骨盆底鬆弛婦女肌纖維細胞及細胞外基質調控之研究

Regulation of Myofibroblasts and Extracellular Matrix Remodeling Associated with Pelvic Organ Prolapse

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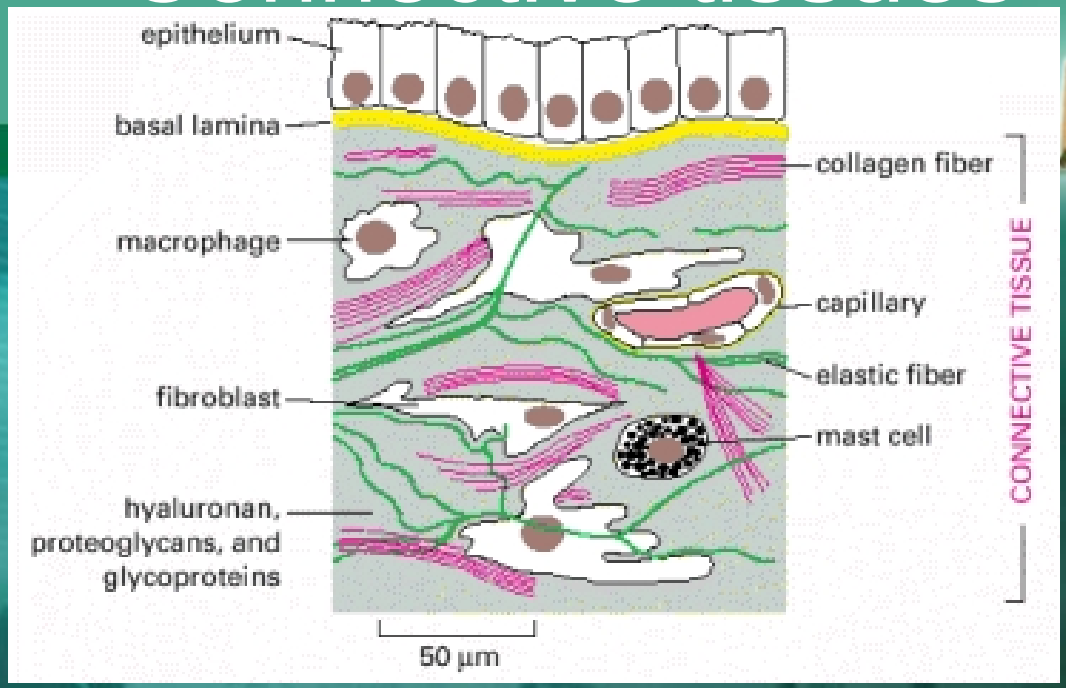
Introduction :

Compassion、Accountability、Effectiveness

- Pelvic organ prolapse (POP) results from a defect of the pelvic supportive tissues and the changes in the extracellular matrix (ECM) status.
- Accelerated remodeling in patients with POP is caused by biochemical changes of
  - stromal cells, e.g. fibroblasts, and
  - ECM components, e.g., collagen, elastin etc.



Connective tissues



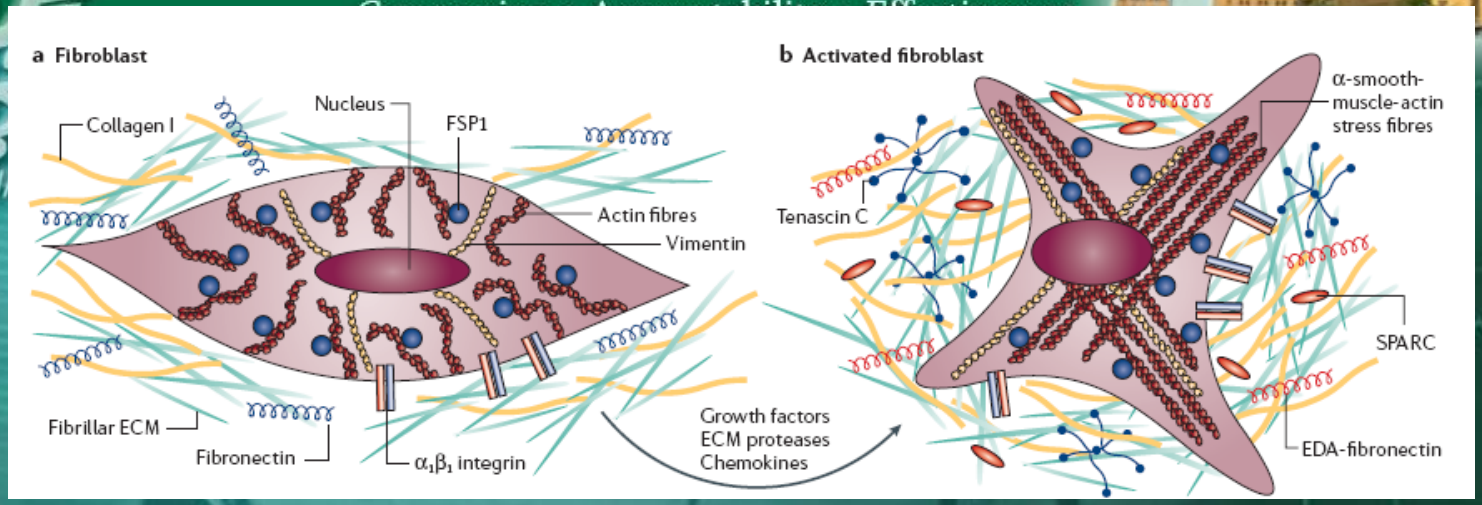
- Tissues that form the architectural framework
  - Extracellular matrix (ECM): plentiful
  - Stroma cells, e.g. fibroblasts, sparsely distributed within it
- Extracellular matrix (ECM):
  - A complex, three-dimensional network of very large macomolecules that provides contextual information and an architectural scaffold for cellular adhesion and migration

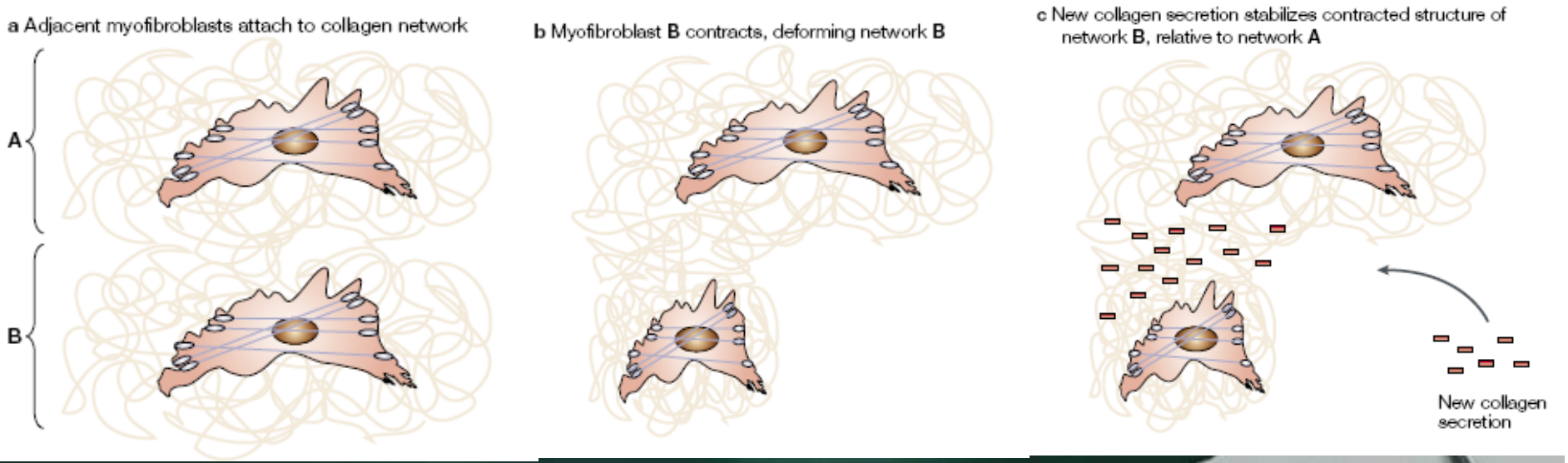
Kalluri R & Zeisberg M, 2006 Nat Reviews Cancer Tomasek J 2002 Nat Rev Mol Cell Biol

Extracellular matrix (ECM) and POP

- Extracellular matrix (ECM) is a major component in the pelvic supportive system
  - Collagen is the main constituent
    - Type I: mature; Type III: loose connective tissue
- Collagen components can affect POP tissue strength
  - increase in collagen III
    - Full-thickness vagina at vaginal apex (Moalli PA 2005 Obstet Gynecol)
  - the decrease of collagen I/ III ratio
    - Utero-sacral ligament, IHC (Gabriel B: 2005 Int Urogynecol J)

CT remodelling and myofibroblasts is essential for wound healing



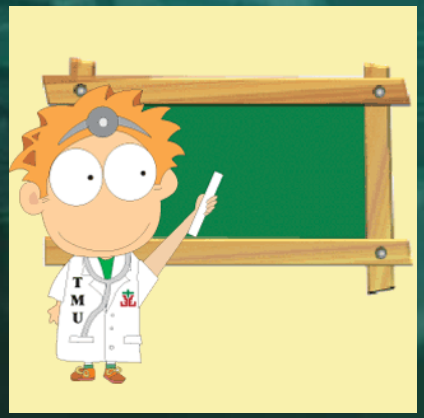


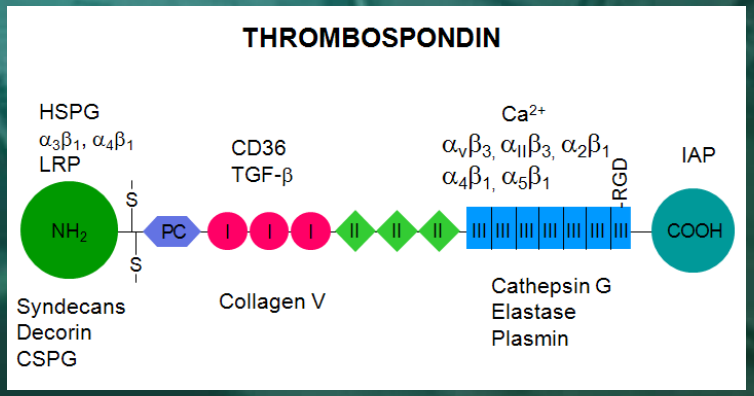
Tomasek J 2002 Nat Rev Mol Cell Biol

Hypothesis

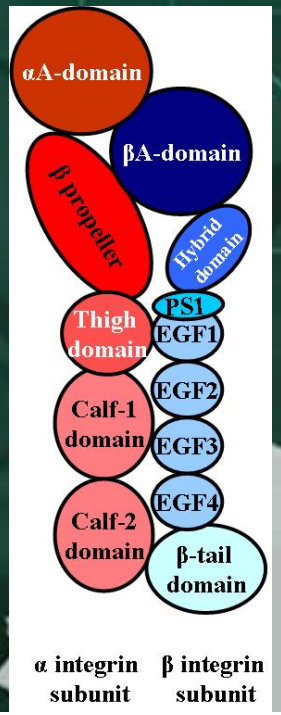
Compassion · Accountability · Effectiveness

- We hypothesized that accelerated remodeling in patients with POP is caused by biochemical changes of ECM proteins, myofibroblasts, and their matricellular regulators
  - Transforming growth factor (TGF), thrombospondin (TSP)





TGF



Materials & methods:

- Frozen tissues of utero-sacral ligaments and anterior vaginal wall from POP (study group) and non-POP women (control group) after IRB approval and informed consents.
- Western blots
- ELISA, zymography.
- Boyden chamber migration assay

LAVH POP

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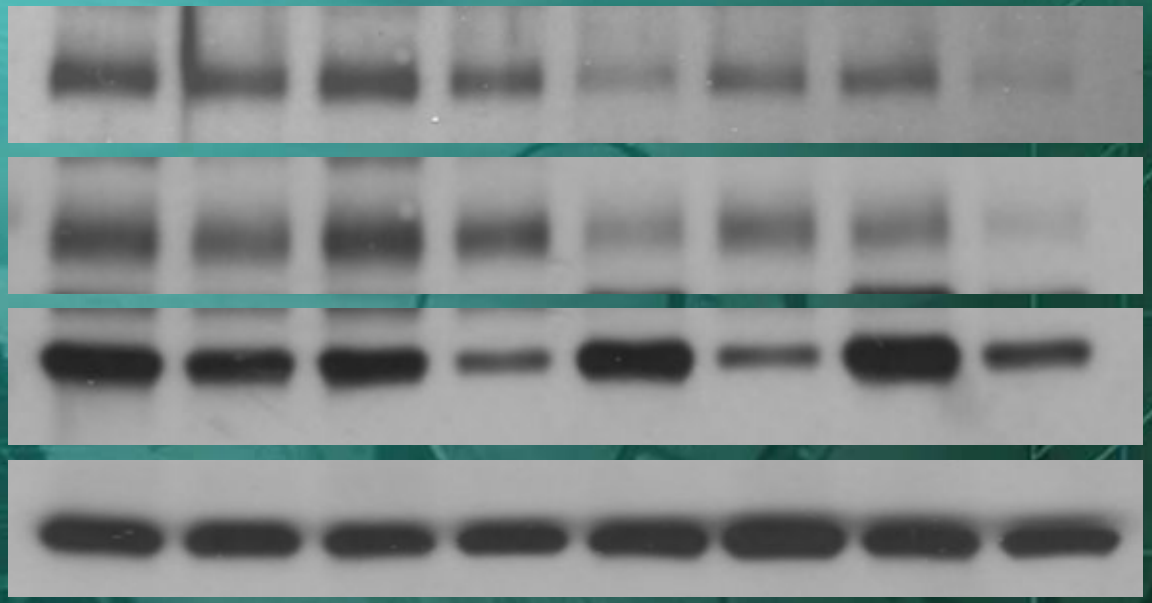
C V C V C V C V



C: cardinal ligament; V: anterior vaginal wall
LAVH: 6/30 cases; mean 45.2 y/o (range 37- 49 y/o)
POP: 6/30 cases; mean 67.3 (range 51-77 y/o)

ECM protein, α-SMA in POP

TAIWAN	Col III	Desmin	α-SMA	
LAVH-C	100	100	100	
LAVH-V	87	72	56	
POP-C	40	45	106	
POP-V	47	46	40	
C/ V ratio				
	Col III	Desmin	α-SMA	
LAVH-C/V	1.15	1.40	1.77	
POP-C/V	0.86	0.99	2.64	

Results

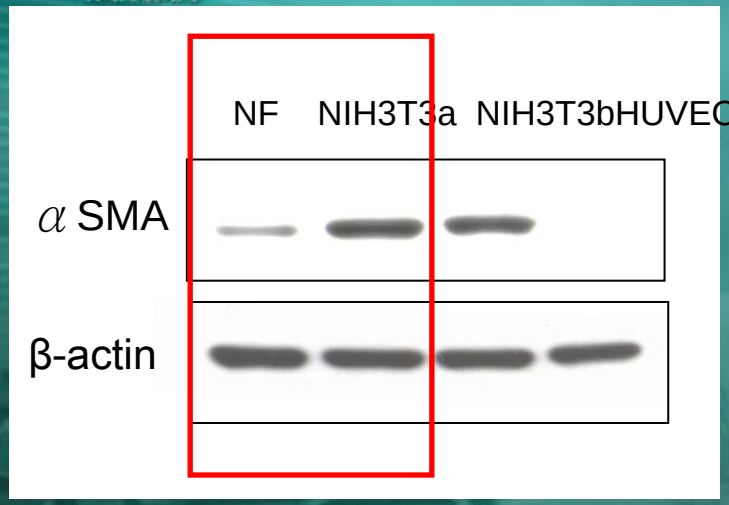
Compassion、Accountability、Effectiveness

- POP women have a disturbed collagen subtype III, desmin amount, as compared with non-POP women.

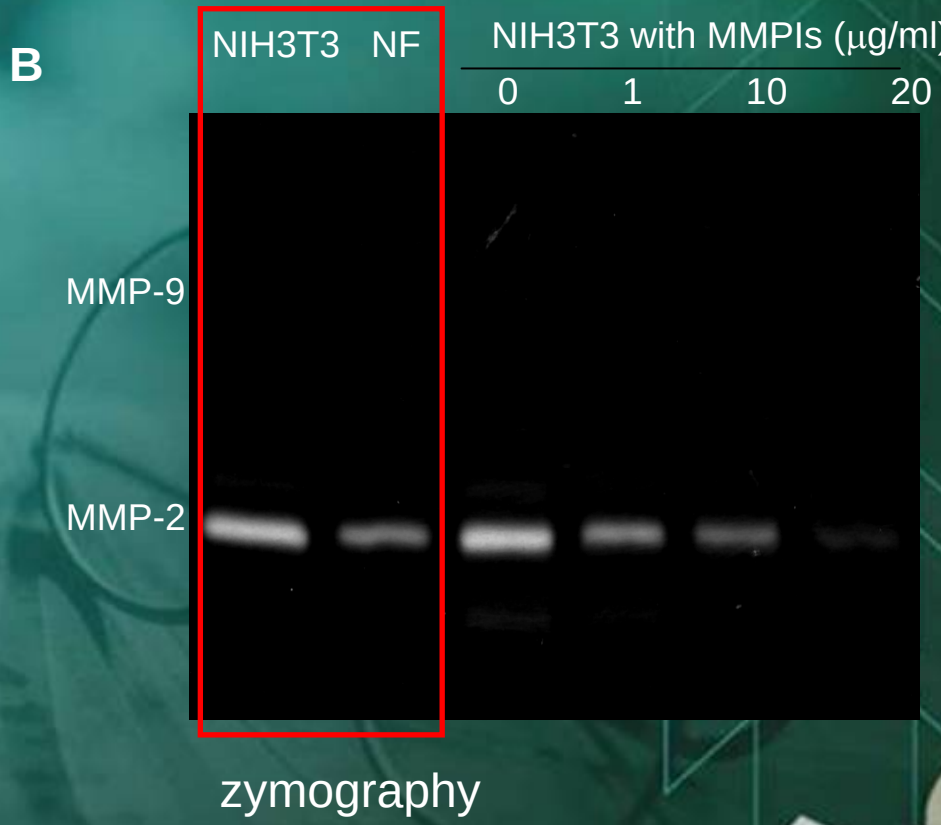
- Myofibroblasts amount cardinal-vaginal (C/V ratio) was higher in POP women by measuring α-smooth muscle actin (SMA) , as compared with non-POP women.

Characterization of myofibroblast

Compassion、Accountability、Effectiveness



Western blot



zymography

NIH3T3: immortalized mouse fibroblasts with α-SMA- expressing from ATCC

NF: normal fibroblasts

The recruitment of stroma cells in different meshes

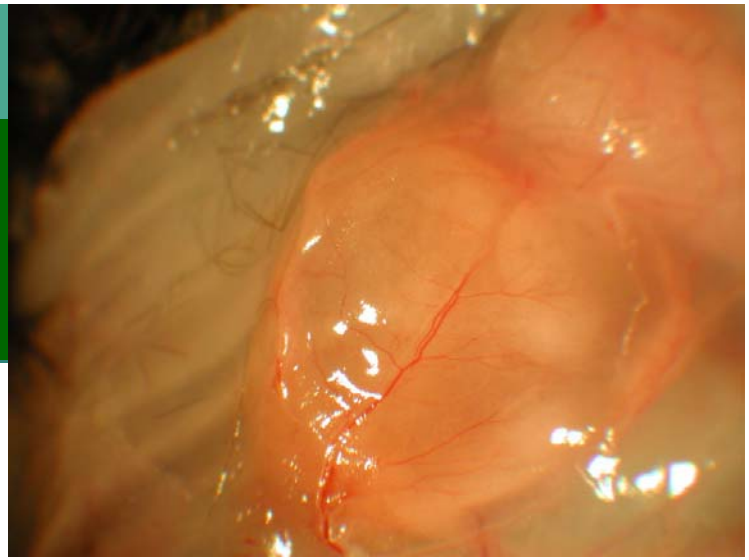
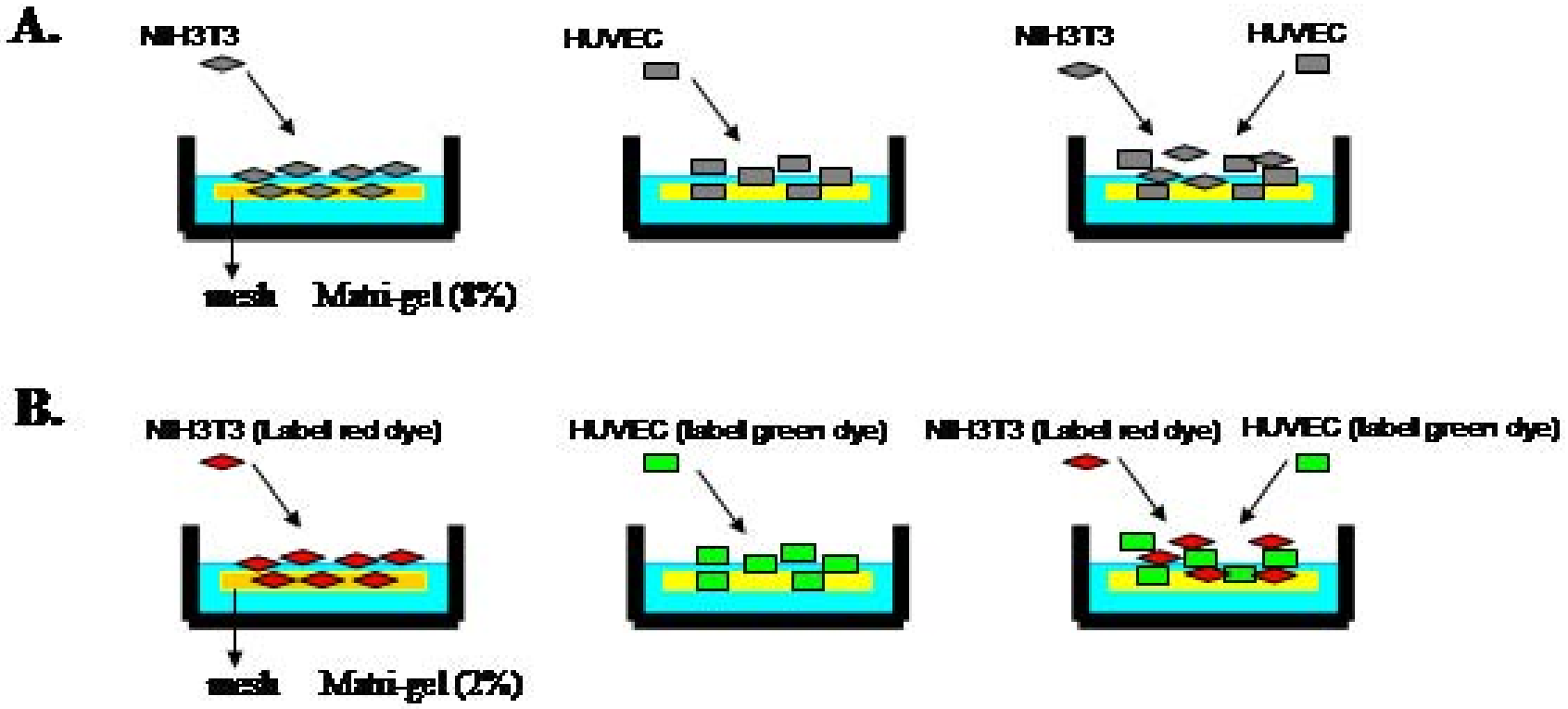
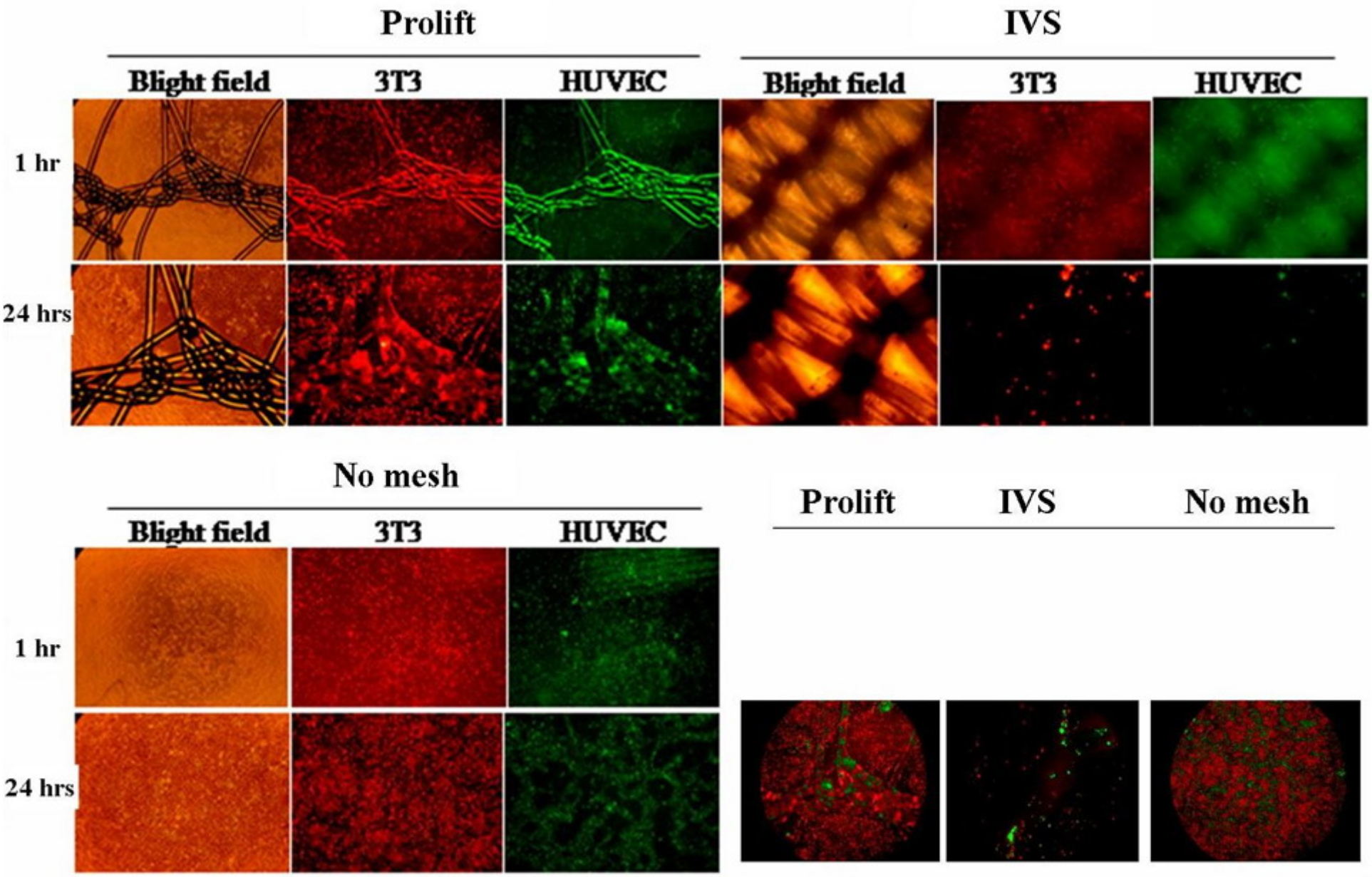


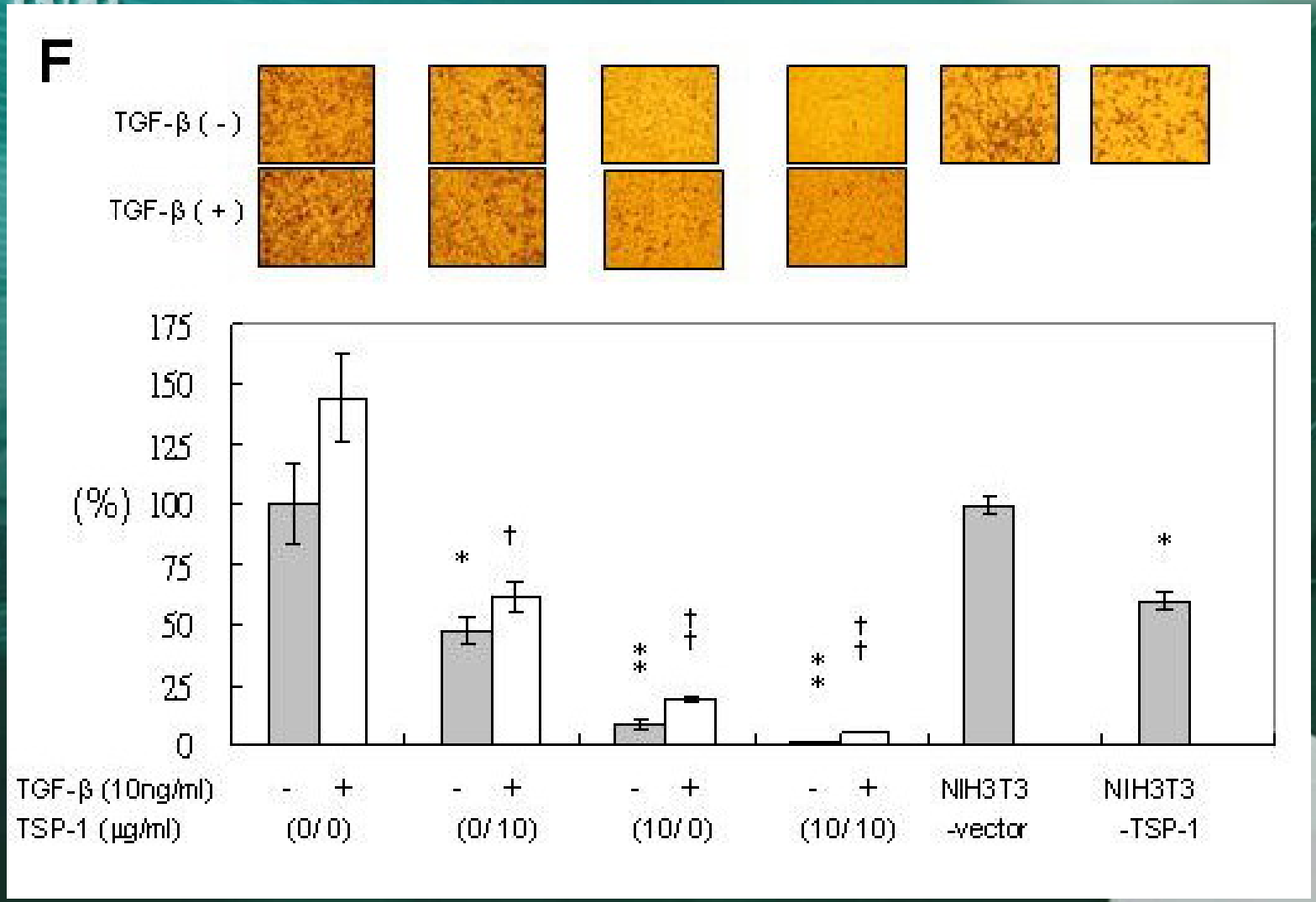
Fig.2. Model





Wu MP 2010 JECM

The effect of matricellular regulators TGF TSP-1 on myofibroblasts migration

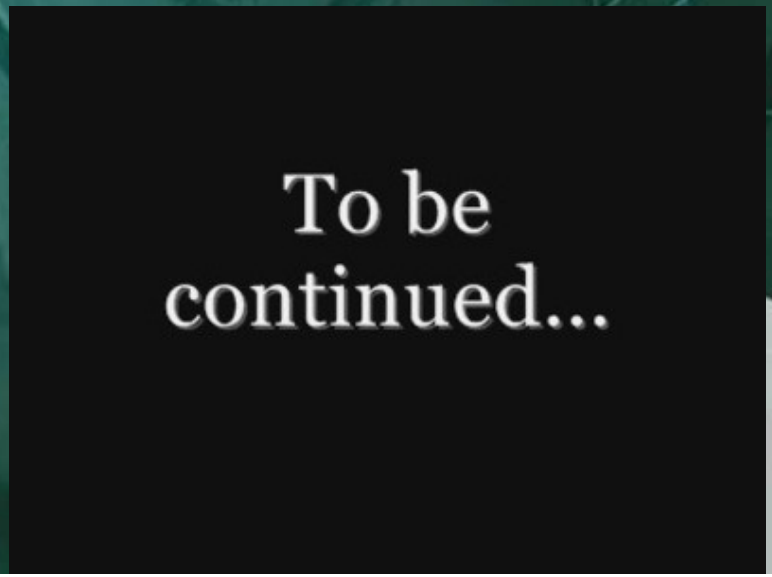


Wu MP 2008 Carcinogenesis

Results

Compassion、Accountability、Effectiveness

- The effects of matricellular regulators, including transformation growth factor (TGF)- β , and thrombosopondin (TSP)-1 may potentially affect the myofibroblasts responses to different protheses via affecting migration.



Conclusion:

Compassion、Accountability、Effectiveness

- Disturbances in the balance between synthesis/assembly and degradation of ECM proteins were associated with POP.
- The homeostasis of myofibroblasts and matricellular regulators, TGF-β TSP-1 were associated with ECM integrity.

奇美醫院門診區整修完工音樂會

2009.12. 15醫樂室內樂團及眷屬舞群