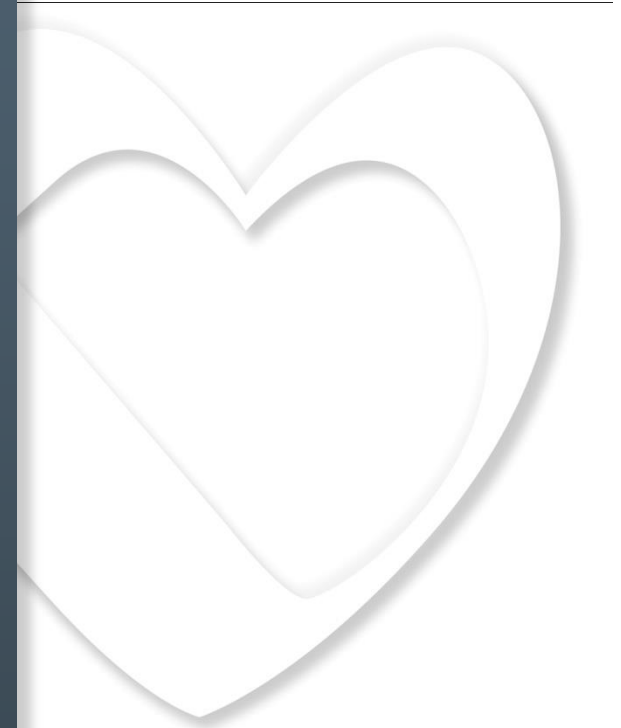


# Extracellular matrix

## Basic and translational science: Highlights of the congress

Stephane Heymans,  
Maastricht University Medical Centre,  
CARIM, Netherlands



HEART FAILURE  
ASSOCIATION  
OF THE ESC



EUROPEAN  
SOCIETY OF  
CARDIOLOGY®

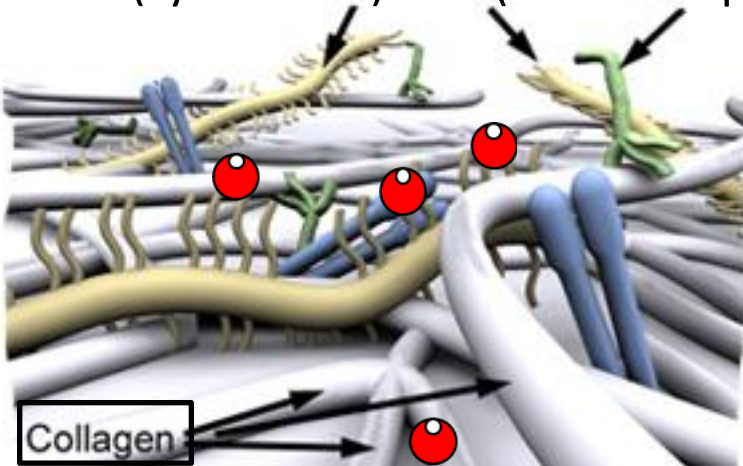
# DECLARATION OF INTEREST

- I have nothing to declare

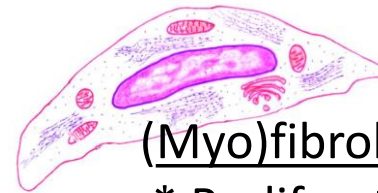
# The extracellular matrix modulates cardiac cellular behaviour

Proteoglycans  
(syndecans)

Glycoproteins  
(thrombospondins)

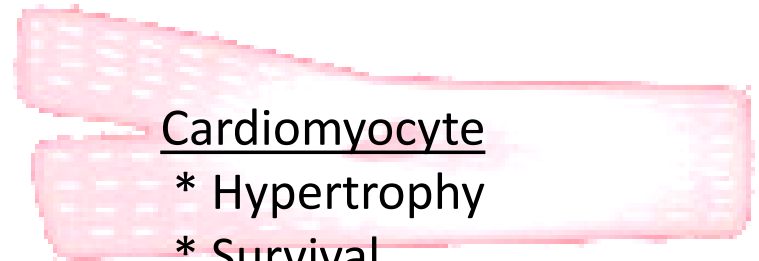


 Exosomes/vesicles (microRNAs)



(Myo)fibroblast

- \* Proliferation
- \* Collagen production and cross-linking

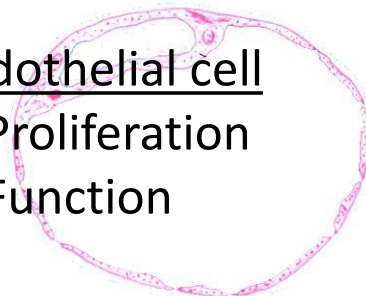


Cardiomyocyte

- \* Hypertrophy
- \* Survival

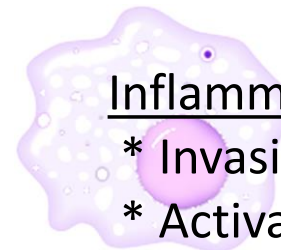
Endothelial cell

- \* Proliferation
- \* Function

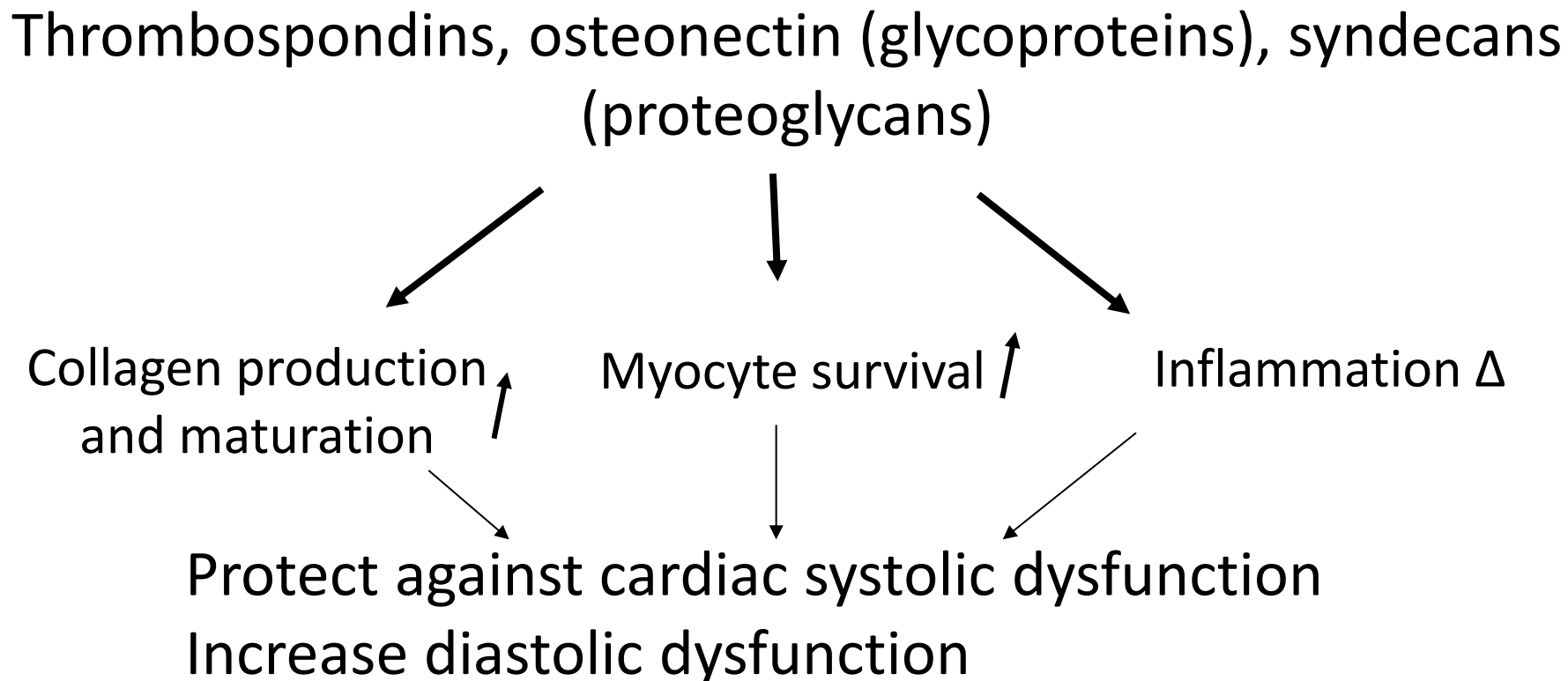


Inflammatory cell

- \* Invasion
- \* Activation



# Proteoglycans and glycoproteins protect against heart failure



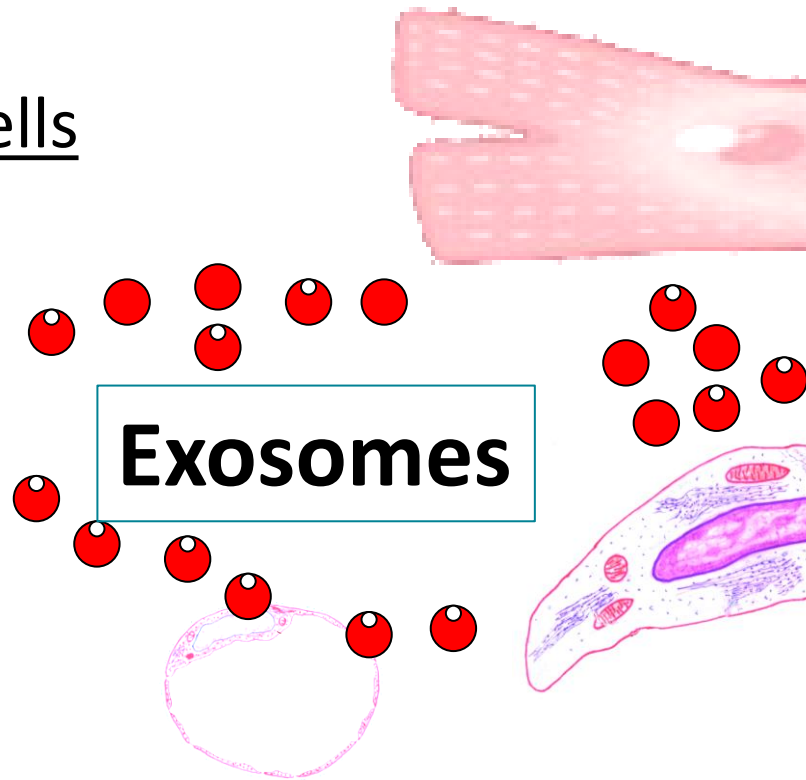
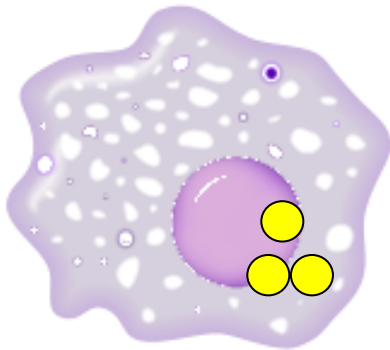
•Lynch JM, CellPapageorgiou A. CVR, 2012; Almen et al., JMCC, 2011; Schellings et al., J.Exp.Med, 2009; Swinnen et al., Circ, 2009;

•Herum KM, J Mol Cell Cardiol. 2013 Jan;54:73-81; Finsen AV, PLoS One. 2011;6(12):e28302;

•Vanhoutte D. Circulation. 2007 Jan 30;115(4):475-82; Schellings M, Hypertension. 2010 Feb;55(2):249-56

# MicroRNAs in matrix-exosomes alters cardiac fibrosis and hypertrophy

Inflammatory cells



Cardiomyocyte

- \* Hypertrophy
- \* Death/apoptosis

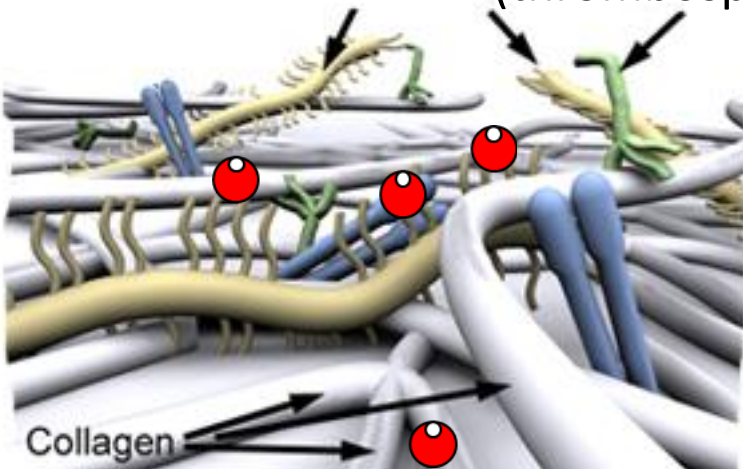
Fibroblast

- \* Proliferation
- \* Fibrosis

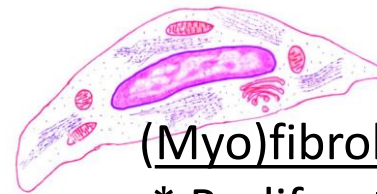
# Extracellular matrix modulates cardiac cellular behaviour

Proteoglycans  
(syndecans)

Glycoproteins  
(thrombospondins)

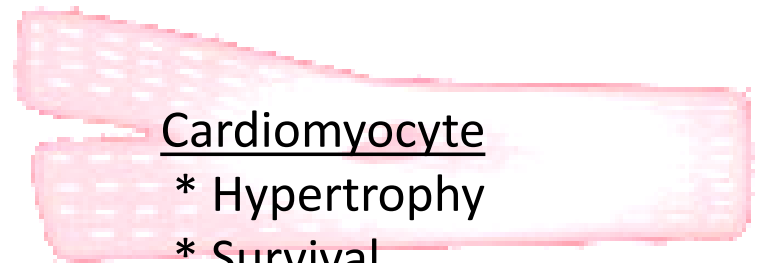


 Exosomes/vesicles (microRNAs)



(Myo)fibroblast

- \* Proliferation
- \* Collagen production and cross-linking

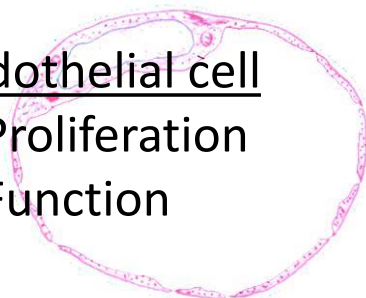


Cardiomyocyte

- \* Hypertrophy
- \* Survival

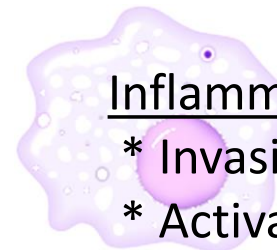
Endothelial cell

- \* Proliferation
- \* Function



Inflammatory cell

- \* Invasion
- \* Activation



# Syndecan-1 and 4 increase collagen production and myocyte hypertrophy

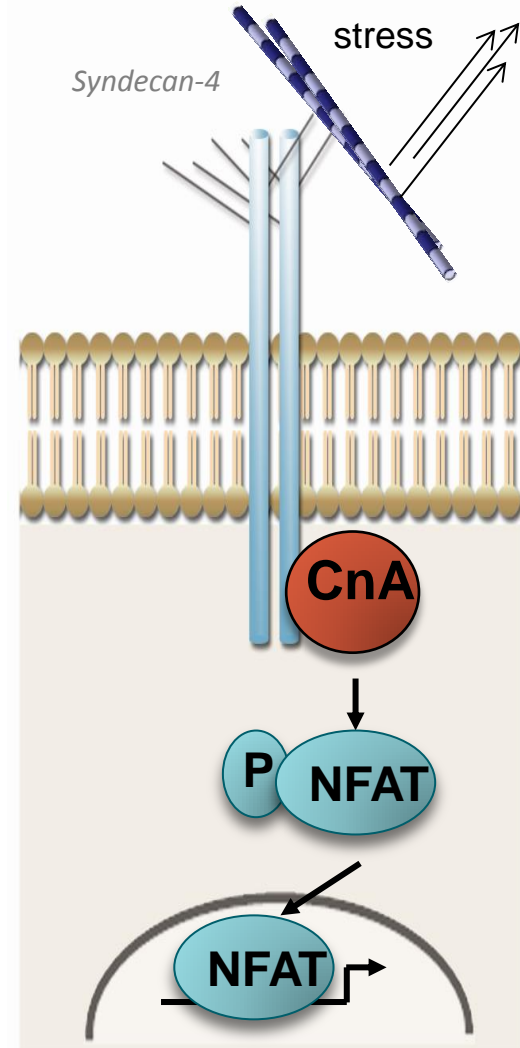
## Syndecan-1 and 4 are cardiac stress sensors

- Syndecan-1 → TGFbeta pathway → fibrosis
  - Syndecan-4 → calcineurin-NFAT pathway → fibrosis/hypertrophy
- **Increases interstitial fibrosis**
    - Increased collagen production & cross-linking
    - ➔ Myocardial stiffness<sup>↑</sup>
  - **Stimulates myocyte hypertrophy**
  - **Decreases cardiac inflammation**

- Strand ME, FEBS J. 2013 May;280(10):2228-47; Herum KM, J Mol Cell Cardiol. 2013 Jan;54:73-81; Finsen AV, PLoS One. 2011;6(12):e28302;
- Vanhoutte D. Circulation. 2007 Jan 30;115(4):475-82; Schellings M, Hypertension. 2010 Feb;55(2):249-56

[www.escardio.org/HFA](http://www.escardio.org/HFA)

*Geir Christensen, Vanhoutte and Kate Herum*



# Syndecan-4 affects myocardial stiffness in the pressure-overloaded heart

## Syndecan-4 KO mice & pressure-overload

- No titin changes
- Reduced total collagen
- Improved diastolic function

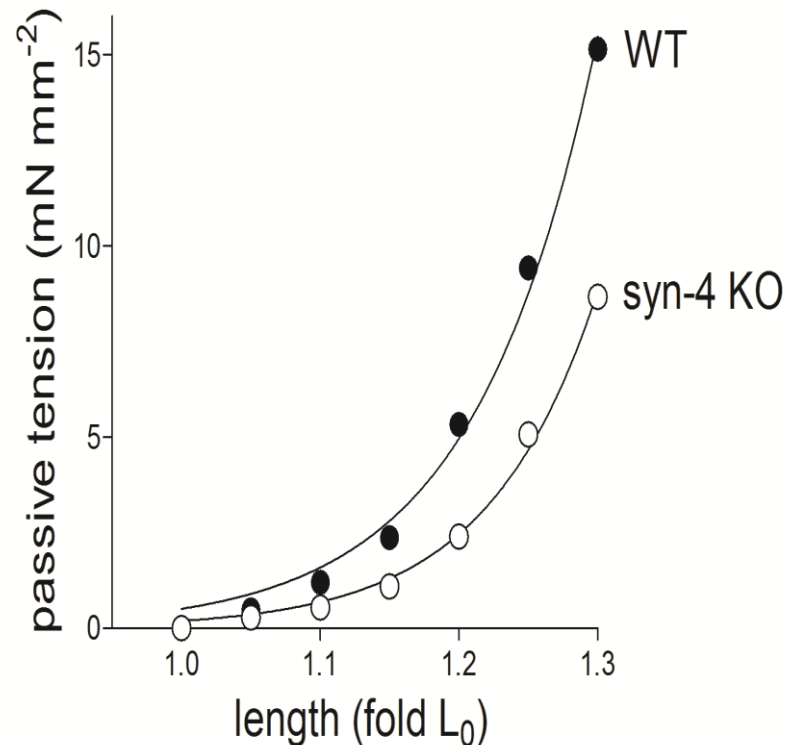
## Syndecan-1 KO mice & pressure-overload

- Reduced total collagen
- Improved diastolic function

>< **After MI: increased infarct rupture and dilatation**

## INCREASED SYND1 and SYND4:

- ✓ **DIASTOLIC DYSFUNCTION** ↑
- ✓ **POST-INFARCT FAILURE** ↓



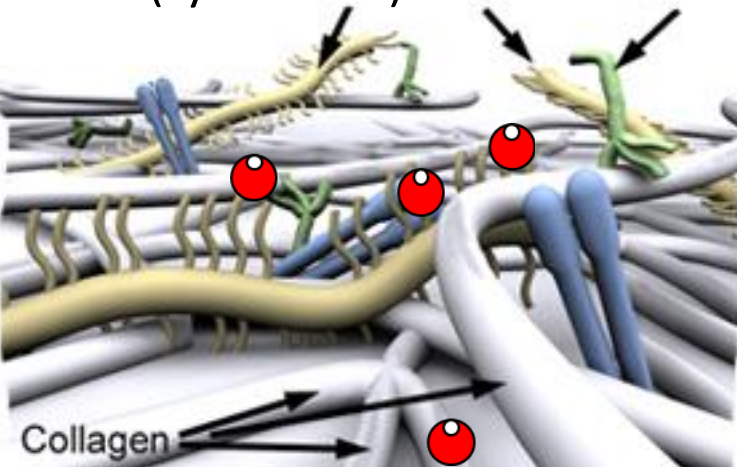
- Herum KM, J Mol Cell Cardiol. 2013 Jan;54:73-81; Finsen AV, PLoS One. 2011;6(12):e28302;
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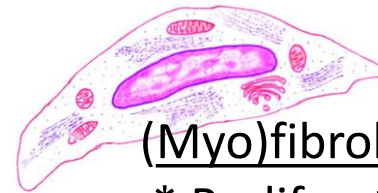
# The extracellular matrix modulates cardiac cellular behaviour

Proteoglycans  
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(thrombospondins)



 Exosomes/vesicles (microRNAs)



(Myo)fibroblast

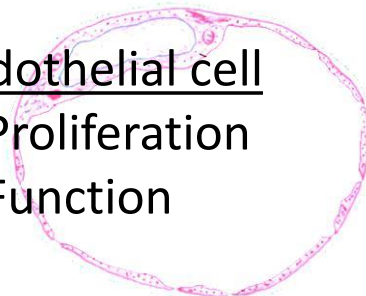
- \* Proliferation
- \* Collagen production and cross-linking

Cardiomyocyte

- \* Hypertrophy
- \* Survival

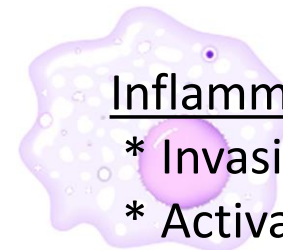
Endothelial cell

- \* Proliferation
- \* Function



Inflammatory cell

- \* Invasion
- \* Activation



# Thrombospondins stimulate myocyte survival and affects cardiac fibrosis

## Thrombospondin-1, -2 and 4 are cardiac stress responders

- TSP-1 → TGFbeta
- TSP-2 → MMPs; CD47; NOS (matrix)
- TSP-4 → endoplasmic reticulum protective response (cardiomyocyte)

### ➤ Thrombospondin-2

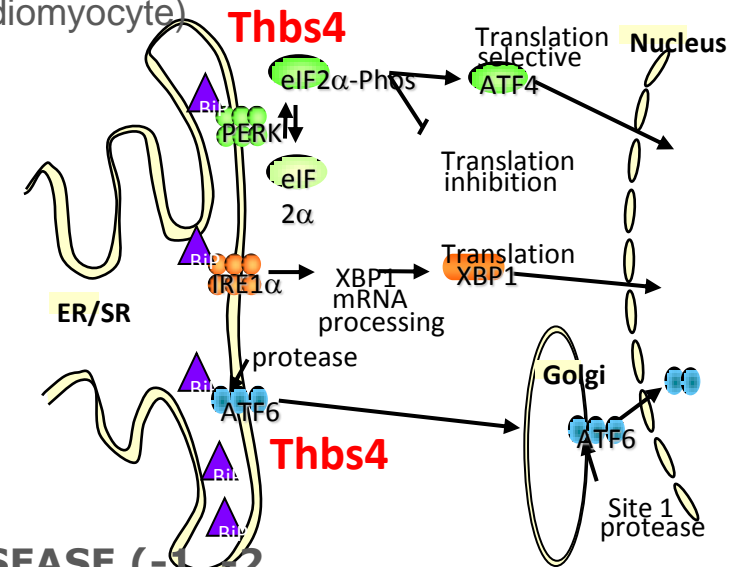
- Collagen maturation improved
- Inflammation reduced
- Cardiomyocyte survival

### ➤ Thrombospondin-4

- Cardiomyocyte survival ← protective ER response
- Prevents adverse cardiomyocyte hypertrophy

### ➔ Increased TSP-1, -2 and -4:

- **PROTECTIVE AGAINST HYPERTENSIVE HEART DISEASE (-1, 2 and -4)**
- **PREVENTS INFARCT RUPTURE AND DILATATION (-1 and -2)**

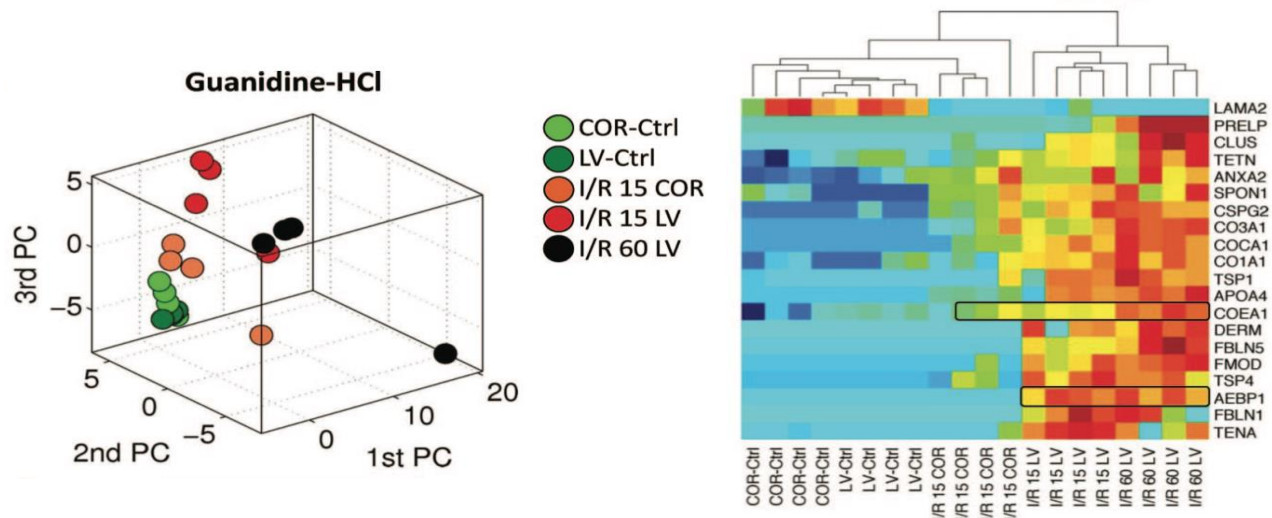


- Lynch JM, Cell. 2012; 149(6):1257-68; Frolova EJ, FASEB J. 2012 Jun;26(6):2363-73.
- Cingolani, Circ Res. 2011 Dec 9;109(12):1410; Frolova EG, FASEB J. 2012 Jun;26(6):2363
- Papageorgiou A. CVR, 2012; Almen et al., JMCC, 2011; Swinnen et al., Circ, 2009
- Xia J, Hypertension 2011 Nov;58(5):902-11

# Proteomics for discovery

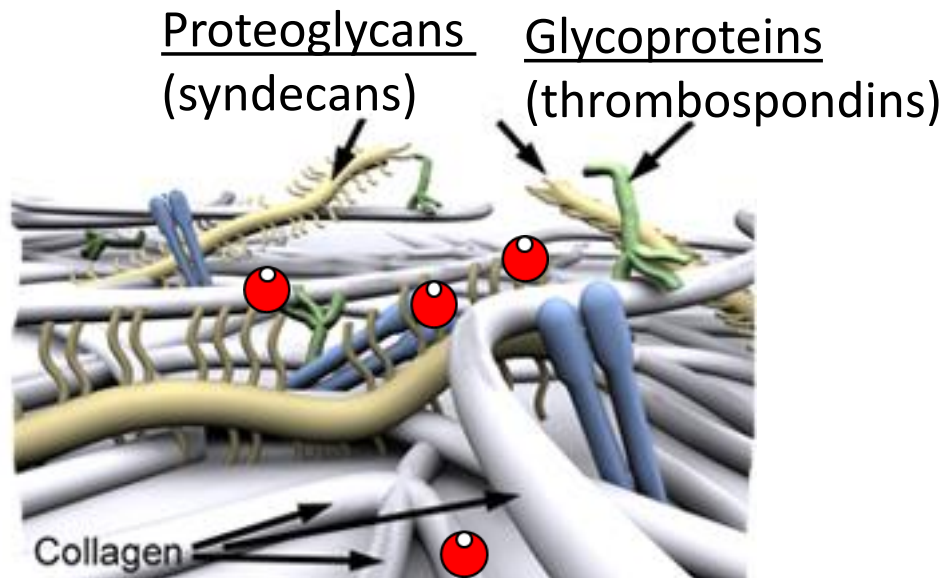
# Extracellular Matrix Remodelling

- **Proteomics as an integrated read-out of pathophysiology**
- **Protein analysis without the constraints of antibodies**
  - Improvement over previous studies that simply evaluated the total concentration of single proteins (i.e., collagen)
  - Often without consideration of type (e.g., type I vs III vs IV) or quality (full-length collagen vs partially degraded)
- Porcine model of ischemia/reperfusion injury and validated in human
- Liquid chromatography tandem mass spectrometry



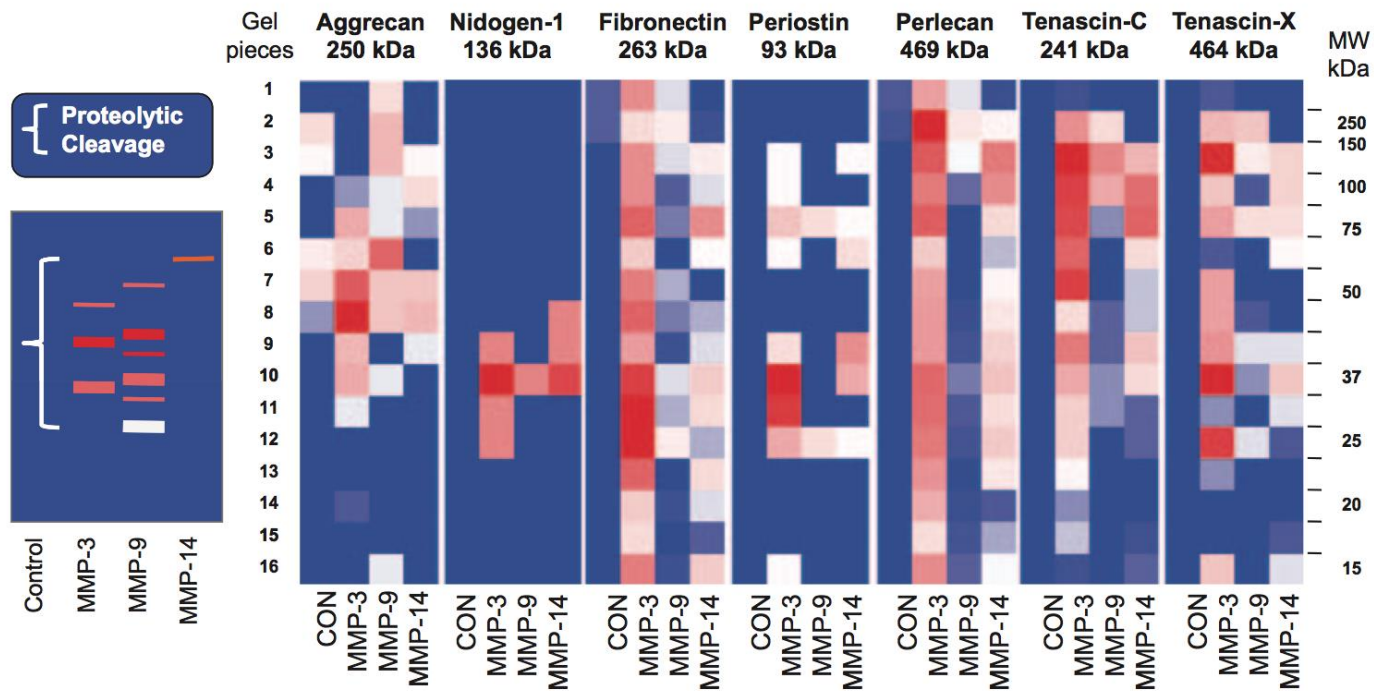
# New matrix targets discovered

- **Cartilage intermediate layer protein 1,**
- **Matrilin-4,**
- **Extracellular adipocyte enhancer binding protein 1,**
- **Asporin**
- **Prolargin**



# Extracellular Matrix Degradation: “degradome”

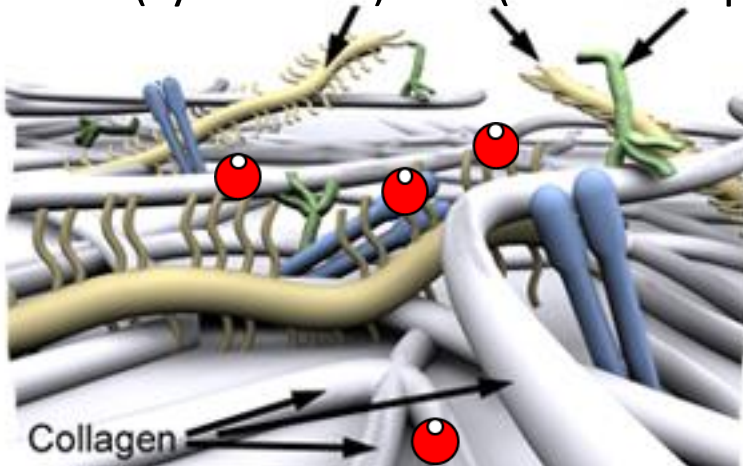
- Proteomics enhances “degradome” resolution
- Discovery pipeline for biomarkers and imaging targets
  - Identify isoform-specific cleavage sites of matrix metalloproteinases
  - Cleavage peptides may harbor as-yet undiscovered bioactive properties



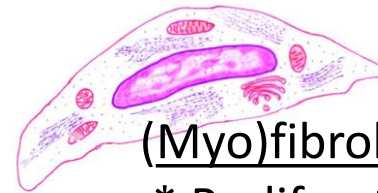
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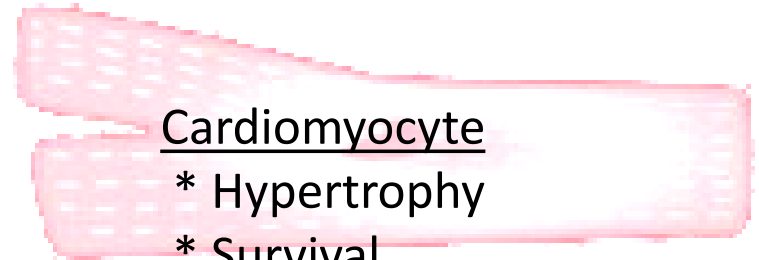


 Exosomes/vesicles (microRNAs)



(Myo)fibroblast

- \* Proliferation
- \* Collagen production and cross-linking

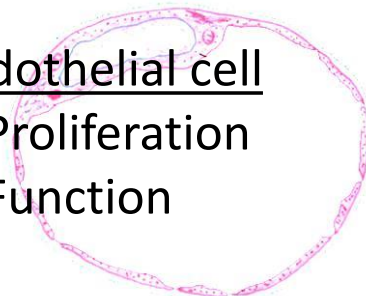


Cardiomyocyte

- \* Hypertrophy
- \* Survival

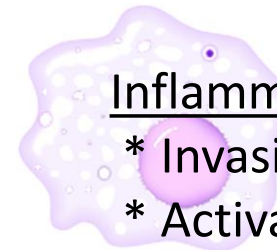
Endothelial cell

- \* Proliferation
- \* Function

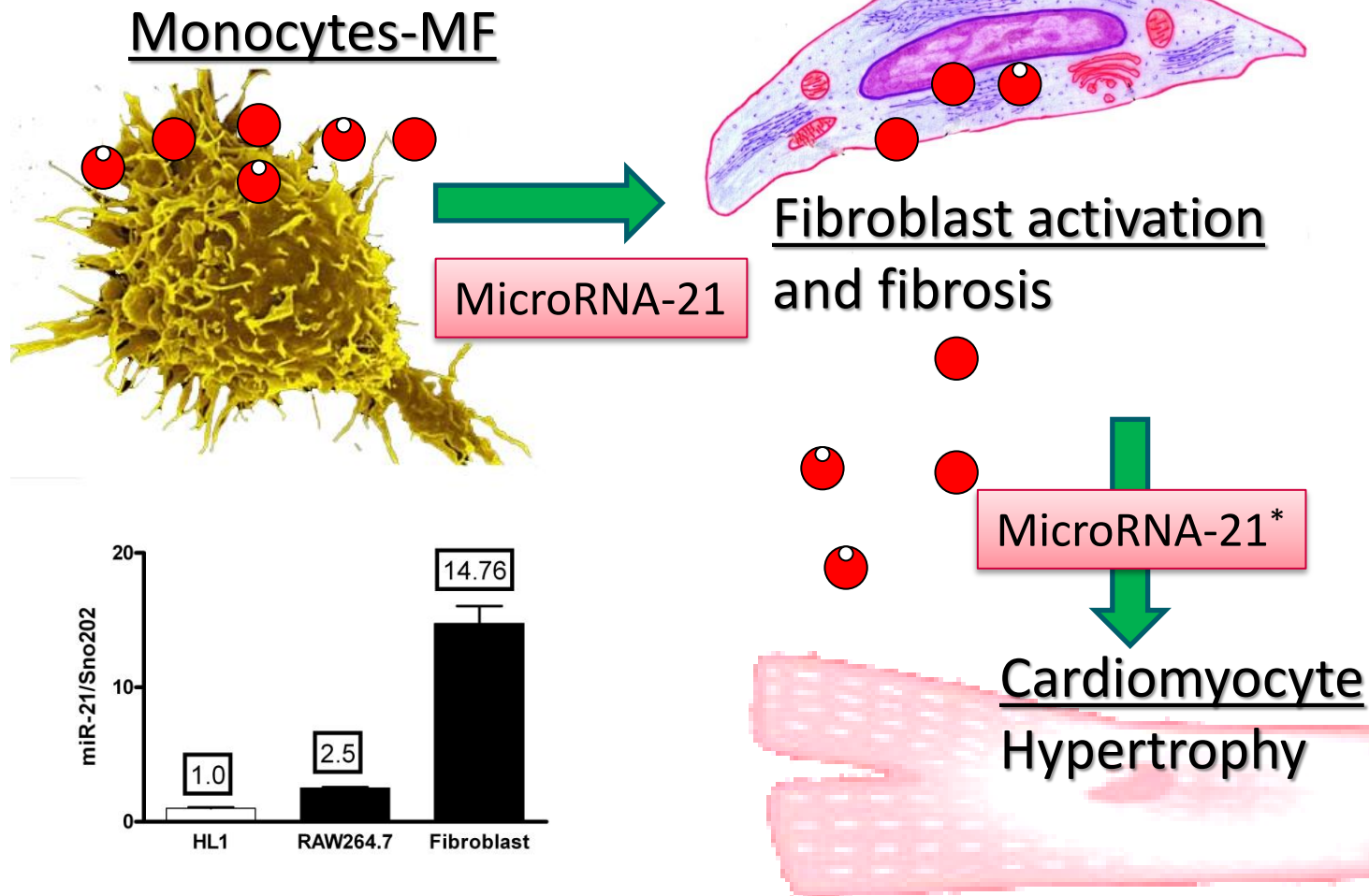


Inflammatory cell

- \* Invasion
- \* Activation



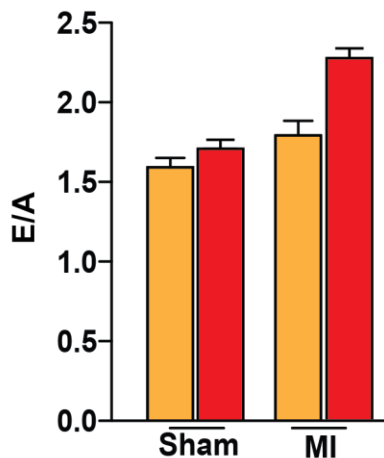
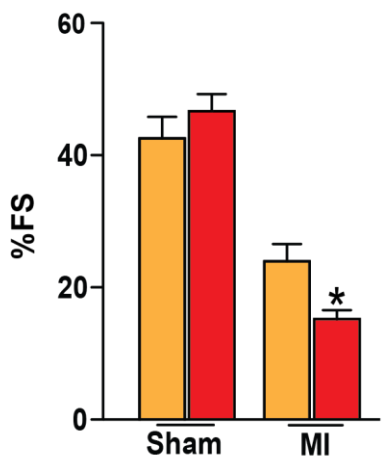
# Exosome-derived microRNA-21 increased cardiomyocyte hypertrophy and fibrosis



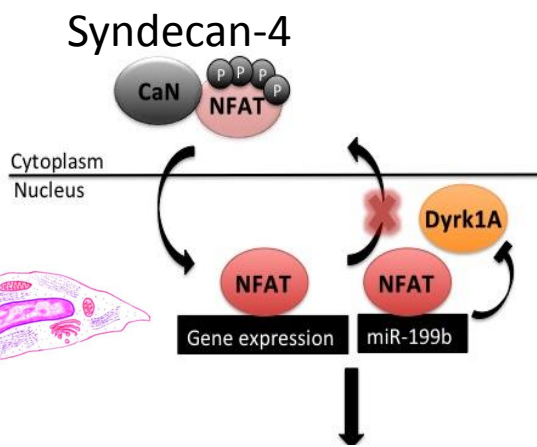


# MHC-miR-199b → NFAT :

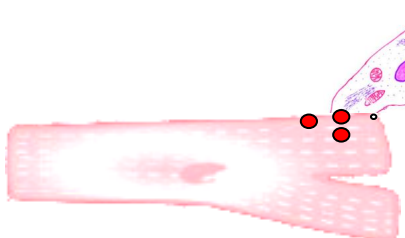
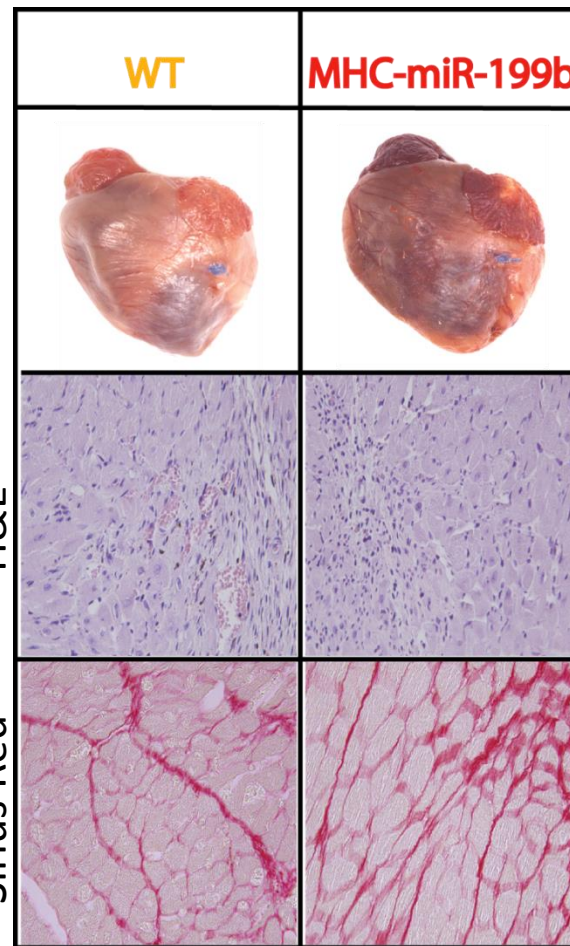
- exaggerated hypertrophy
- increased fibrosis



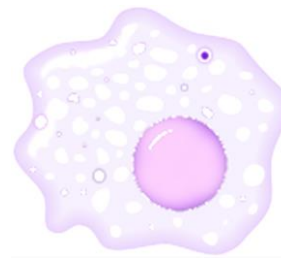
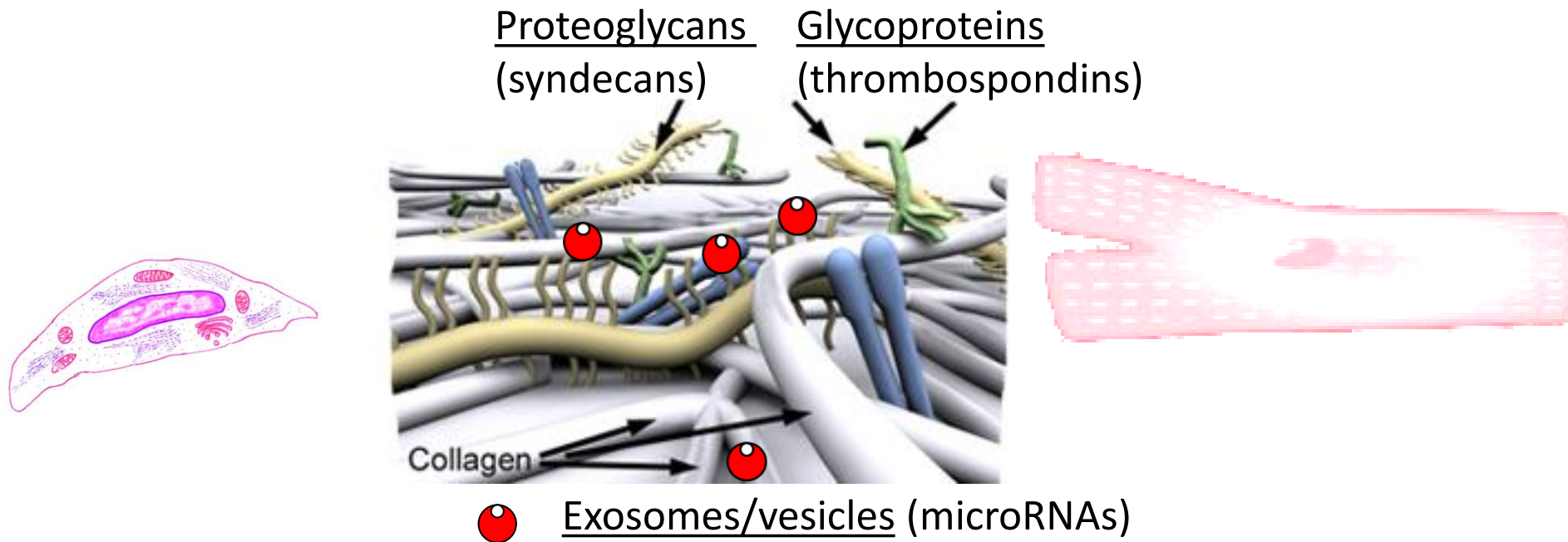
■ WT  
■ MHC-miR-199b



Myocyte hypertrophy  
 Increased collagen

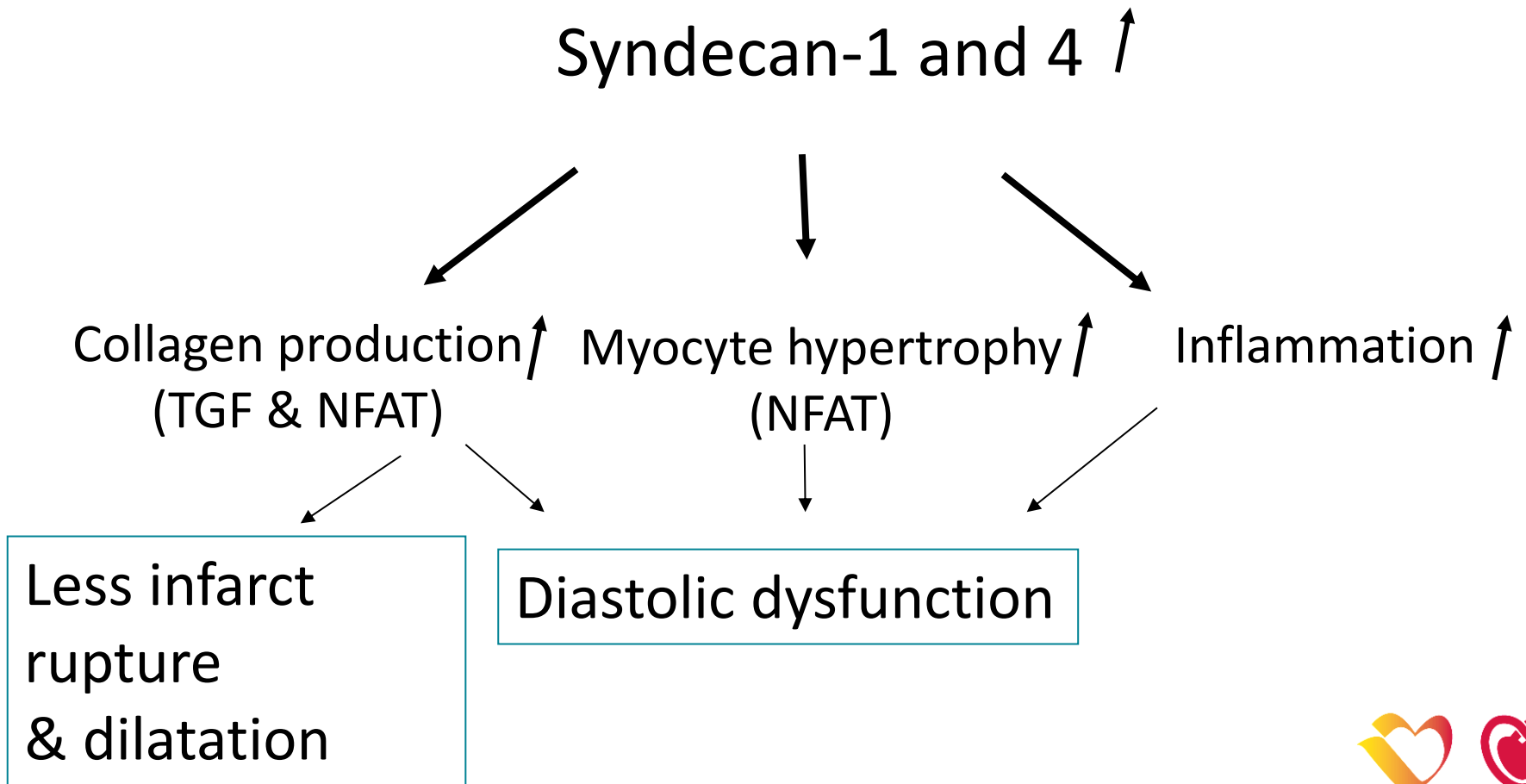


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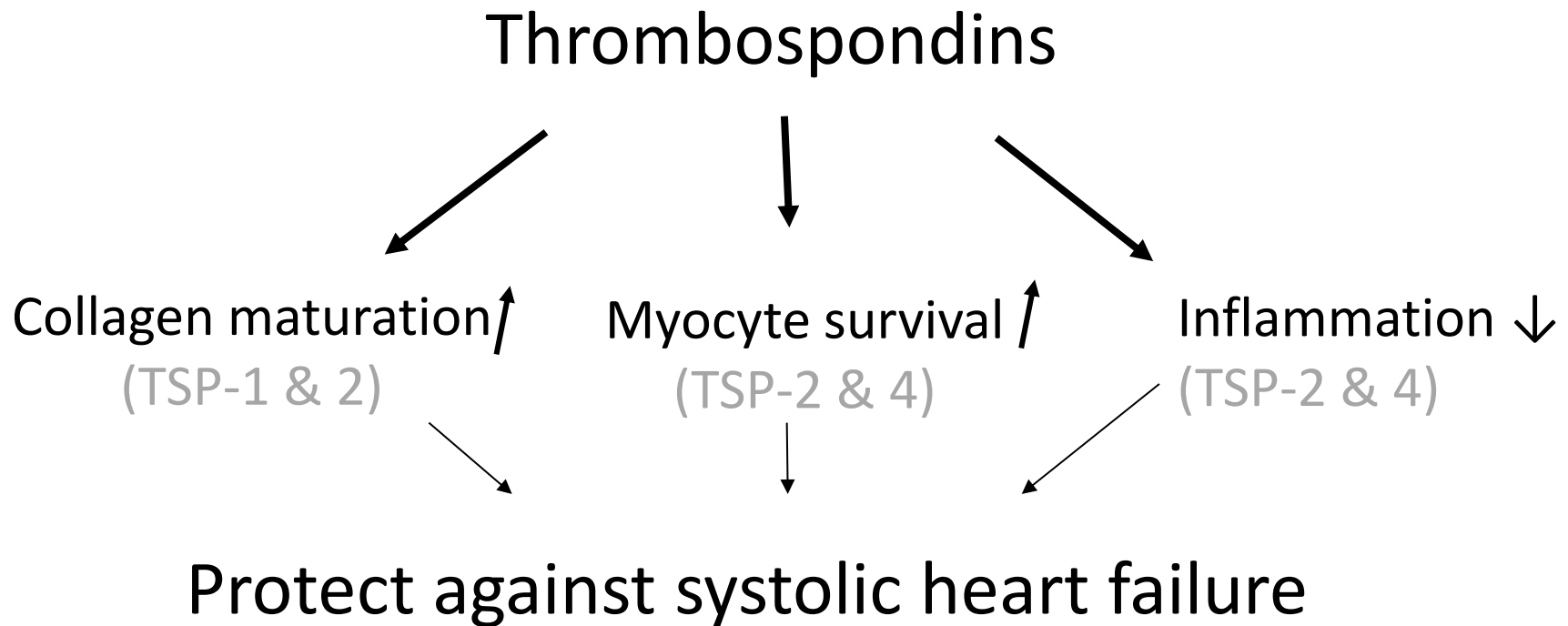


*S Heymans*

# Increased synd-1 and -4 causes diastolic dysfunction but prevent infarct dilatation

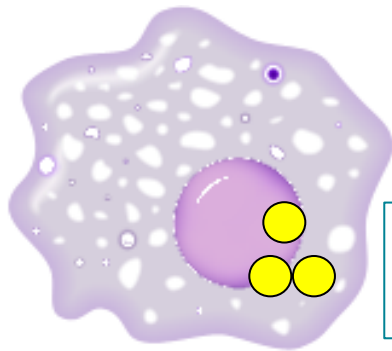


# Thrombospondins protect against diastolic and systolic heart failure



# MicroRNAs in matrix-exosomes alters cardiac fibrosis and hypertrophy

Inflammatory cells



MicroRNA-199b

Cardiomyocyte  
\* Hypertrophy

MicroRNA-(21<sup>(\*)</sup>)

Fibroblast  
\* Collagen production