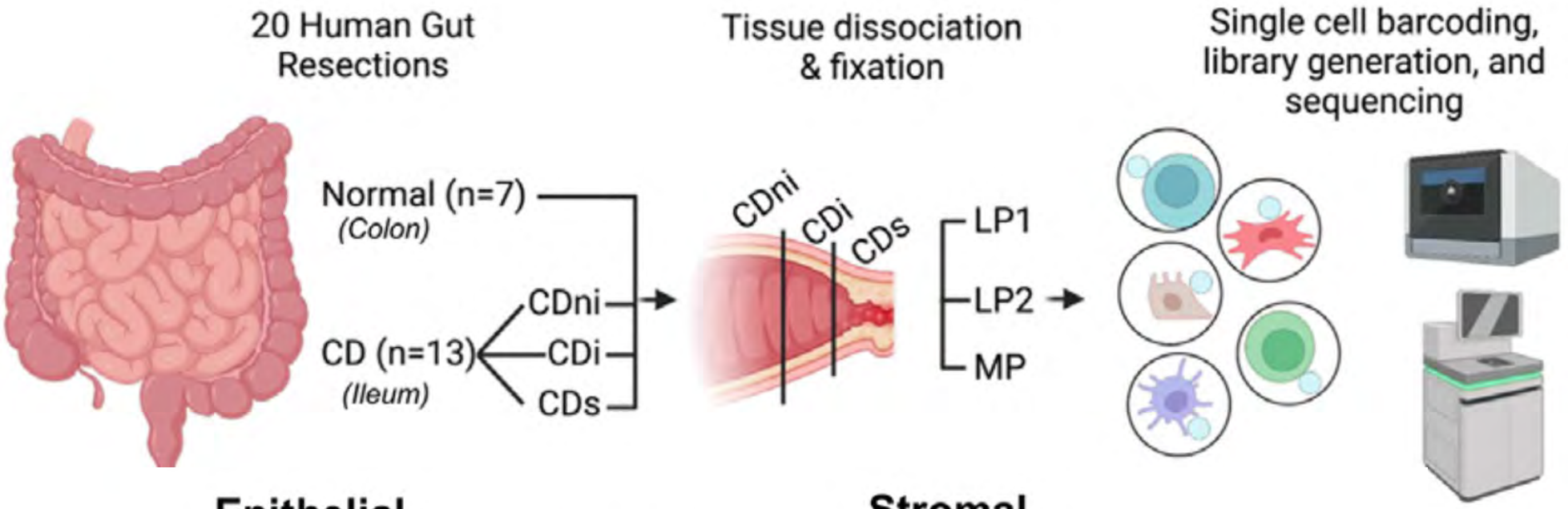


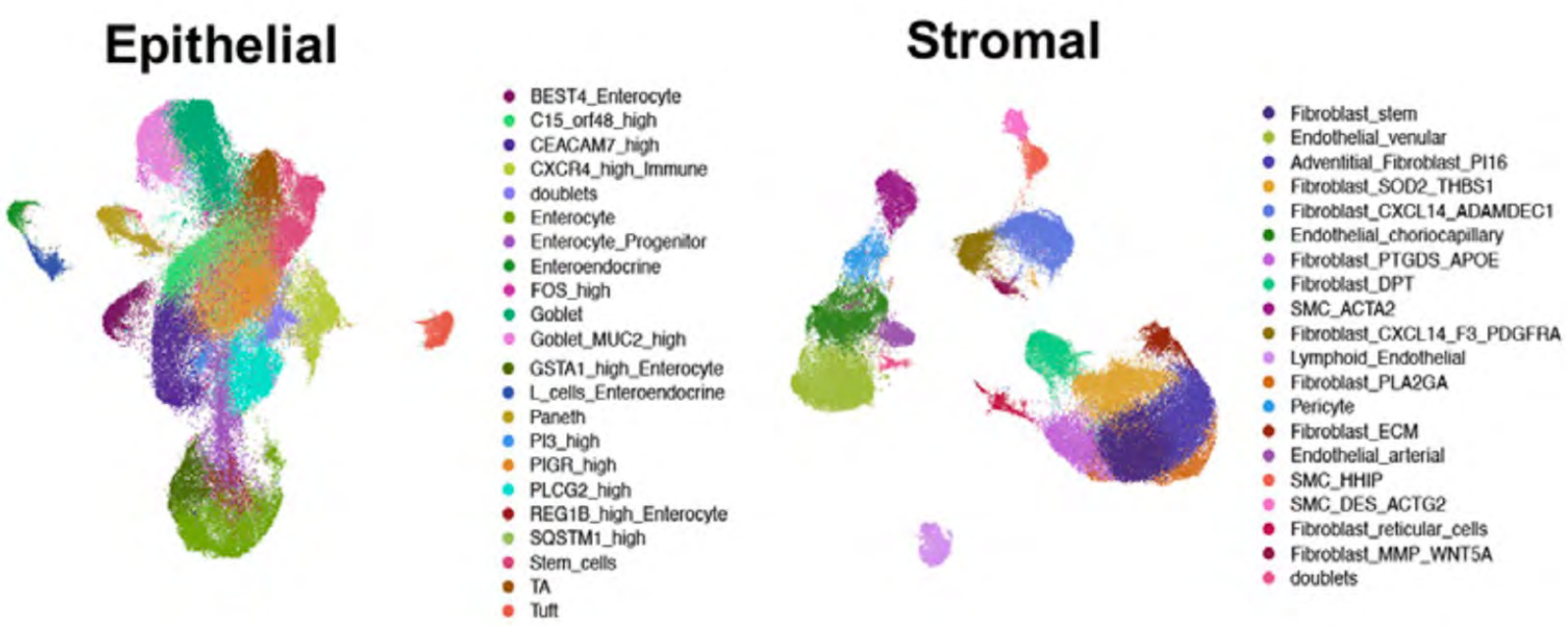
Fibrostenotic CD is associated with increased amphiregulin expression



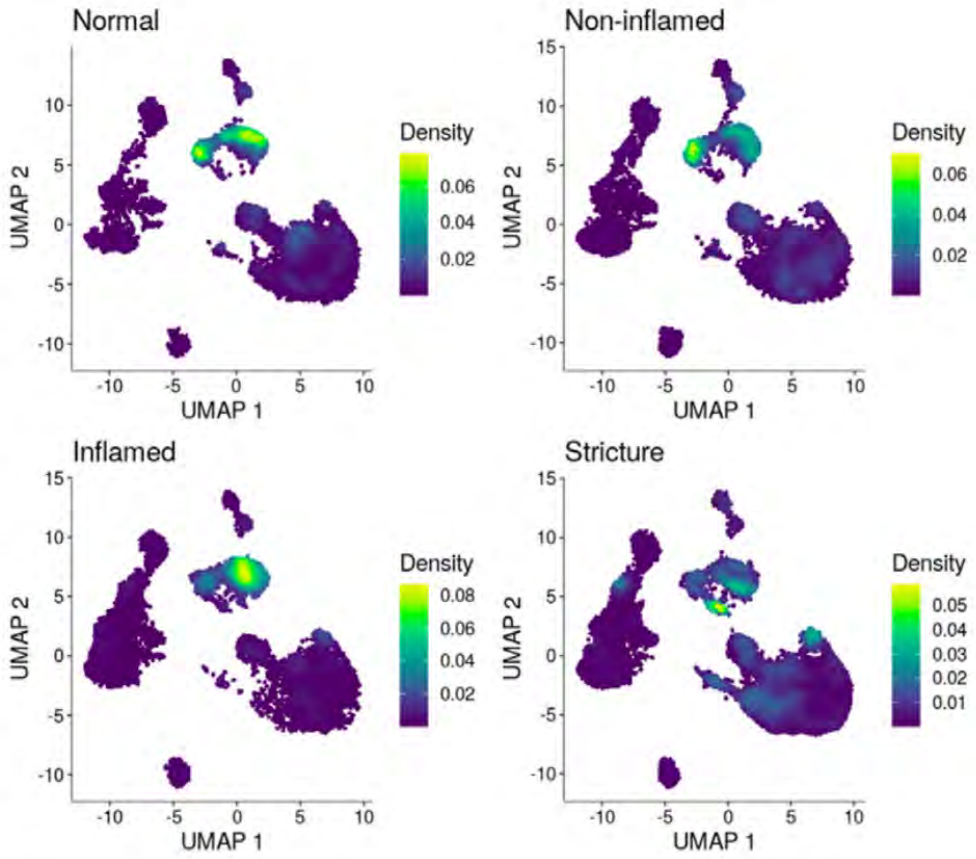
Zhao et al., 2023

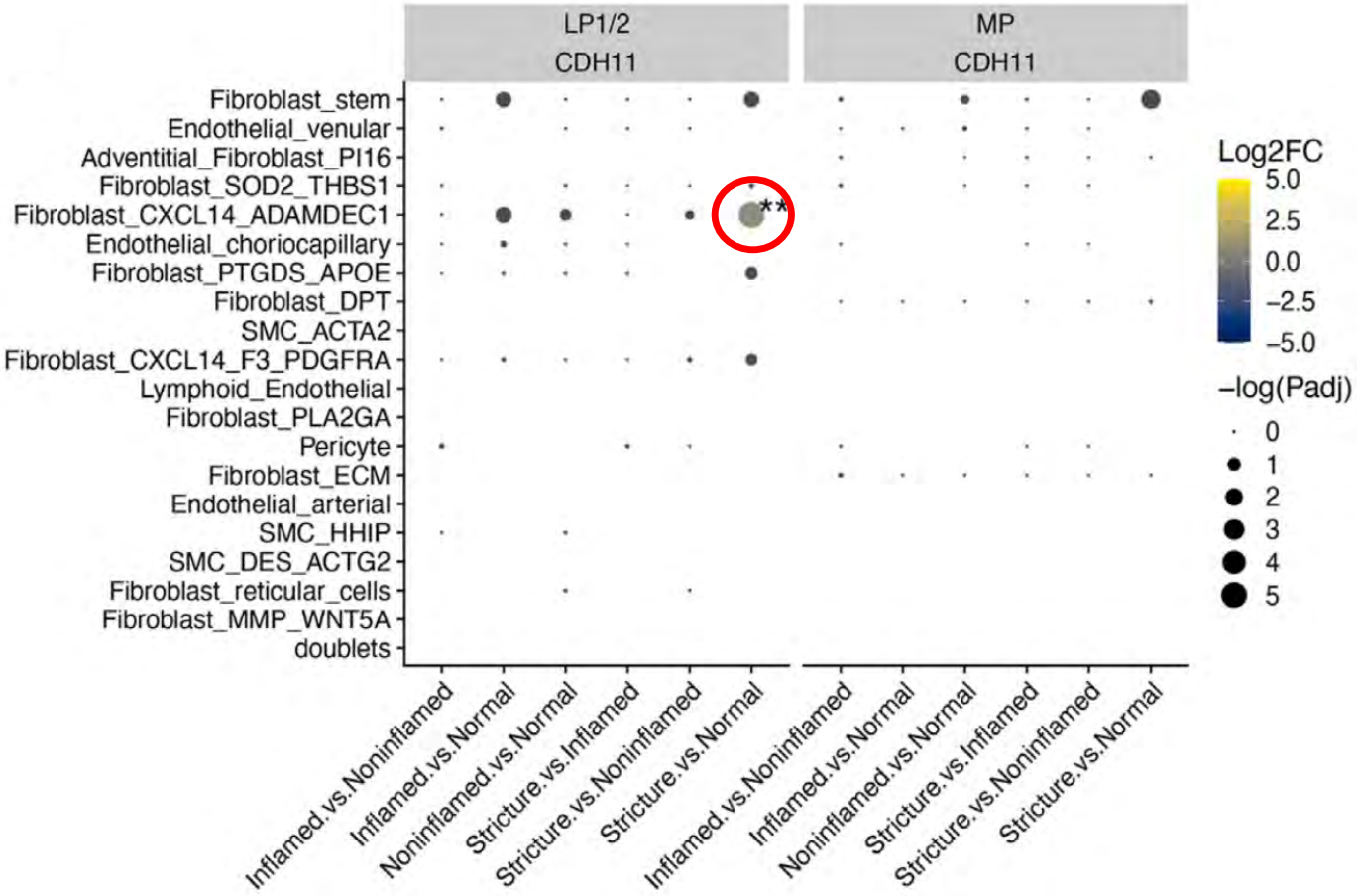
Cadherin-11



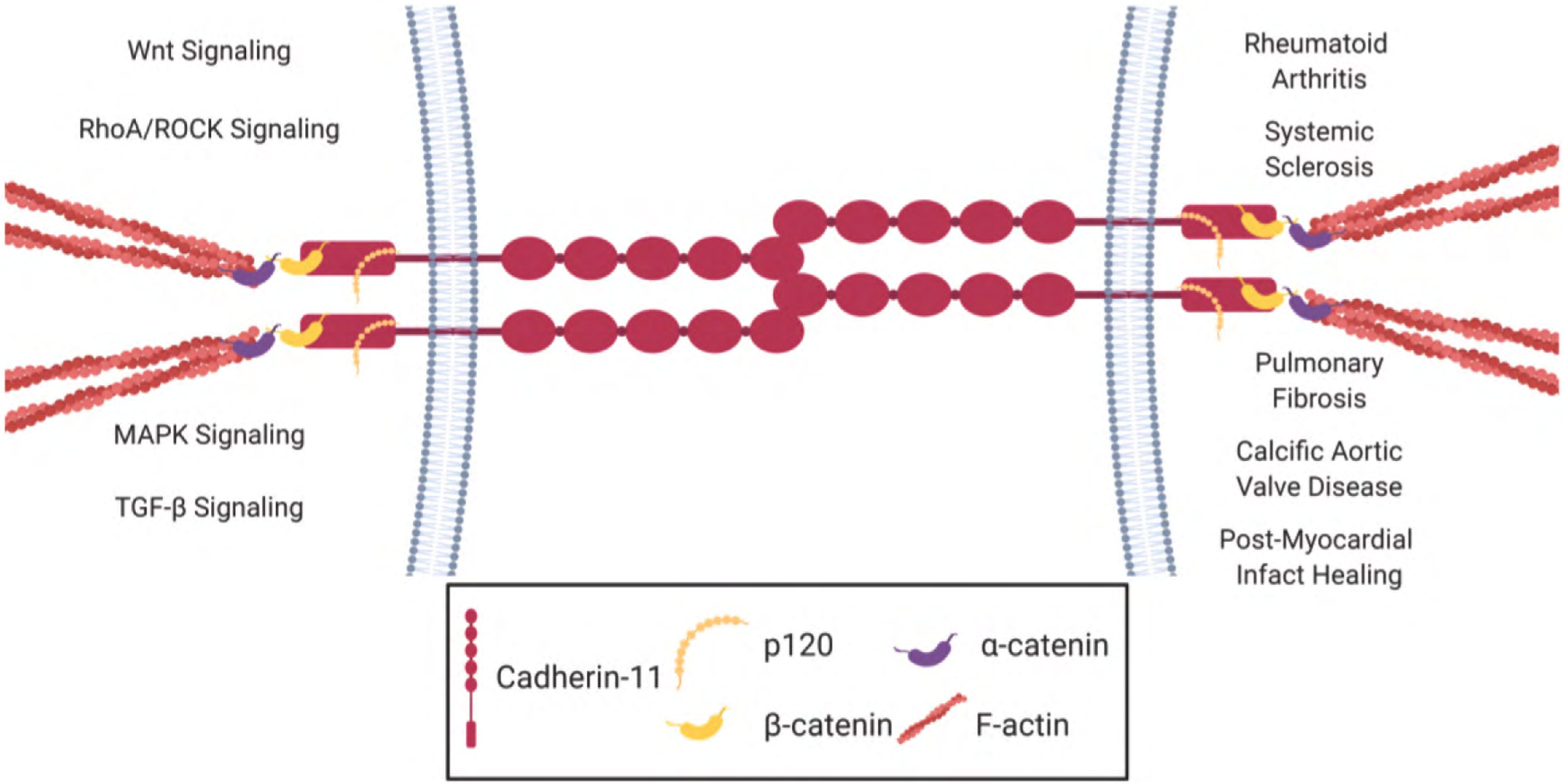


Mukherjee et al., 2023



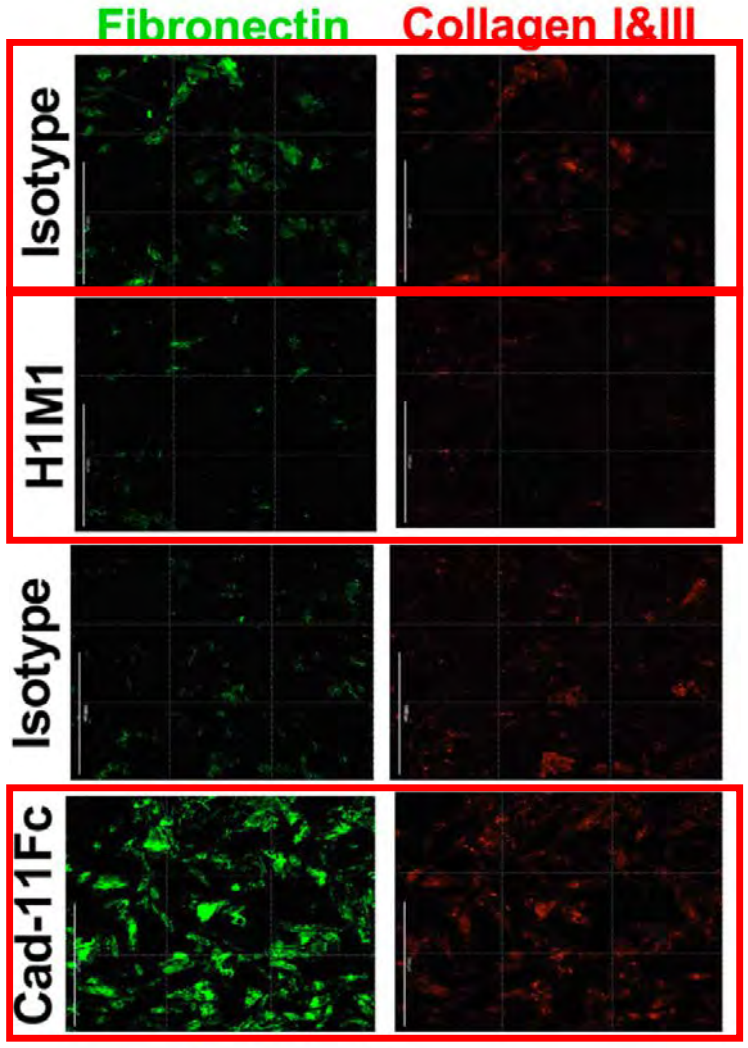


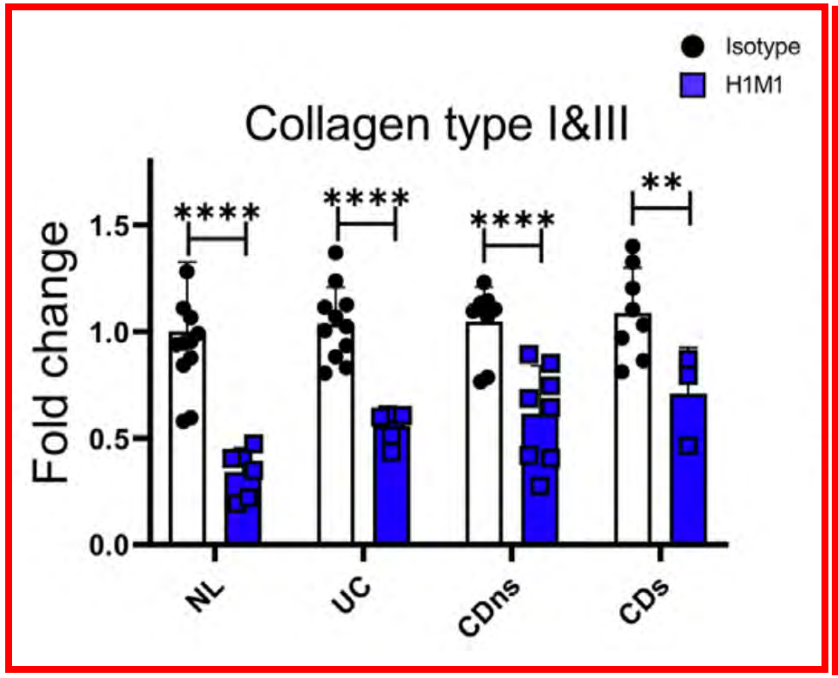
Mukherjee et al., 2023

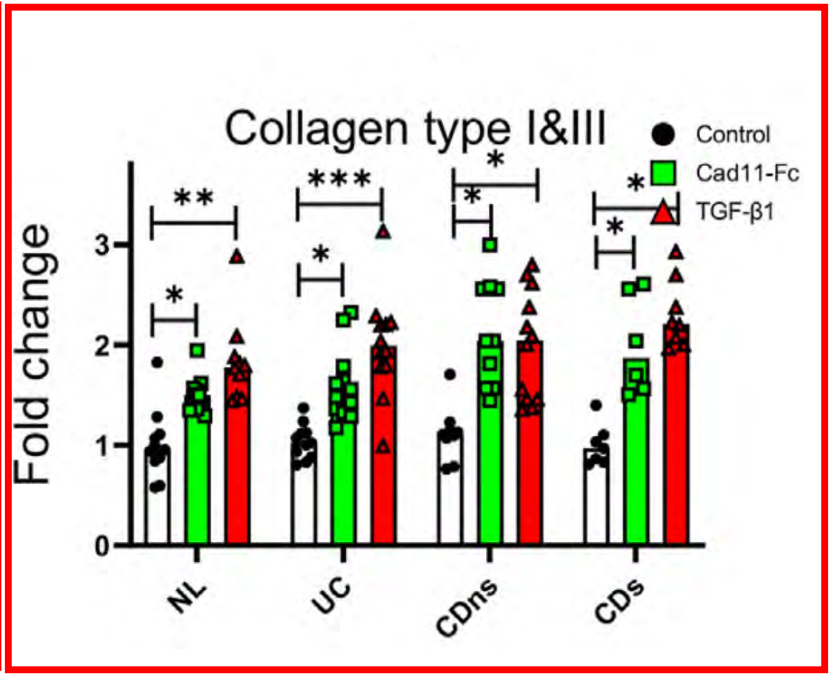


Riley & W.D. Merryman, 2021

Modulation of cadherin-11 alters ECM production







Mukherjee et al., 2023

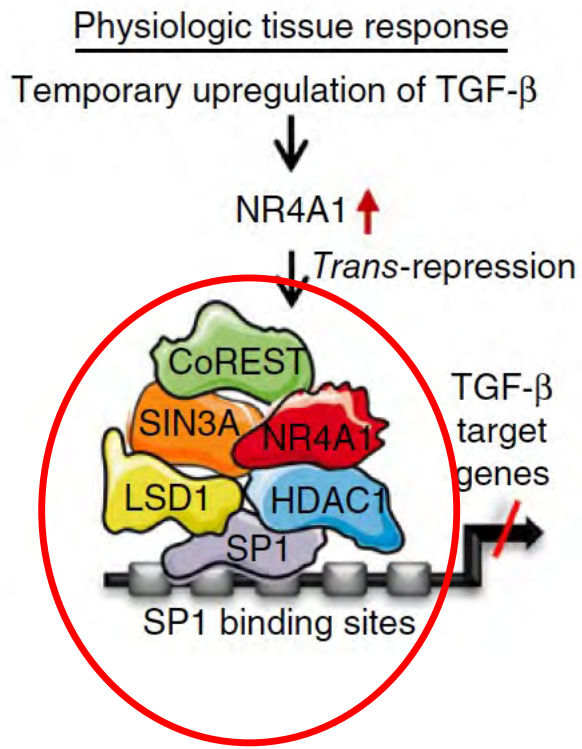
What can we learn from other organ systems?

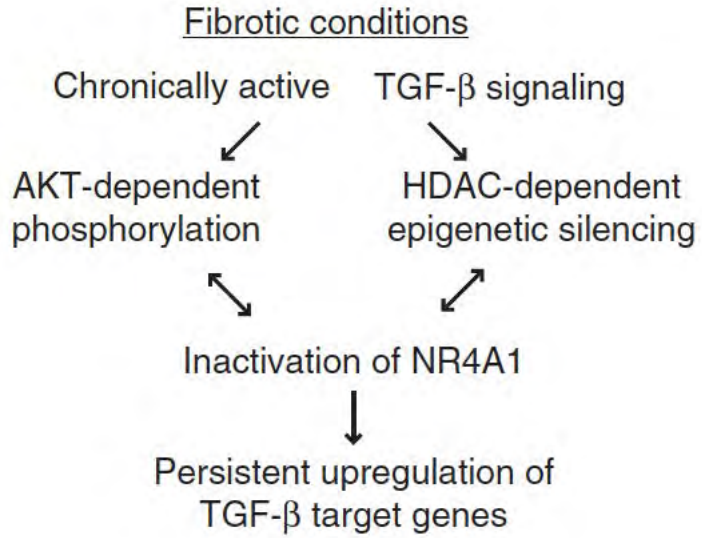
nature medicine

Orphan nuclear receptor NR4A1 regulates transforming growth factor-β signaling and fibrosis

Katrin Palumbo-Zerr[1], Pawel Zerr[1,7], Alfiya Distler[1,7], Judith Fliehr[1], Rossella Mancuso[1], Jingang Huang[1], Dirk Mielenz[2], Michal Tomcik[1,3], Barbara G Fürnrohr[2,4], Carina Scholtysek[1], Clara Dees[1], Christian Beyer[1], Gerhard Krönke[1], Daniel Metzger[5], Oliver Distler[6], Georg Schett[1] & Jörg H W Distler[1]

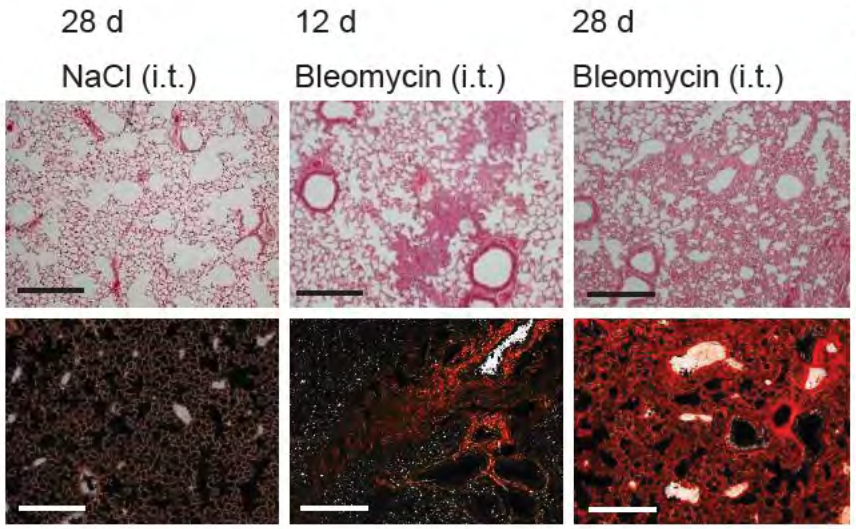
NR4A1 regulation – acute vs chronic TGF-β signaling

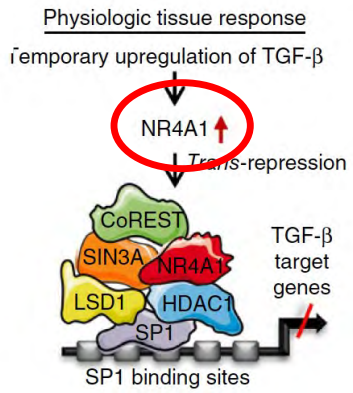


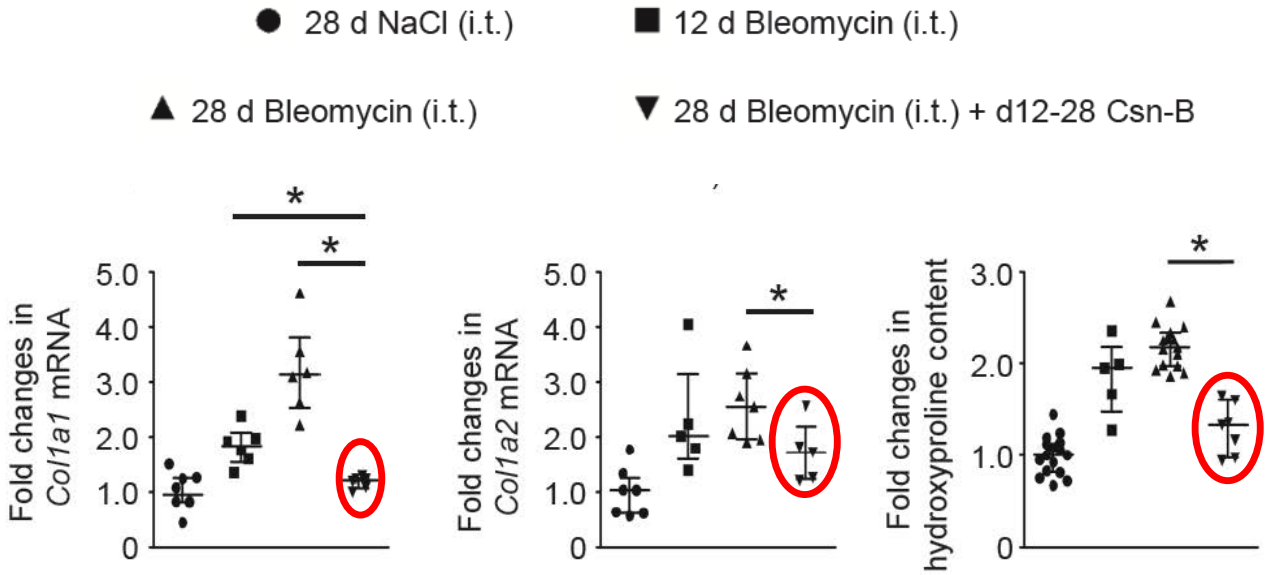


Palumbo-Zerr et al., 2015

NR4A1 activation reverses established fibrosis

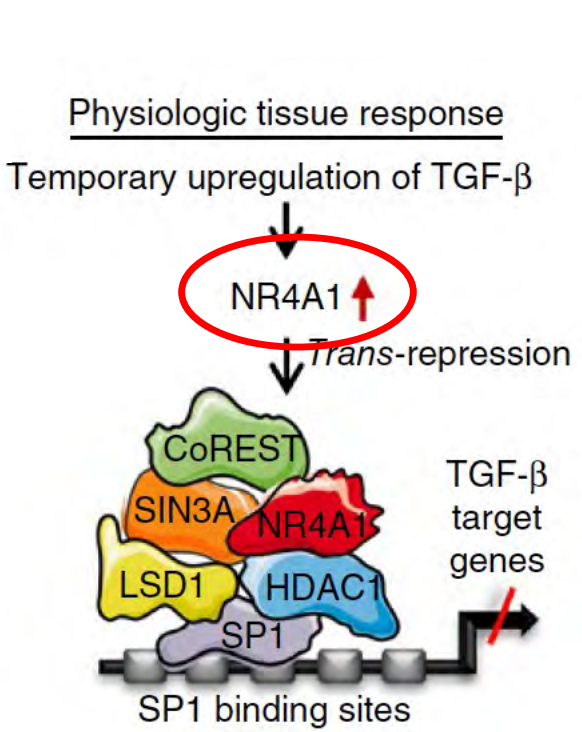


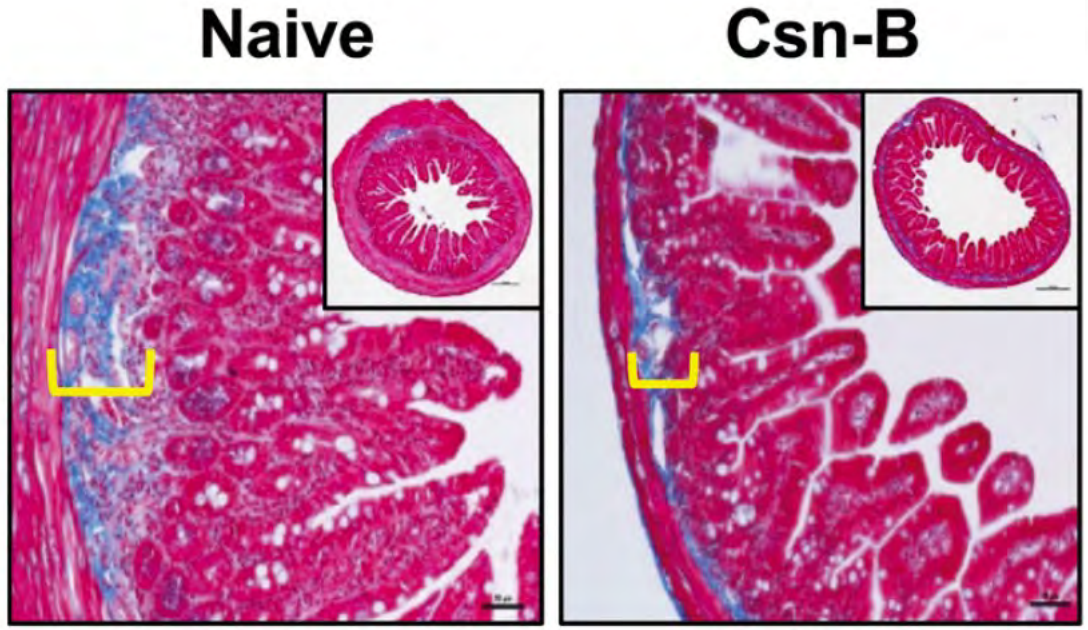


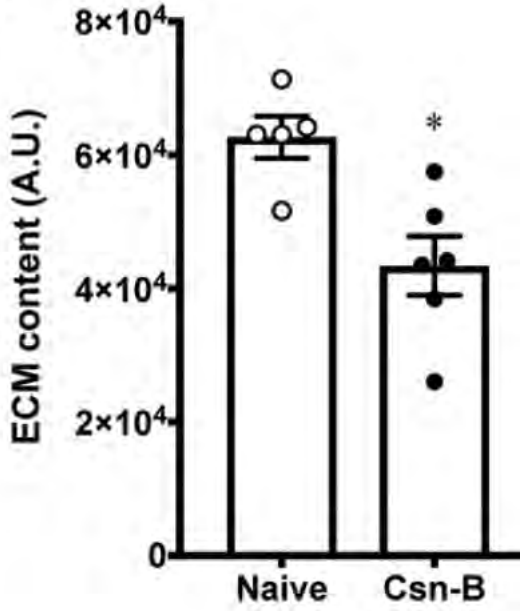


Palumbo-Zerr et al., 2015

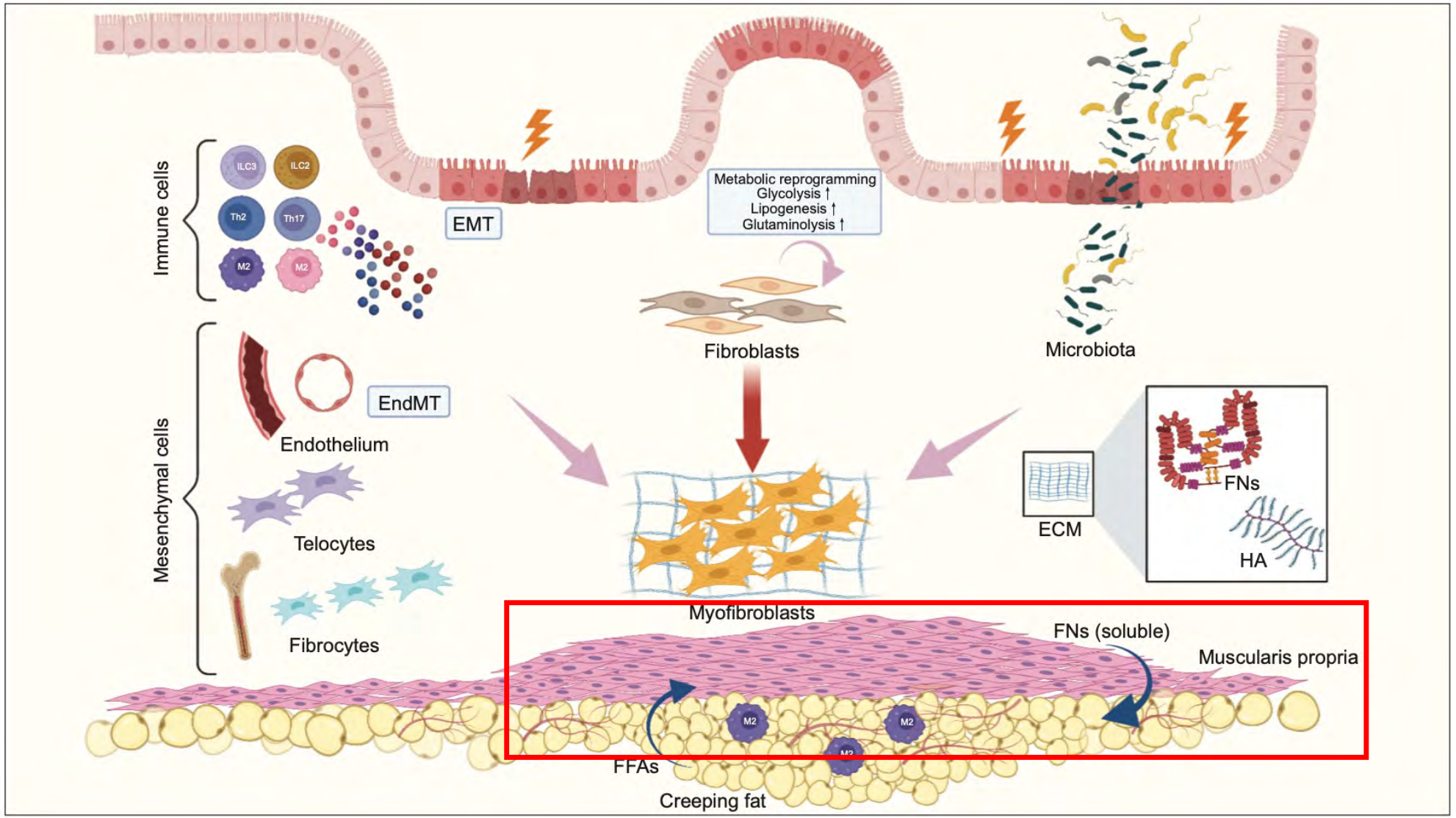
NR4A1 regulates inflammation-associated intestinal fibrosis







Venu et al., 2021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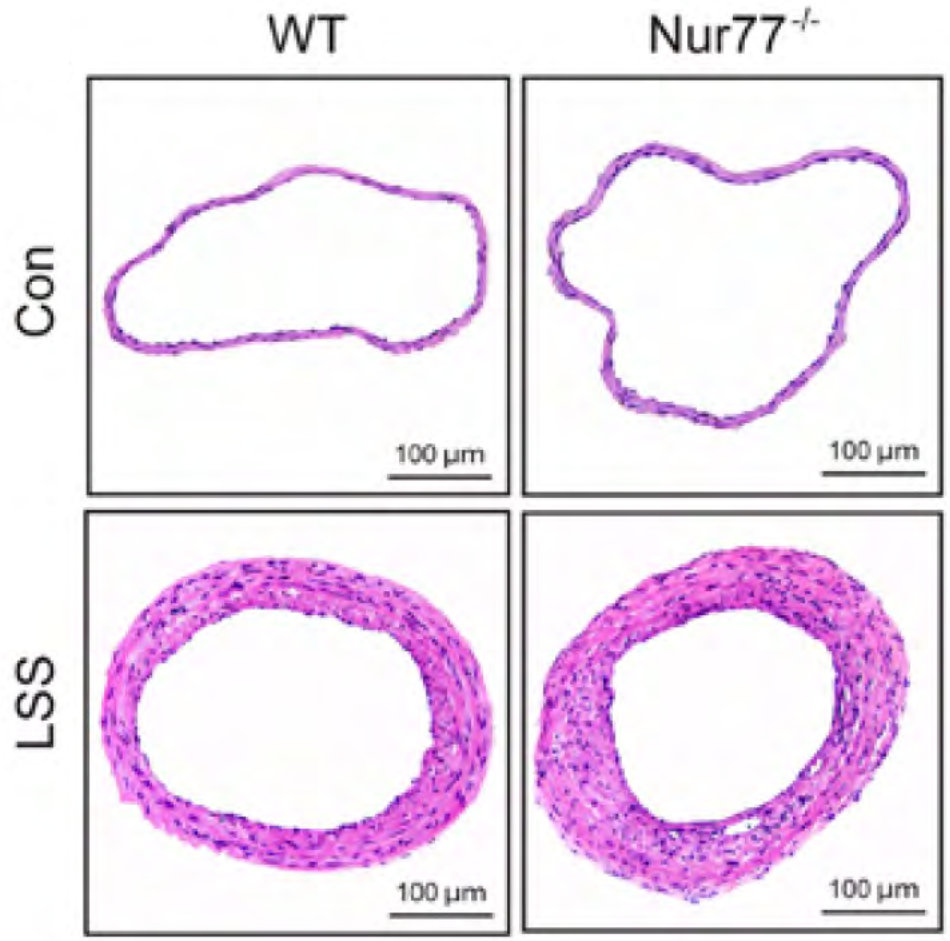
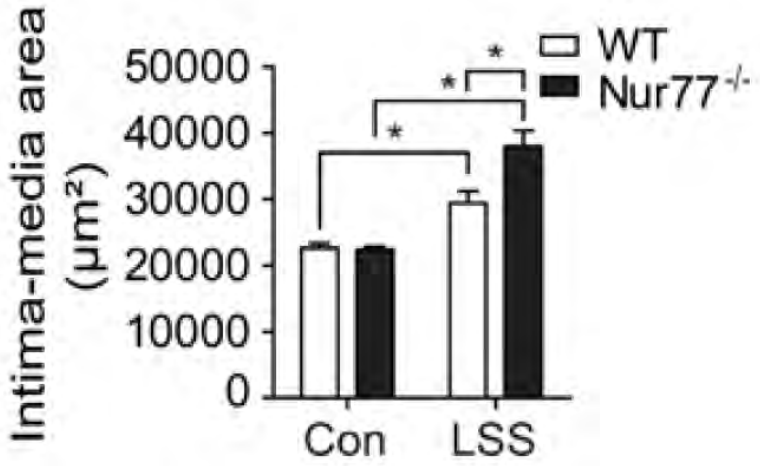
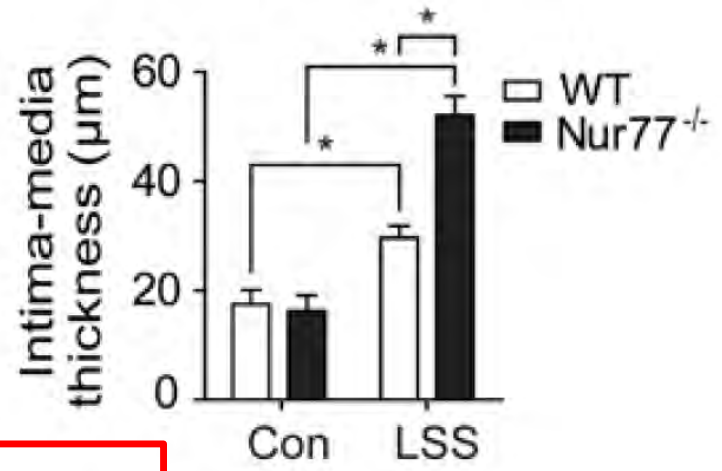
Wu et al., 2023

NR4A1 dampens vascular remodeling



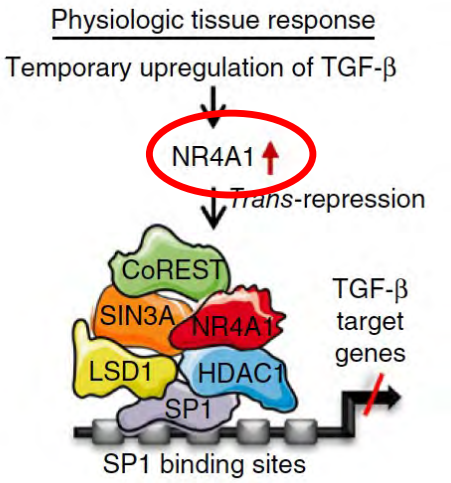




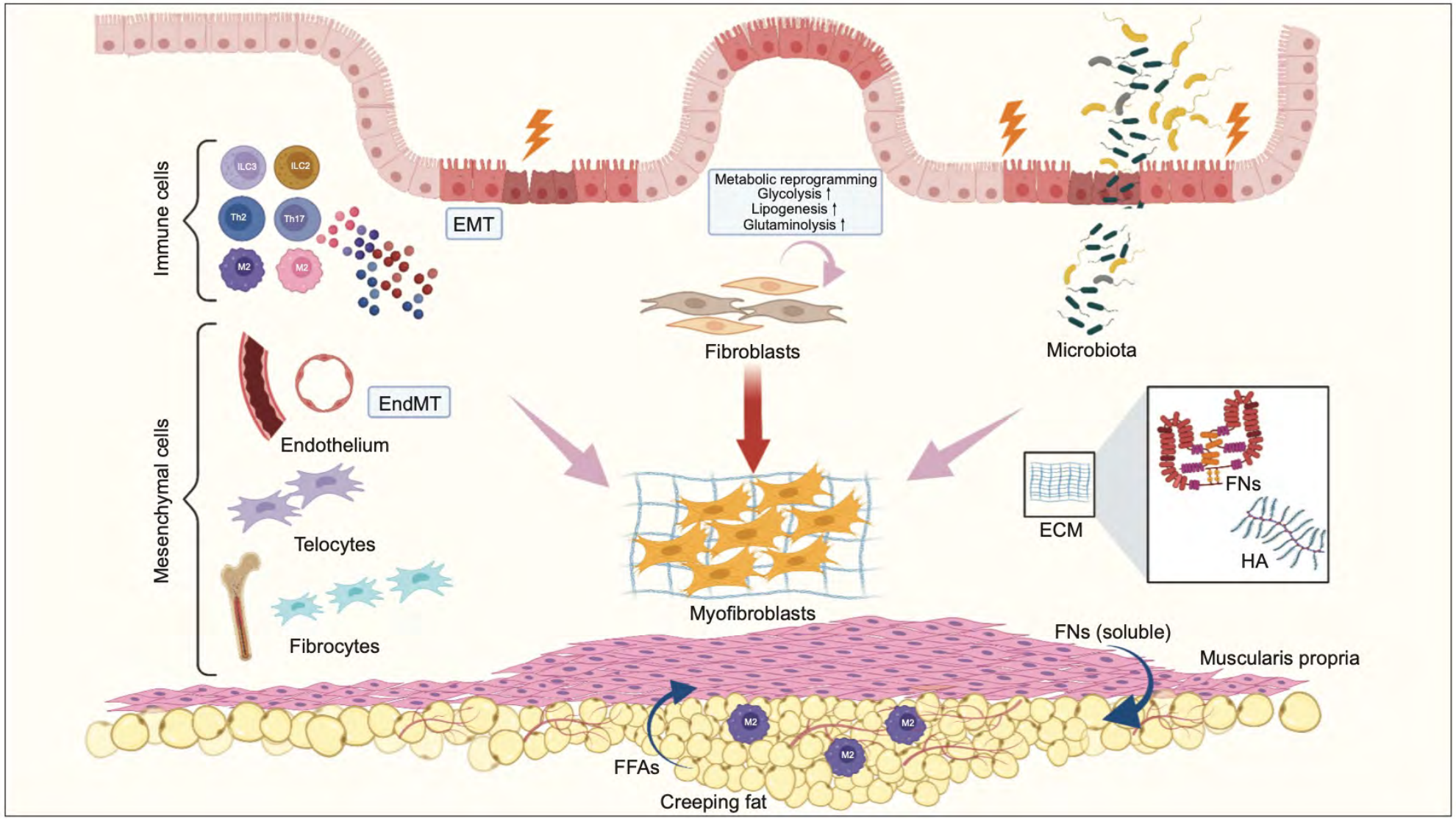
Nur77 = NR4A1

Yu et al., 2015

NR4A1 activation dampens inflammation-associated intestinal smooth muscle thickening



Szczepanski et al., 2022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Wu et al., 2023

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Elizabeth Hughes

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Michael Taylor

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Dr. Sridhar Mani

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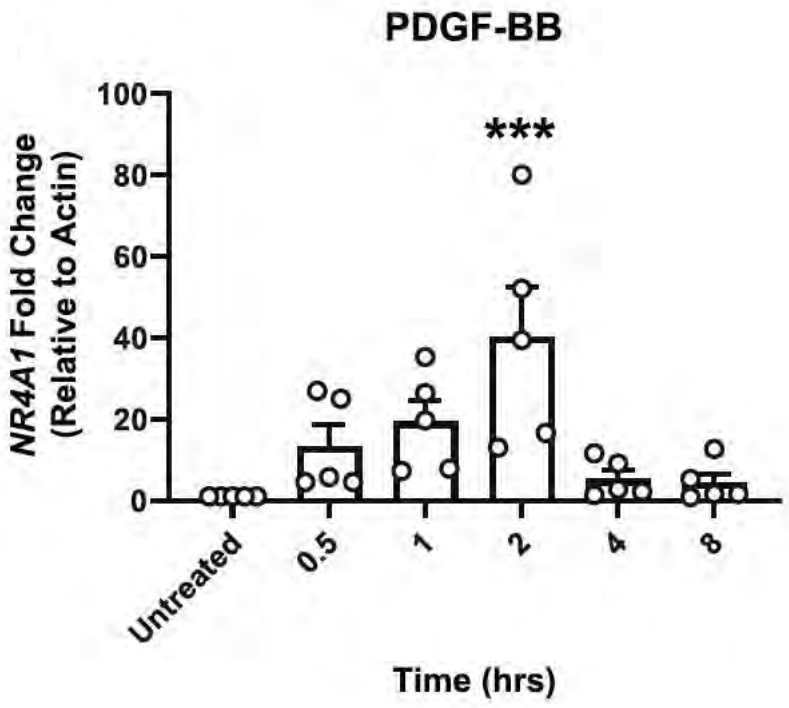
Funding Sources

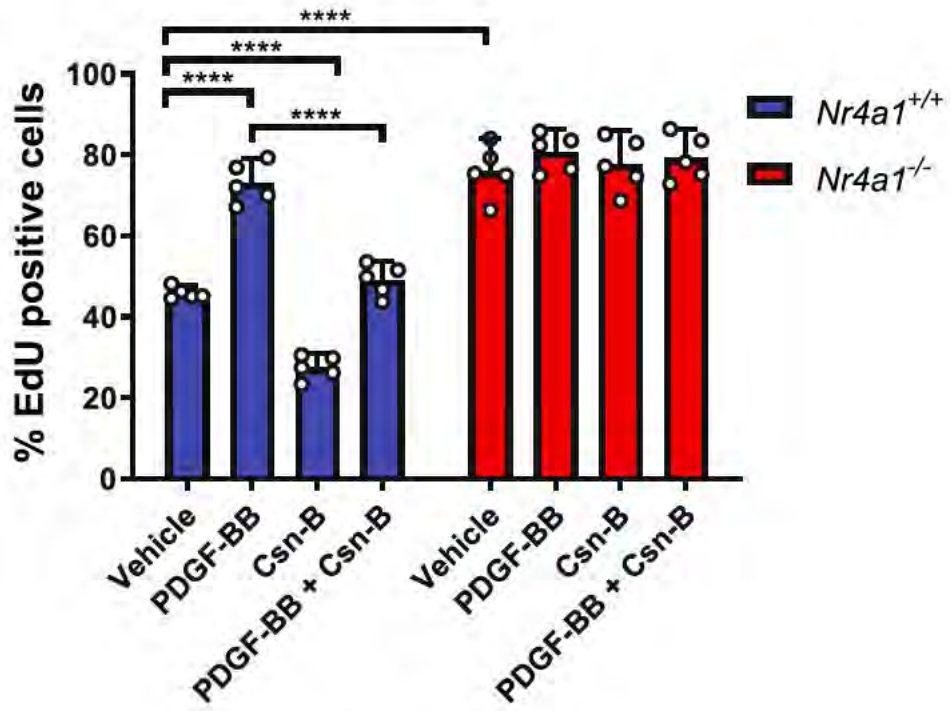
ALBERTA INNOVATES

CIHR IRSC

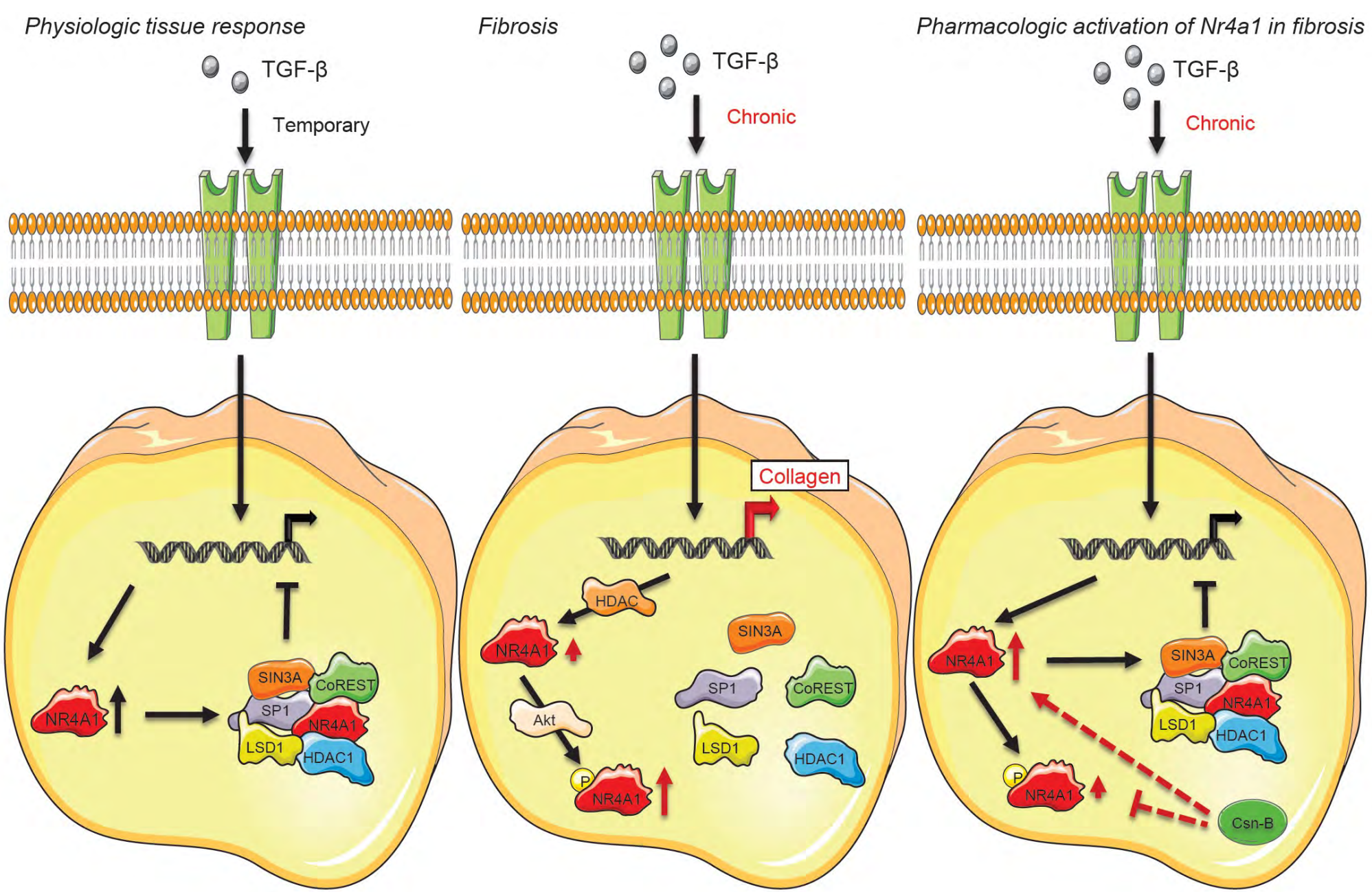
Weston Family Foundation

NR4A1 regulates mitogen-induced intestinal smooth muscle cell proliferation



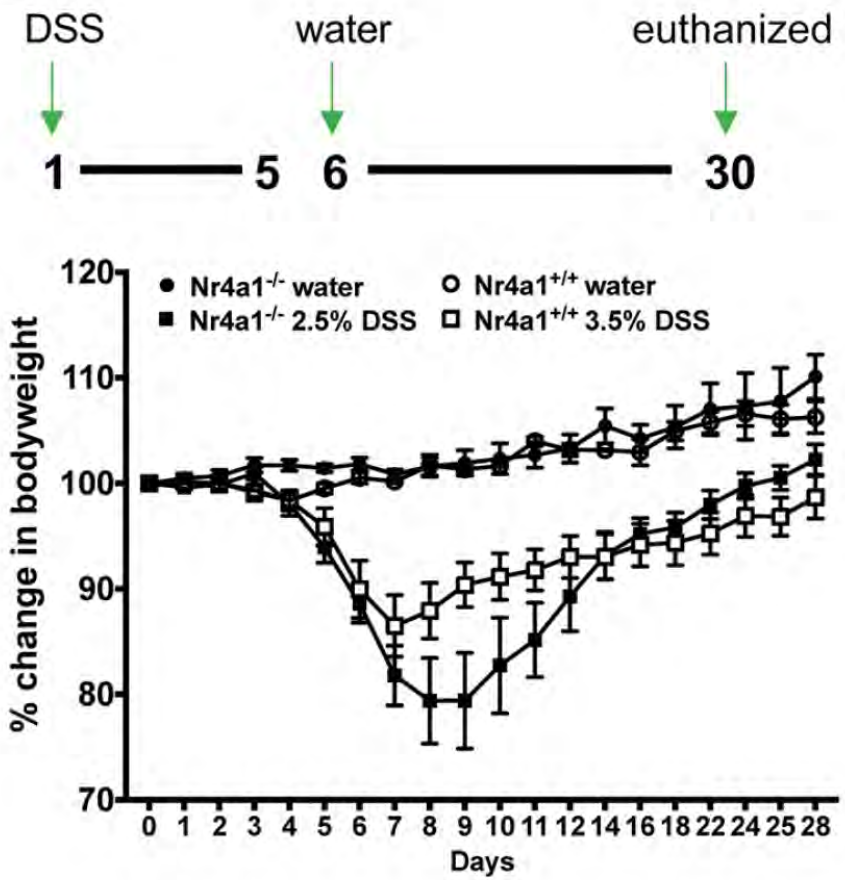


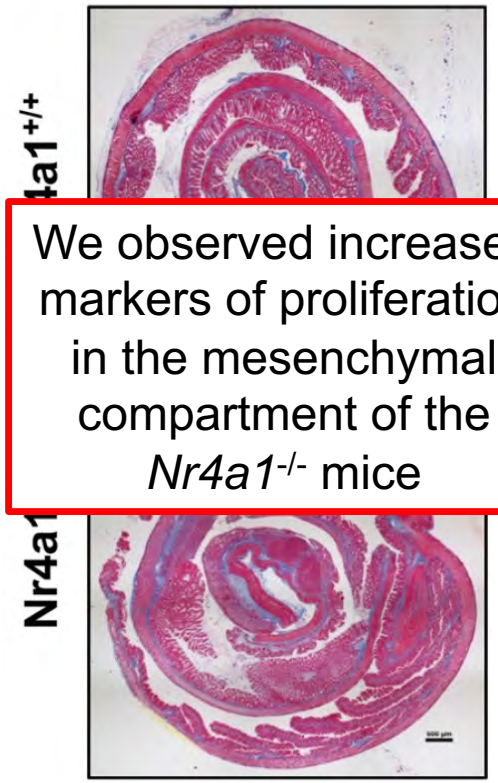
Szczepanski et al., 2022



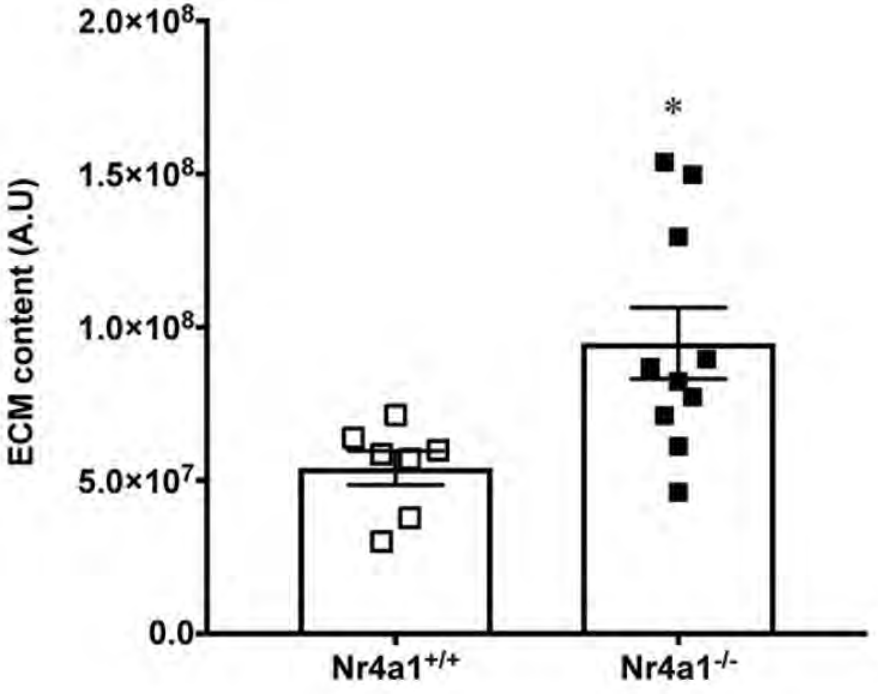
Palumbo-Zerr et al., 2015

NR4A1 regulates inflammation-associated intestinal fibrosis





We observed increased markers of proliferation in the mesenchymal compartment of the *Nr4a1*$^{-/-}$ mice



Venu et al., 2021

TABLE 1. Factors That Initiate or Perpetuate Fibrosis in Crohn's Disease

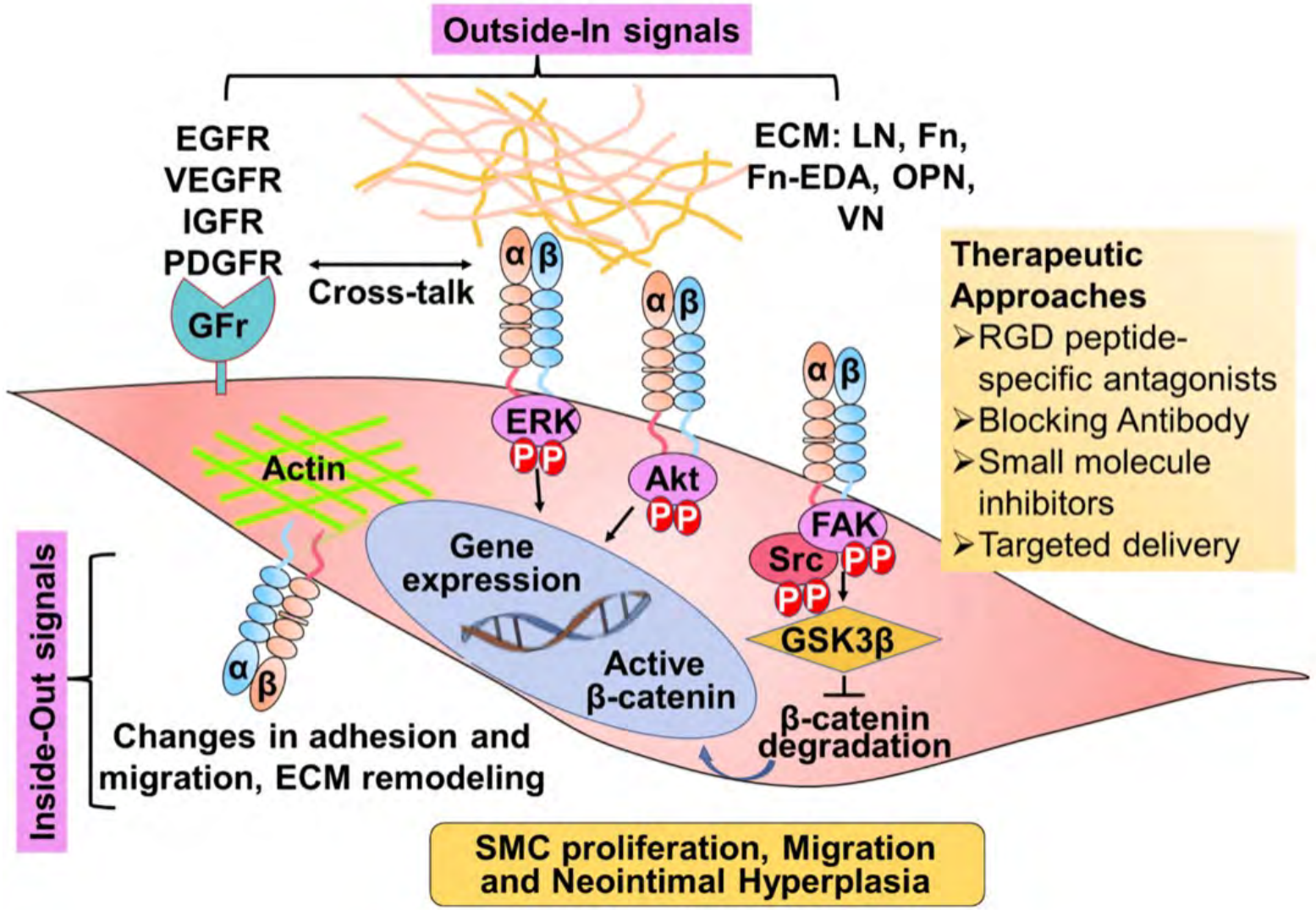
Cytokines	IL-1, IL-4, IL-6, IL-13, IL-17, IL-12, IL-23, IL-33, TNF-α, MCP-1, IFN-γ
Growth factors	TGF-β, CTGF, bFGF, IGF-I/II, IGFBP-5, PDGF, endothelin
Matrix proteins	MMPs, TIMPs, collagens (types I, III, and V), vitronectin, fibronectin, osteopontin, thrombospondin
Bacterial products	Muramyl dipeptide (NOD2 ligand), flagellin (TLR-5 ligand), PAMPs
Mediators	Endothelin, ROS, PPAR

bFGF, basic fibroblast growth factor; IFN-γ, interferon γ; MCP-1, monocyte chemoattractant protein 1; PAMPs, pathogen-associated molecular patterns; PPAR, peroxysome proliferator activated receptors; ROS, reactive oxygen species.

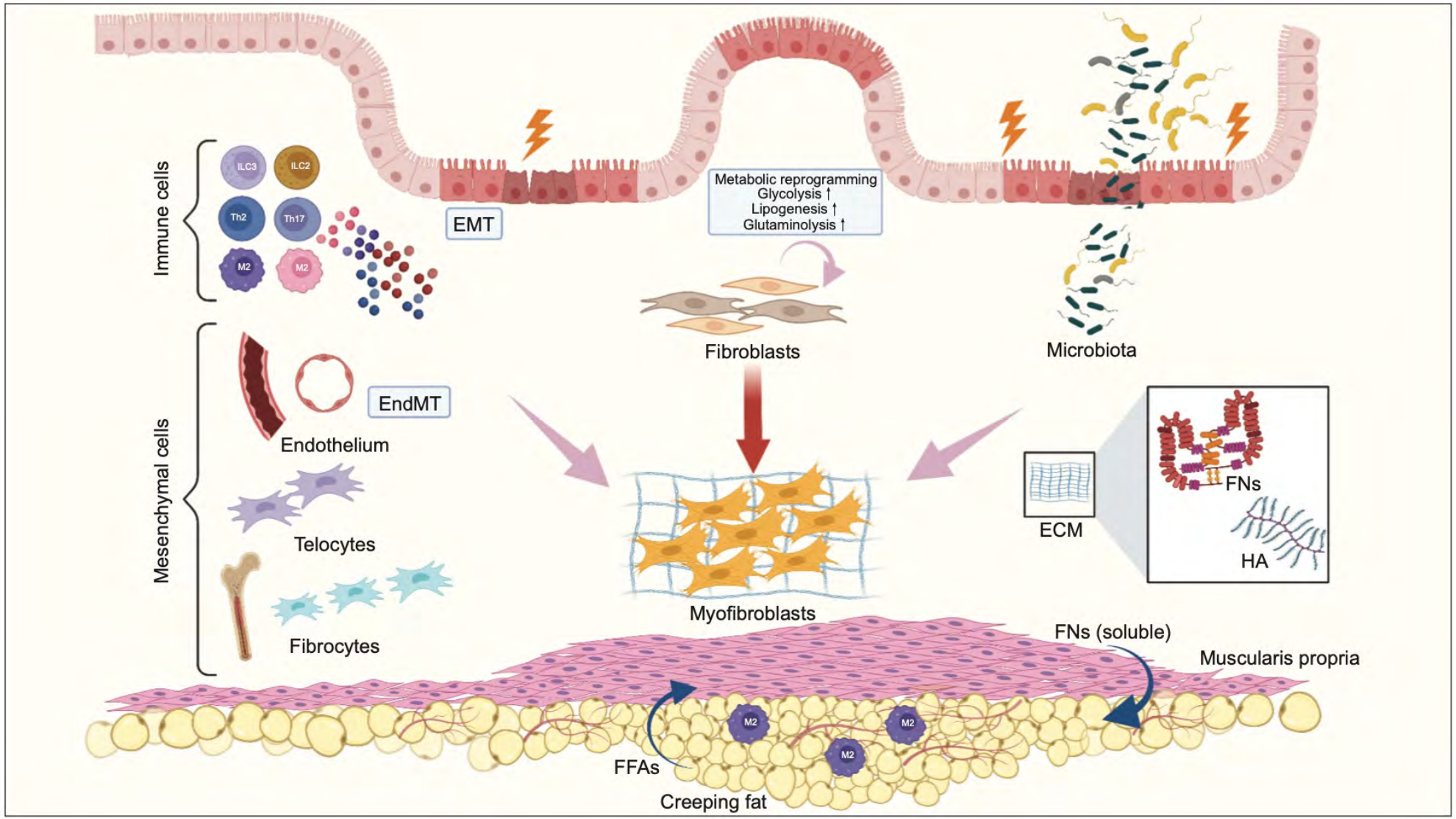
Li and Kuemmerle, 2014

Fibroblasts source	comparison	mRNA	Protein	Activity
Stenotic	Stenotic versus non-stenotic fibroblasts	↔ MMP-1, -16 and -17 [51]; ↓ MMP-3, -10, -11 and -24 [51]; ↑ MMP-2 and TIMP-2 [51]; ↑ TIMP-1 [60,84]	↓ MMP-12 [60,80]; ↔ MMP-3 [60,80]; ↑ TIMP-1 [60,84]; ↔ TIMP-1 [80]; ↔ TIMP-2 [84]	↓ MMP-12 [60] ↑ MMP-2 and -3 [51]

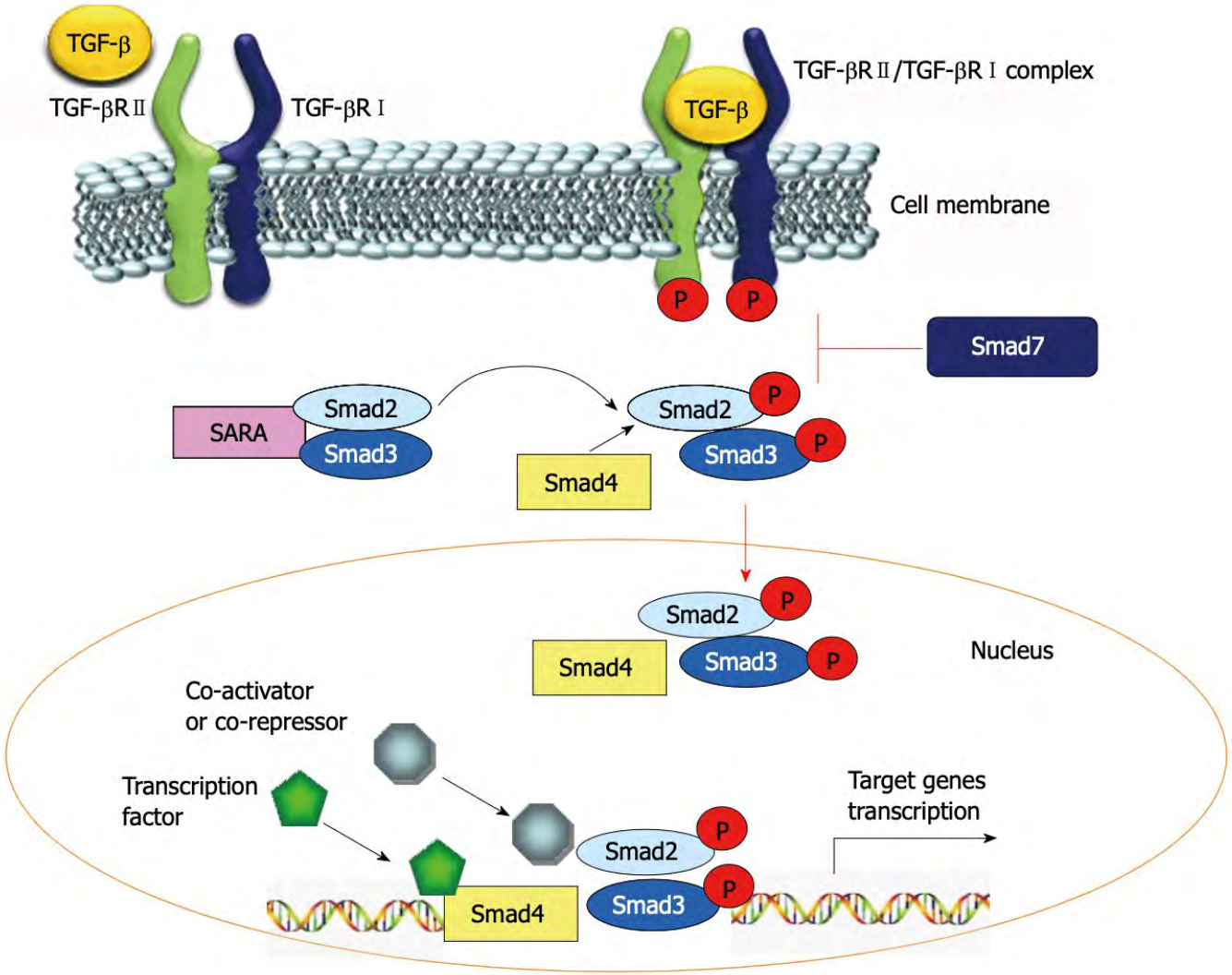
Biel et al., 2023



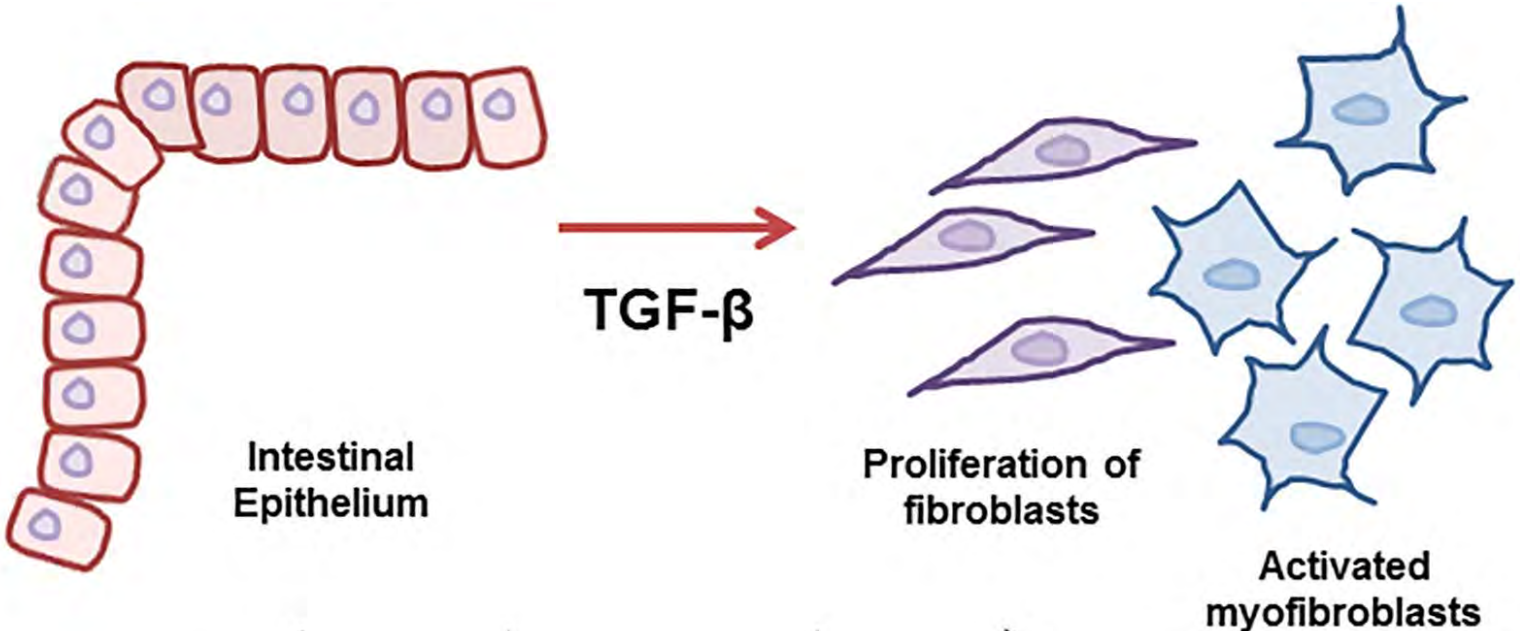
Jain & Chauhan, 2022


Immune cells
ILC3
ILC2
Th2
Th17
M2
M2
EMT
Metabolic reprogramming
Glycolysis ↑
Lipogenesis ↑
Glutaminolysis ↑
Fibroblasts
Microbiota
Mesenchymal cells
EndMT
Endothelium
Telocytes
Fibrocytes
Myofibroblasts
ECM
FNs
HA
FNs (soluble)
Muscularis propria
M2
M2
M2
FFAs
Creeping fat

Wu et al., 2023



Speca et al., 2012



TGF-β signaling pathway

- TGF-β
- Smad3
- Smad7

EMT and EndMT

- EMT-related genes (SLUG and FAP)
- EndMT-related genes (Collagen I alpha 2)

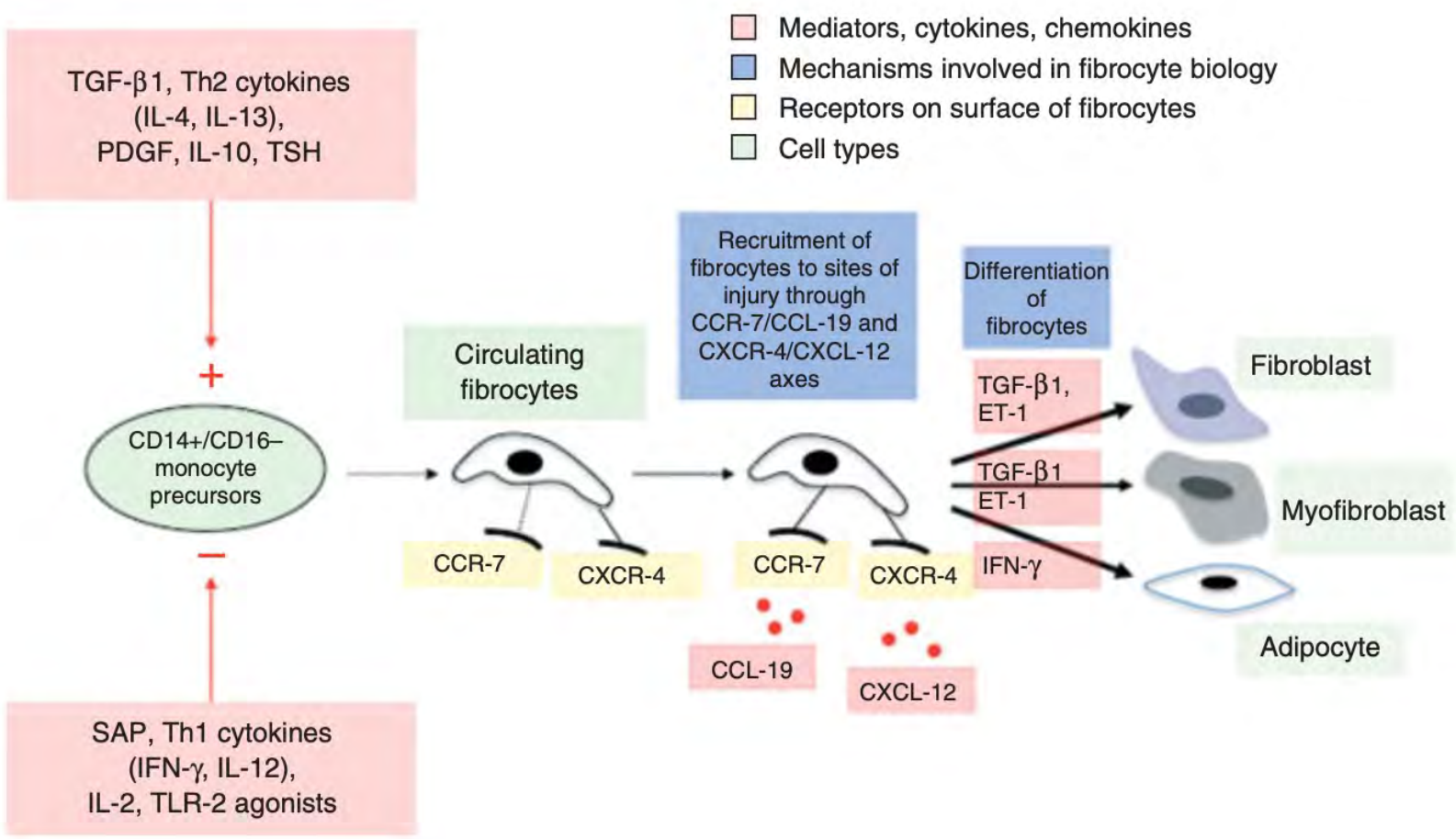
ECM

- Myofibroblasts
- Smooth muscle cells
- Collagen
- Matrix metalloproteinases

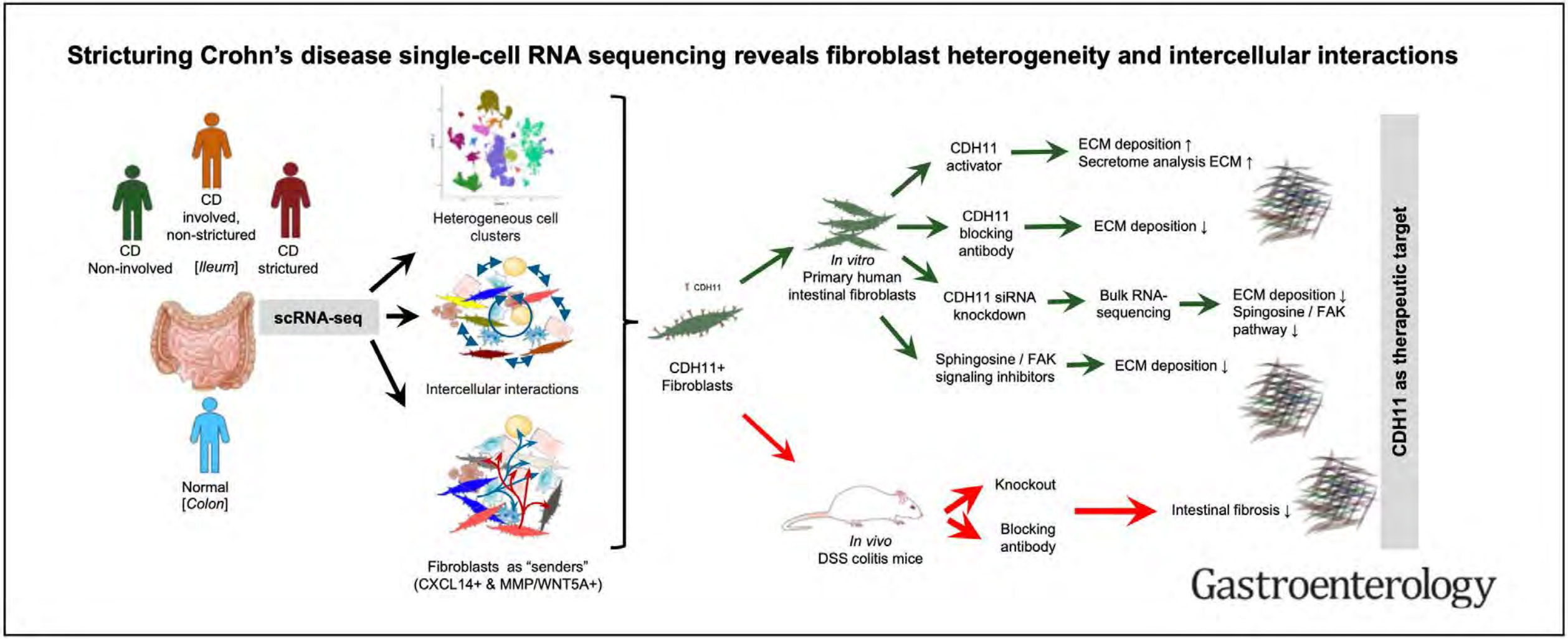
Miscellaneous

- PDGF
- TSP1
- PPAR-γ
- IL-17 and IL-13
- IL-1β and IFN-γ

Yun et al., 2019

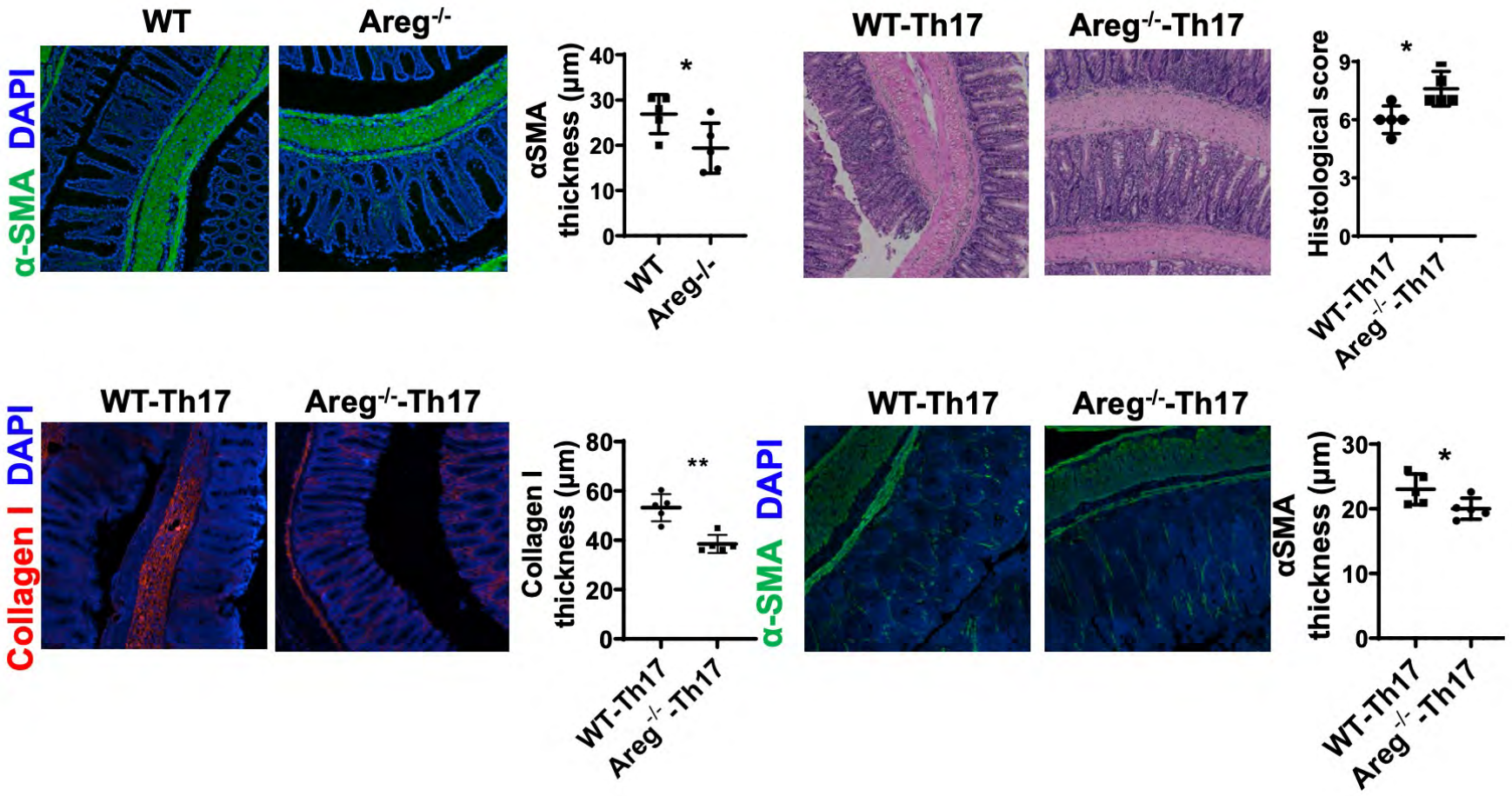


Sahebally et al., 2013



Mukherjee et al., 2023

Th17-derived amphiregulin drives fibrosis



Zhao et al., 2023