

A SZÍV MOLEKULÁRIS ÉLETTANA ÉS A SZÍVÉRRENDSZERI KÓRKÉPEK ÁTTEKINTŐ PATOMECHANIZMUSA

2017. 06. 06



AHA FELMÉRÉS ÉS PREDIKCIÓ

	Össz- kardiovaszkuláris betegség	Hipertónia	Szívkoronária betegség	Szívelégtelenség	Stroke
év					
2010	36.9	33.9	8.0	2.8	3.2
2015	37.8	34.8	8.3	3.0	3.4
2020	38.7	35.7	8.6	3.1	3.6
2025	39.7	36.5	8.9	3.3	3.8
2030	40.5	37.3	9.3	3.5	4.0
% változás	9.9	9.9	16.6	25.0	24.9

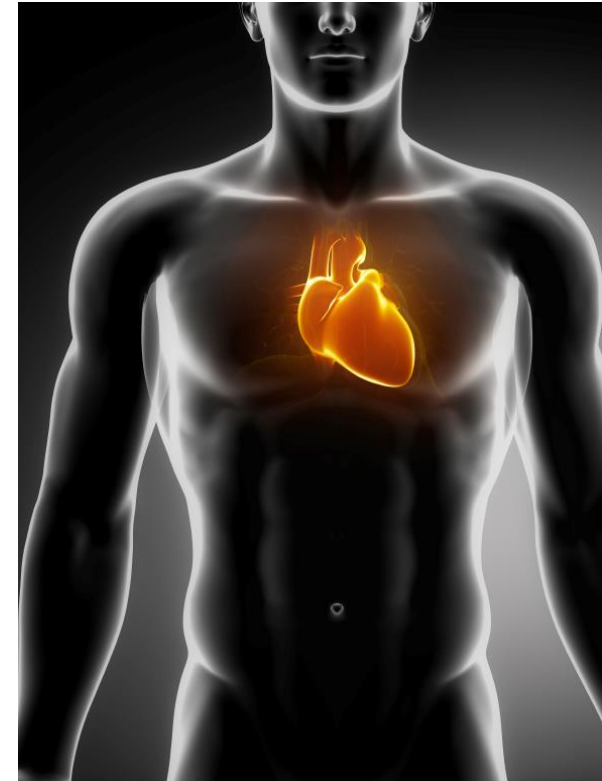


I. Szív molekuláris élettana:

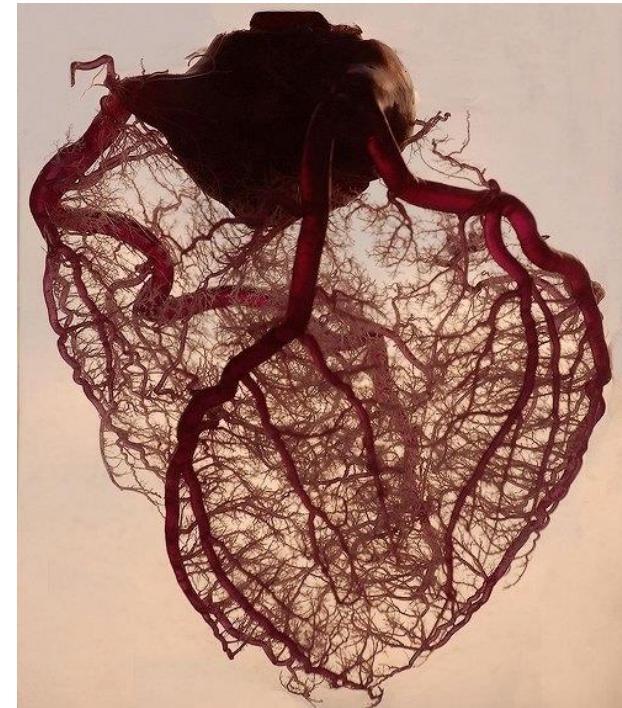
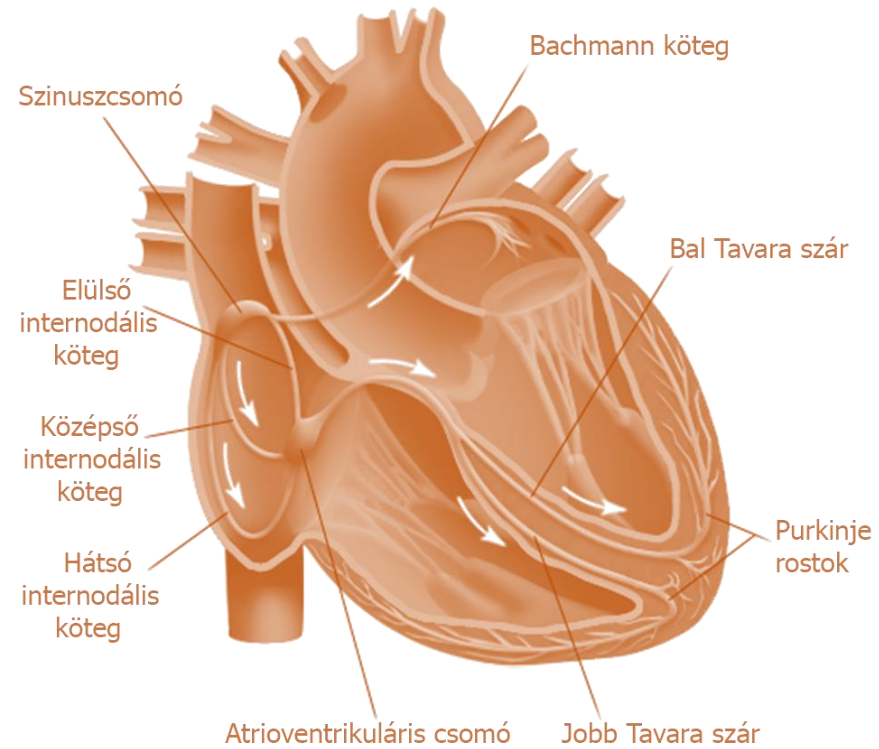
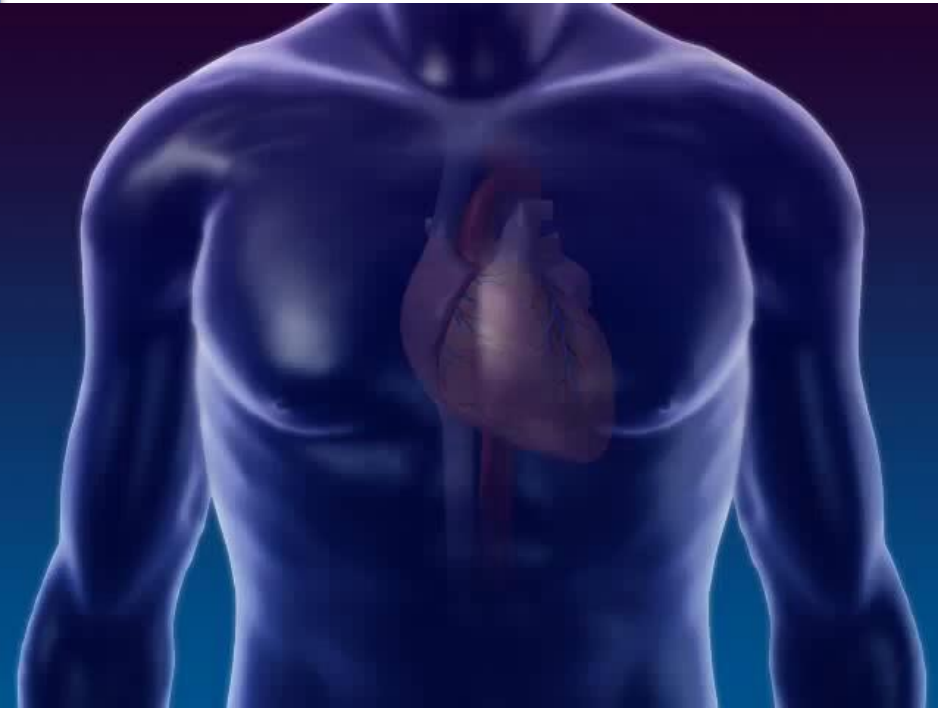
- A. A szív sejtjeinek strukturális és funkcionális áttekintése
- B. Molekuláris élettan integrált transzkriptomja
- C. Intercelluláris kommunikációs hálózat

II. Cardiovascularis kórképek patomechanizmusa

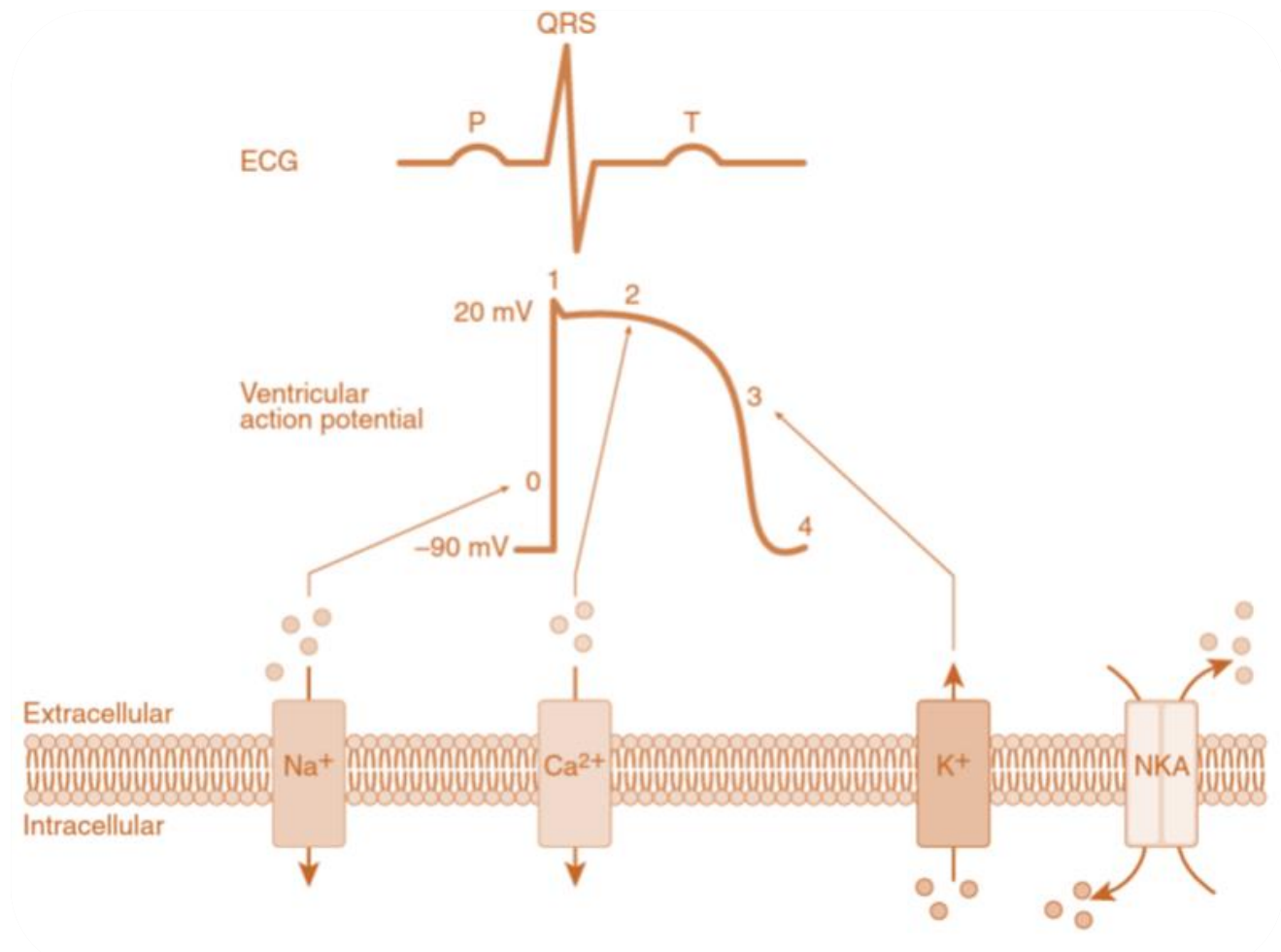
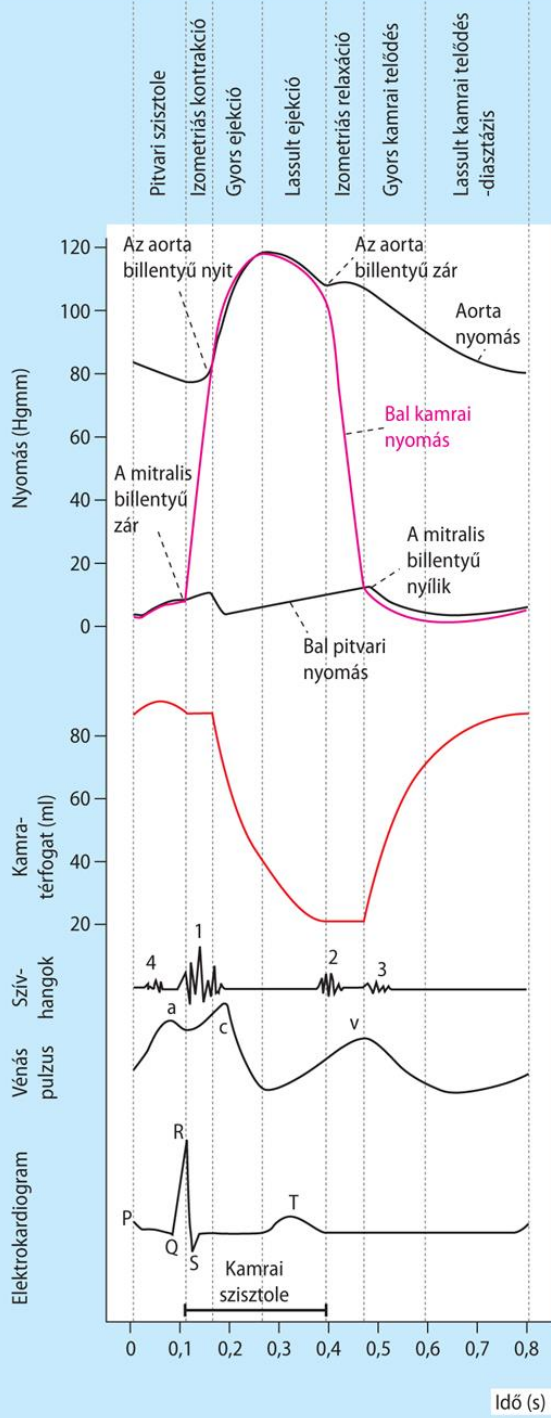
- A. Kardiovaszkuláris kórképhálózat
- B. Szívérrendszeri kórképek közös molekuláris patomechanizmusa
- C. ISEV 2017: EV-k szerepe a kardiovaszkuláris kórképek patomechanizmusában



MAKROSZKÓPIKUS ÁTTEKINTÉS

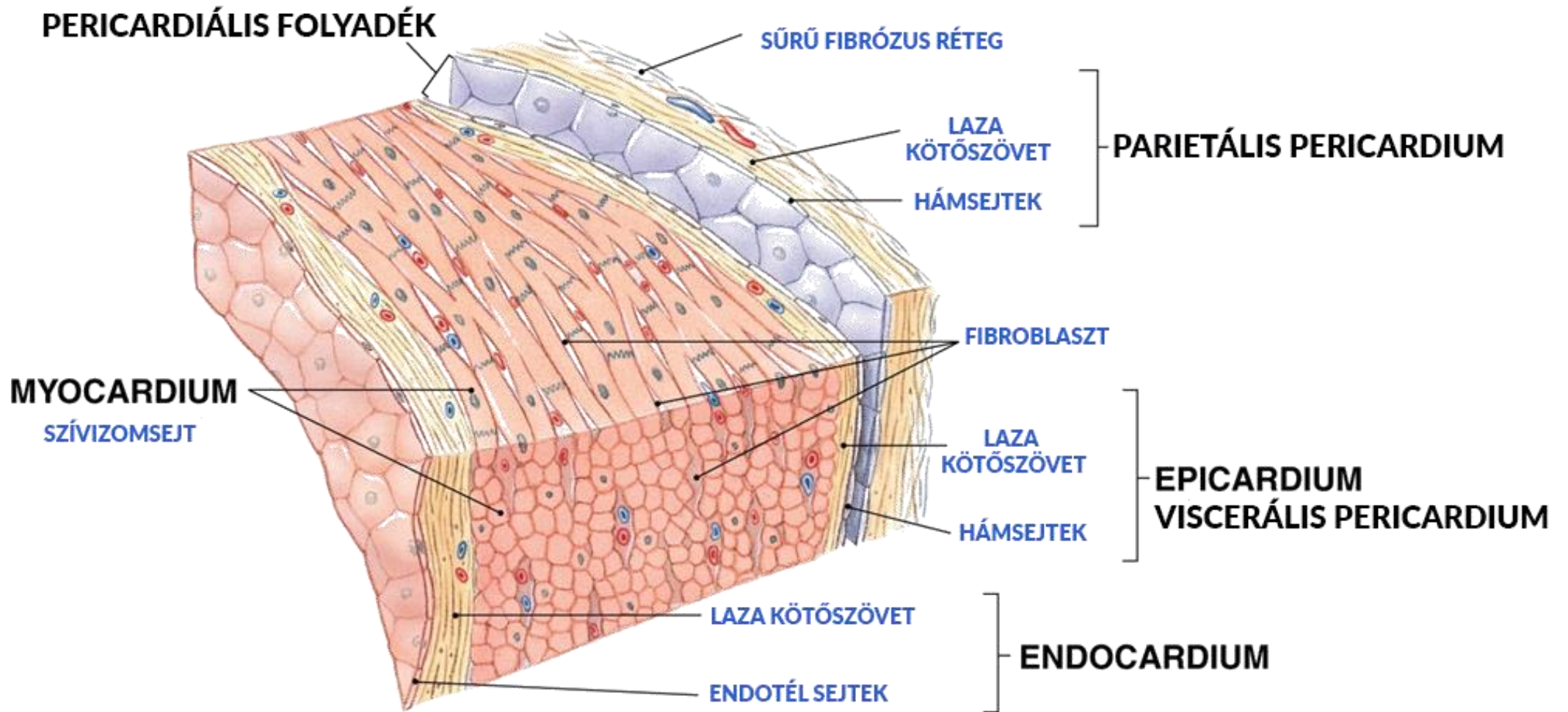


SZÍVCIKLUS



MOLEKULÁRIS ÉLETTAN ÁTTEKINTÉS

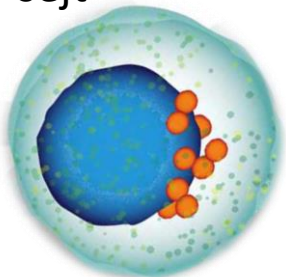
szupracelluláris szint



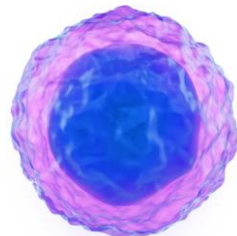
MOLEKULÁRIS ÉLETTAN ÁTTEKINTÉS

sejtszint

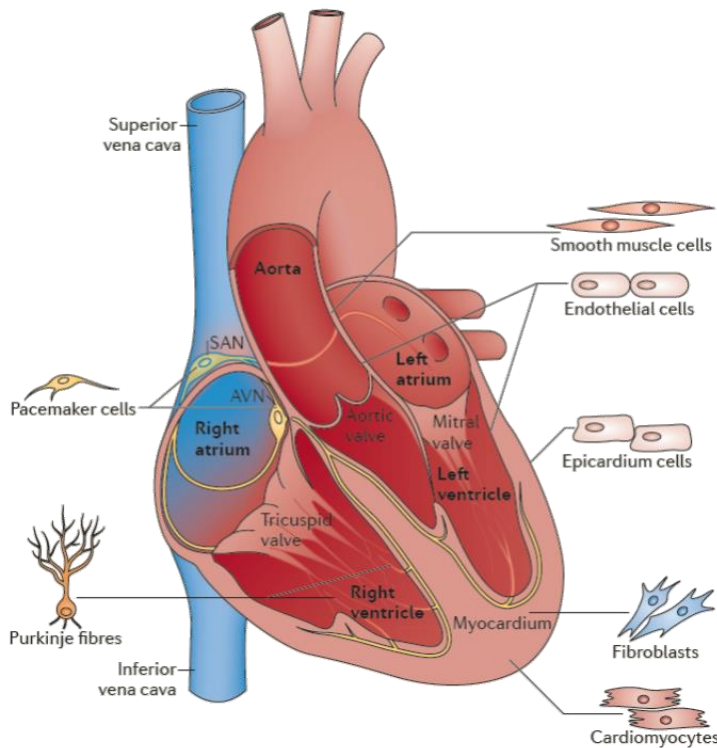
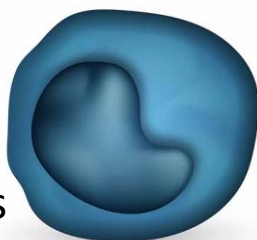
NKT-sejt



T-sejt



Cardialis
Monocyta/macrophag



Endotél



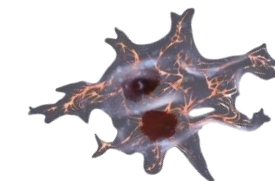
Epicardiális
adipocita



Szívizomsejt

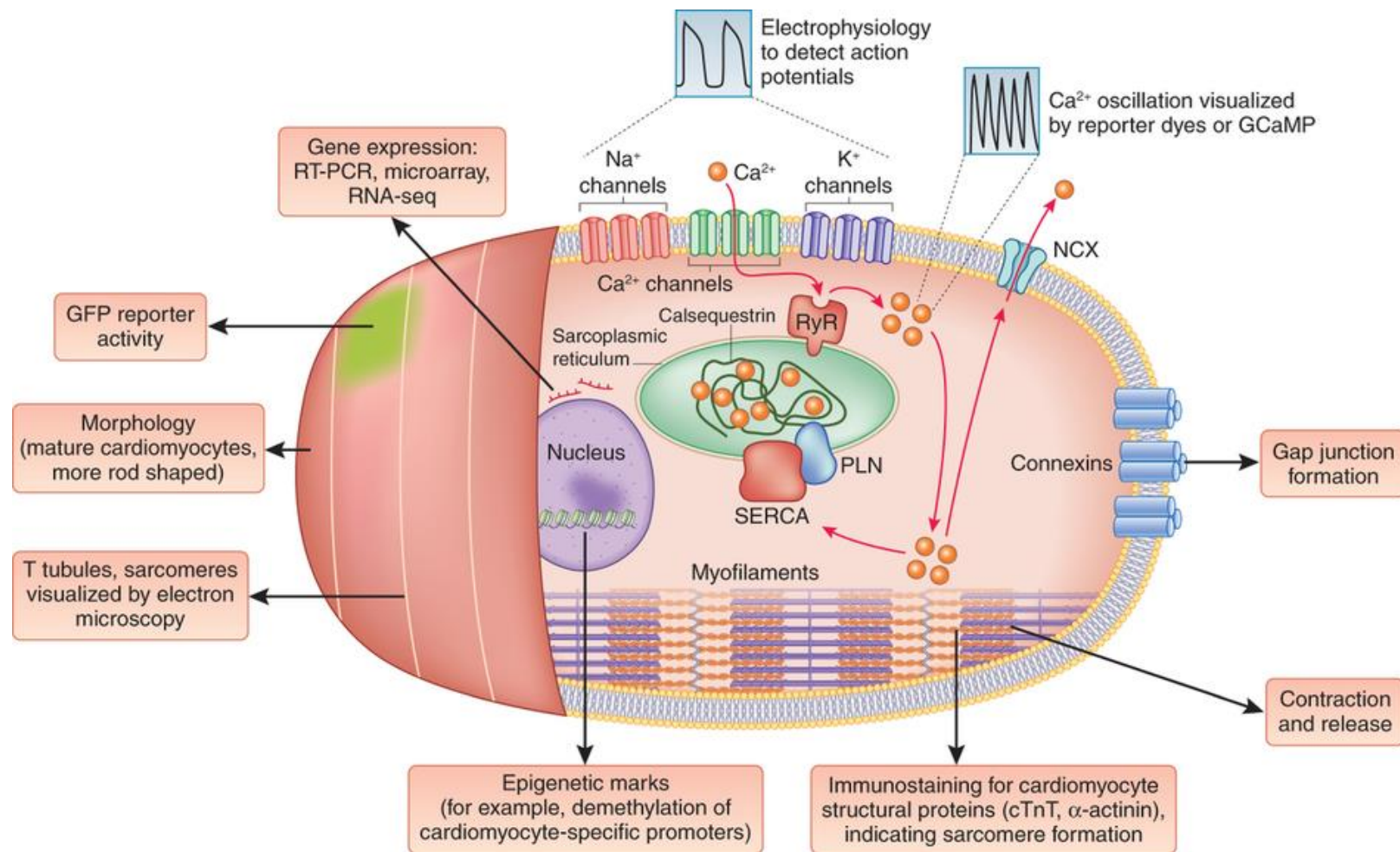
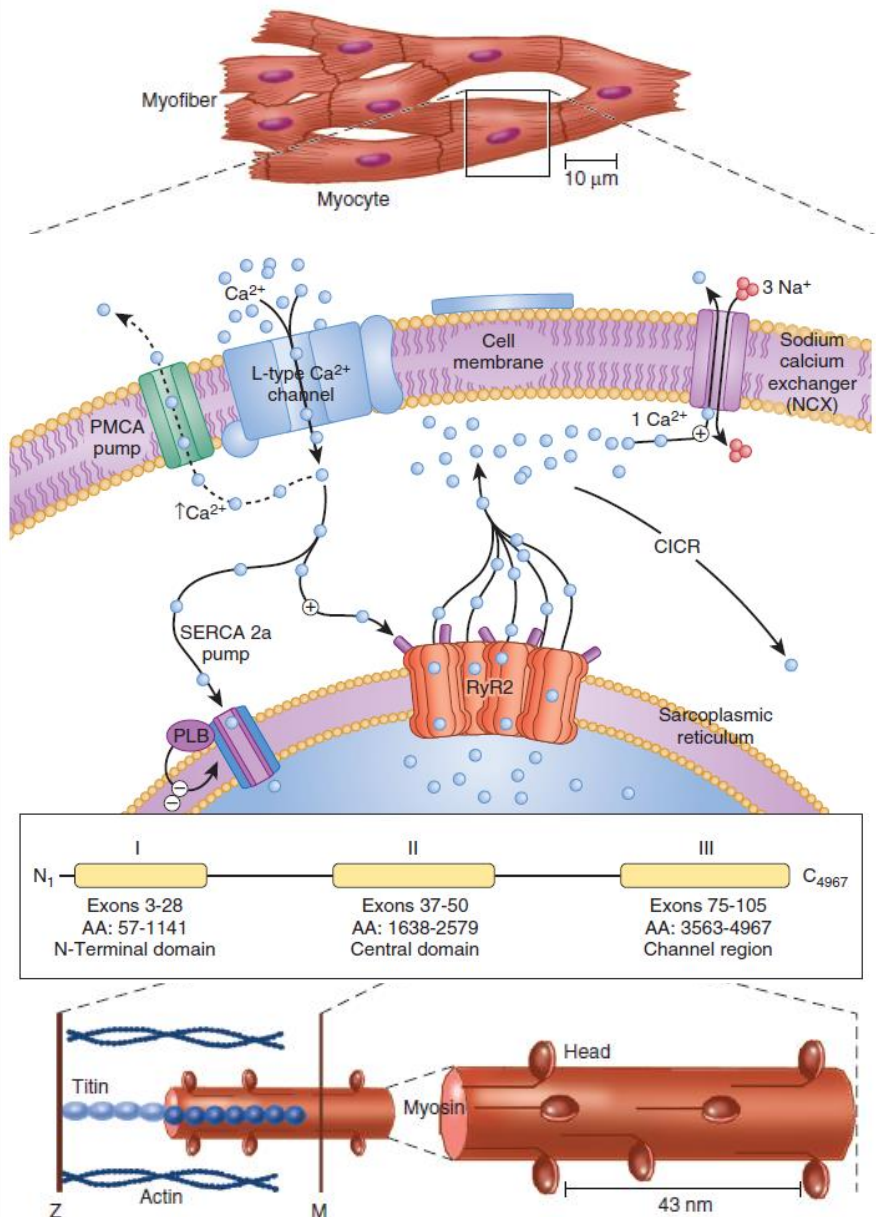


Cardialis fibroblast



MOLEKULÁRIS ÉLETTAN ÁTTEKINTÉS

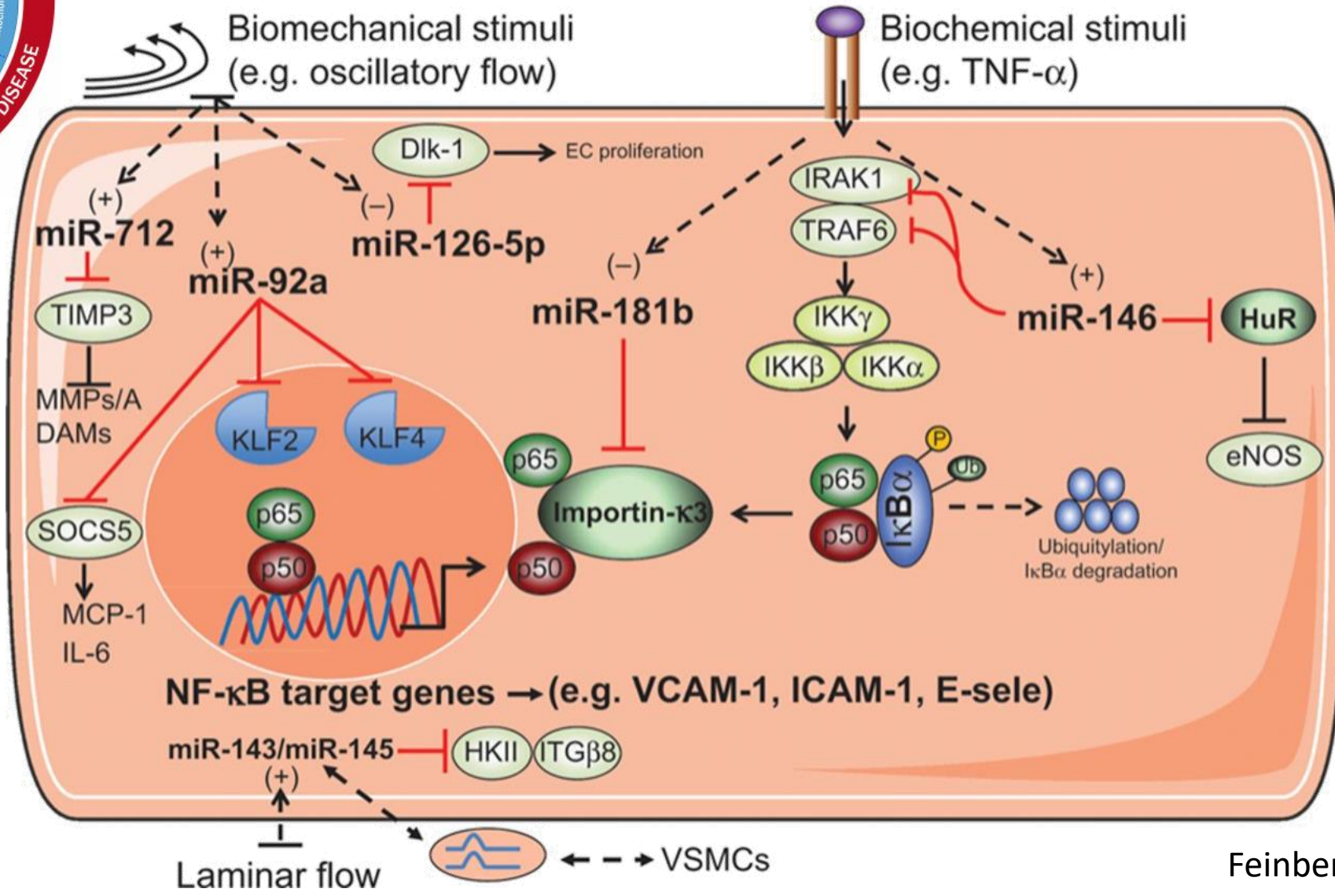
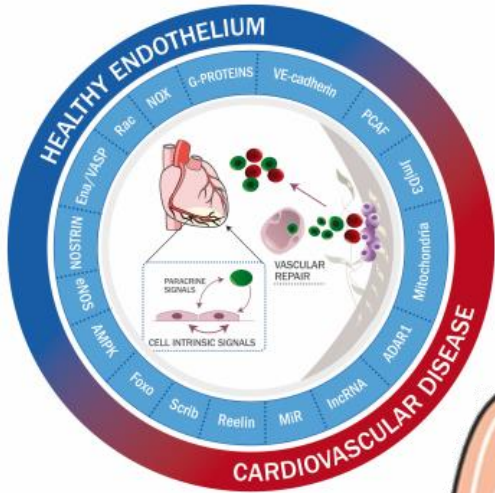
szubcelluláris szint Szívizomsejt



MOLEKULÁRIS ÉLETTAN ÁTTEKINTÉS

szubcelluláris szint

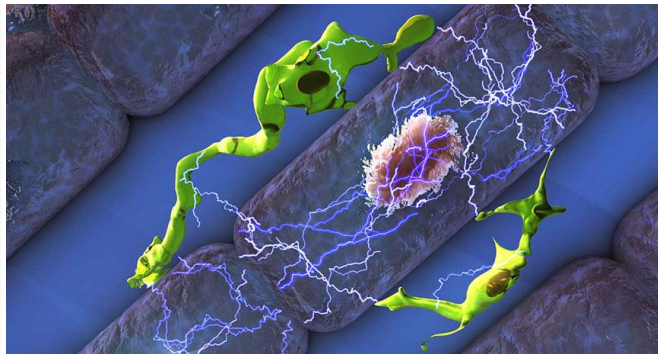
Endotél sejt



MOLEKULÁRIS ÉLETTAN ÁTTEKINTÉS

szubcelluláris szint

Cardiális monocyta/ macrophag sejt

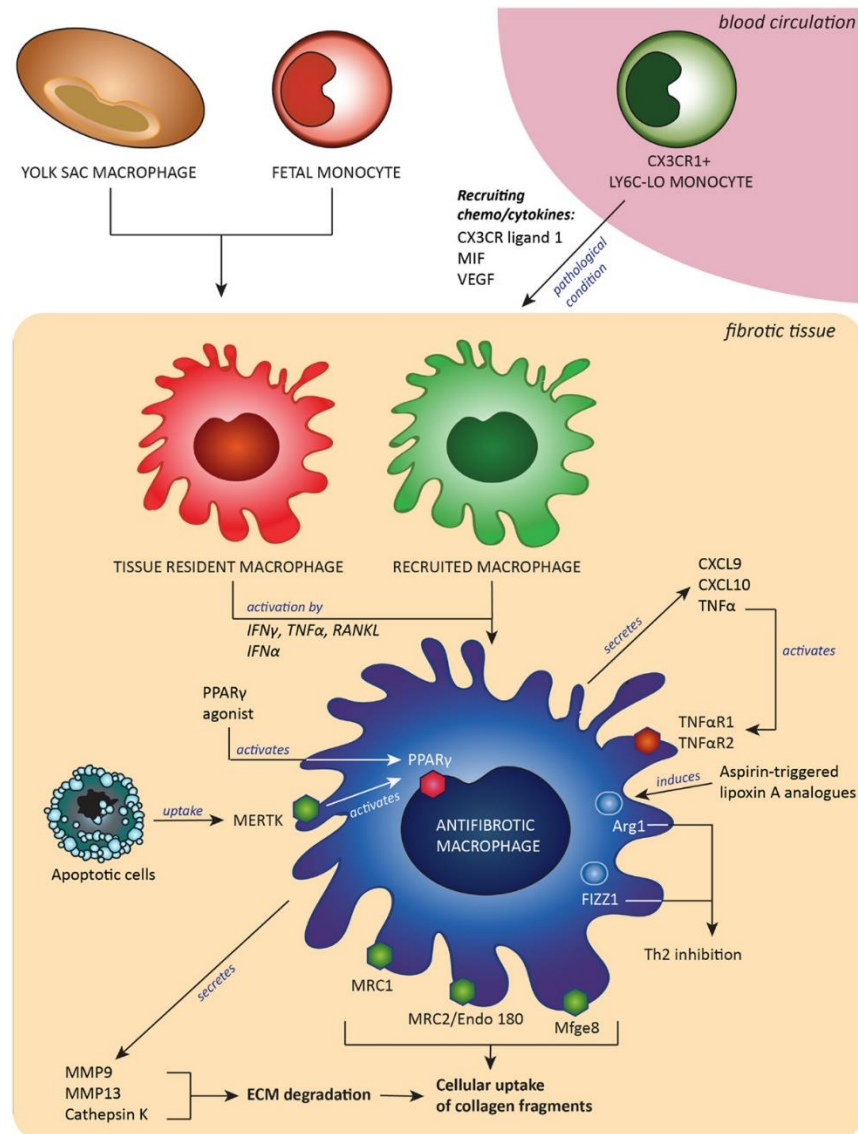


Eredet:

szik hólyag,
magzati máj monocitái,
felnőtt HSC

Azonosítás: Ly6C^{lo}

AREG → Szívizomsejt hipertrófia



Profibrótikus MF

Markers

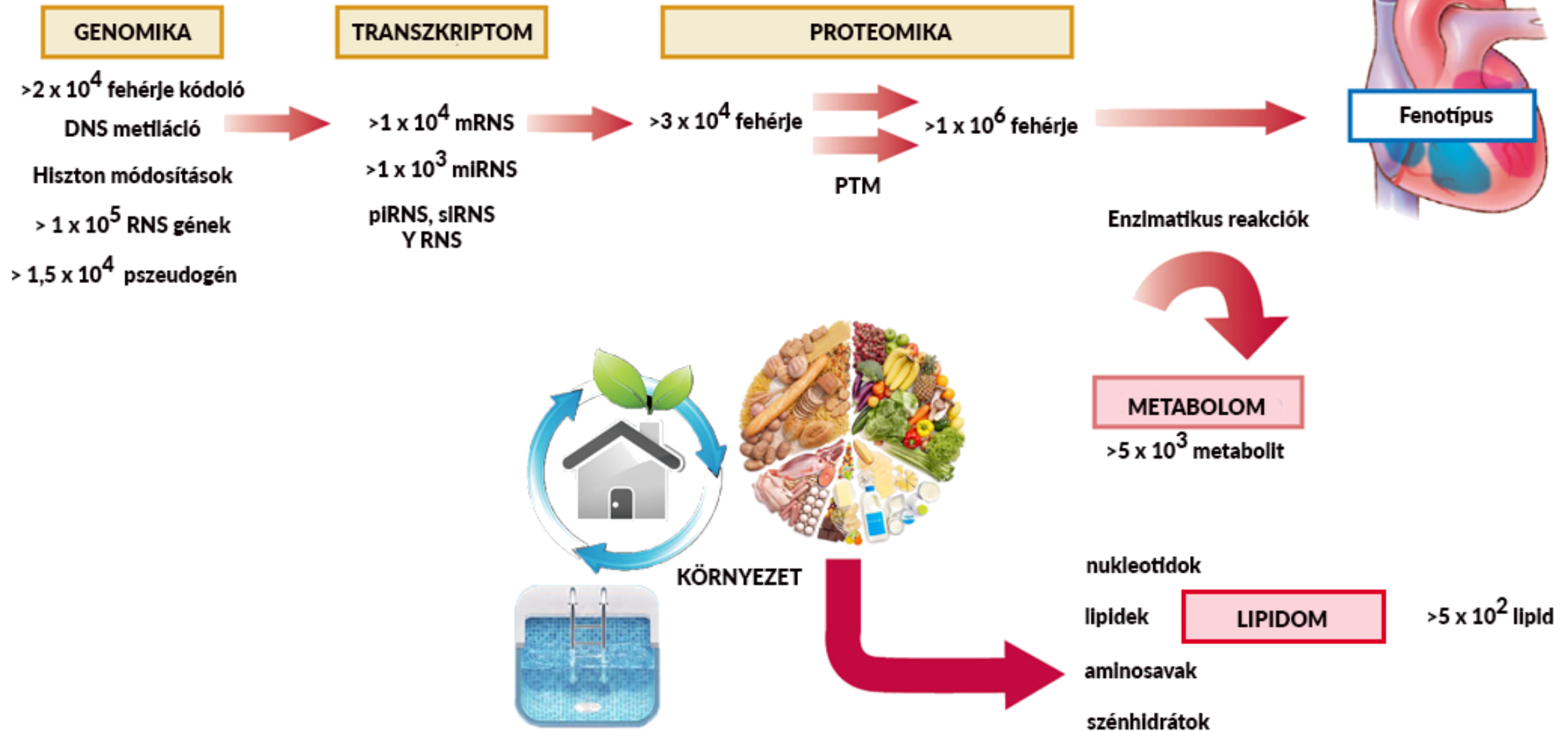
- TNF receptor (109, 110)
- CX3CR1 (60)
- TNF α (106, 107, 111)
- CXCL10 (59, 117, 118)
- CXCL9 (117, 118)
- MMP9 (73–75)
- MMP13 (68, 118)
- Cathepsin K (66, 71, 77, 78)
- MERTK(89, 90)
- PPAR γ (93–100)
- MRC1 (120)
- MRC2 (121)
- MFGE8 (6, 65, 85)
- Arg-1 (17)
- FIZZ1 (22)

Fujiu et al, Nat Med, 2017

Adhyatmika et al, Front Med, 2015

MOLEKULÁRIS ÉLETTAN ÁTTEKINTÉS

transzkriptomikai szint



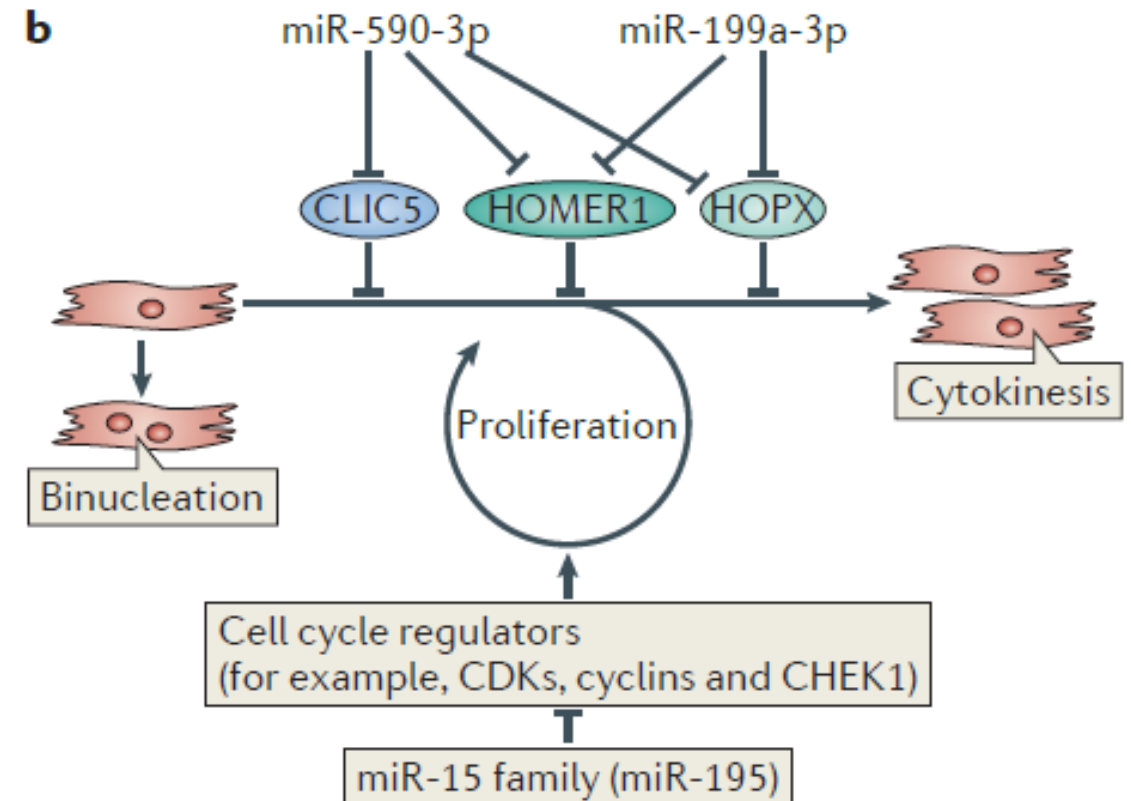
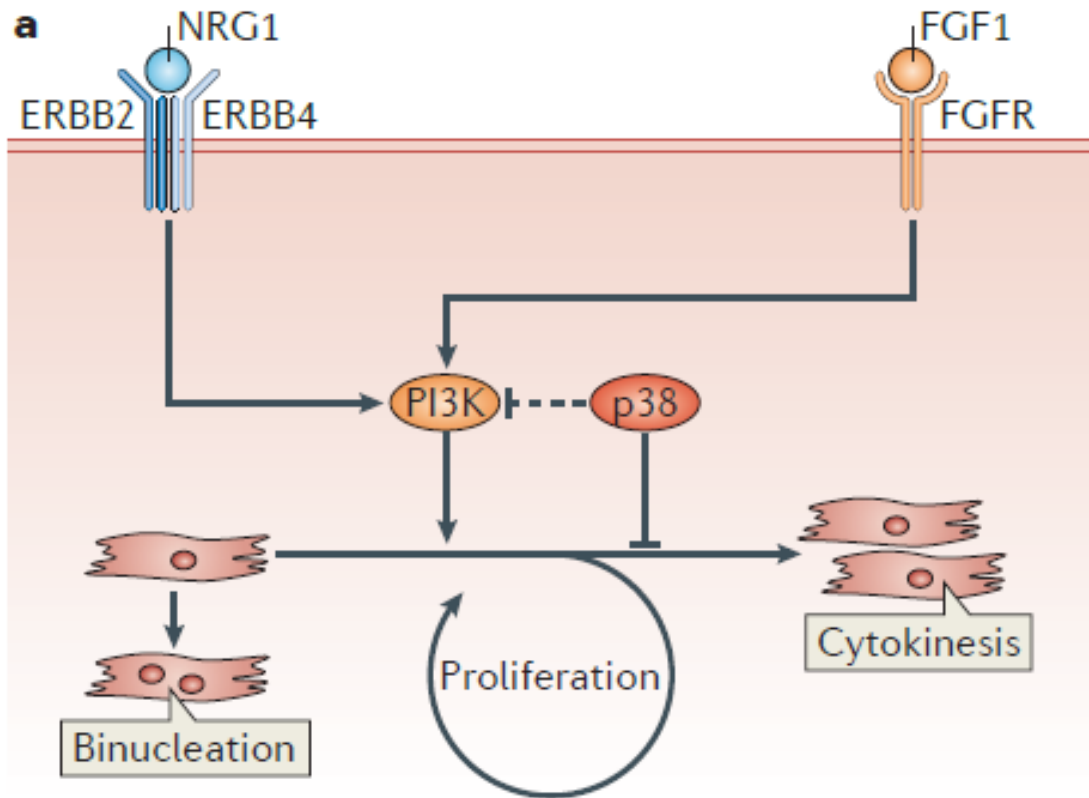
GENOM – FENOM KAPCSOLAT

Biobank	Web site	Enrolment locations	Initial enrolment	Enrolment to date	Target enrolment
<i>Commercial funding</i>					
deCODE Genetics (Amgen)	http://www.decode.com/	Iceland	1996	>200,000	Unknown
Geisinger MyCode Community Health (Regeneron Pharmaceuticals and others)	http://www.geisinger.org/for-researchers/partnering-with-patients/pages/mycode-health-initiative.html	Geisinger Health System (Danville, PA, USA)	2007	>50,000	Unknown
<i>Government funding</i>					
China Kadoorie Biobank	http://www.ckbiobank.org/site	China	2004	>500,000	Enrolment completed
UK Biobank	https://www.ukbiobank.ac.uk	UK	2006	>500,000	Enrolment completed
Electronic Medical Records and Genomics (eMERGE) Network	https://emerge.mc.vanderbilt.edu/about-emerge	United States Hospital Sites	2007	>50,000	Unknown
Million Veterans Program	http://www.research.va.gov/mvp	Veterans Affairs Hospitals, USA	2011	>500,000	~1,000,000
All of Us Research Program (part of the Precision Medicine Initiative)	https://www.nih.gov/research-training/allofus-research-program	USA	Early 2017	–	~1,000,000
<i>Institutional funding</i>					
BioVu Biorepository	https://victr.vanderbilt.edu/pub/biovu	Vanderbilt University Medical Center (Nashville, TN, USA)	2007	>215,000	Unknown
Kaiser Permanente Research Bank	http://researchbank.kaiserpermanente.org	USA	2016	>250,000	~500,000
Partners Healthcare Biobank	https://biobank.partners.org	Partners Health Care (Boston, MA, USA)	2010	>50,000	~100,000

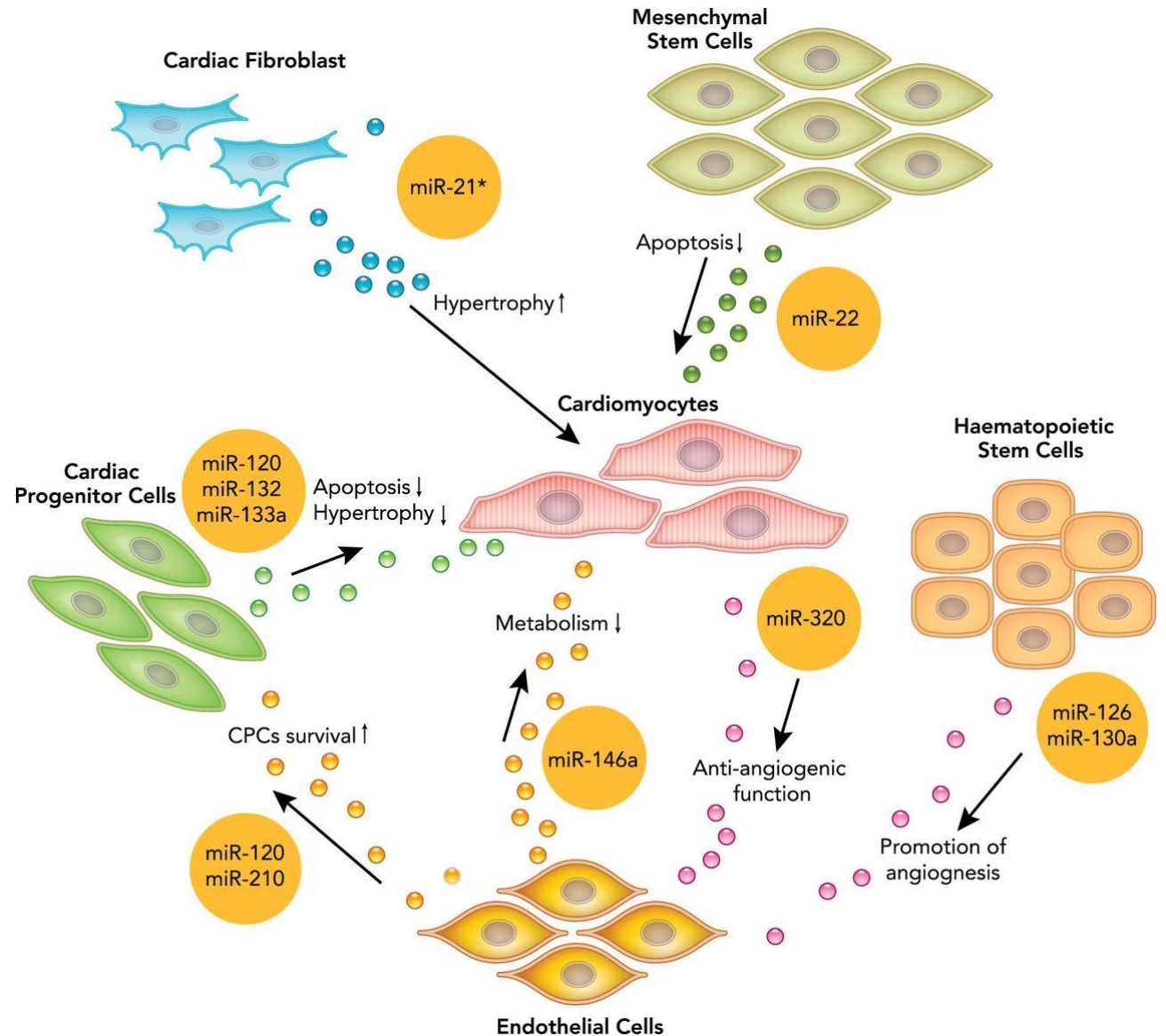
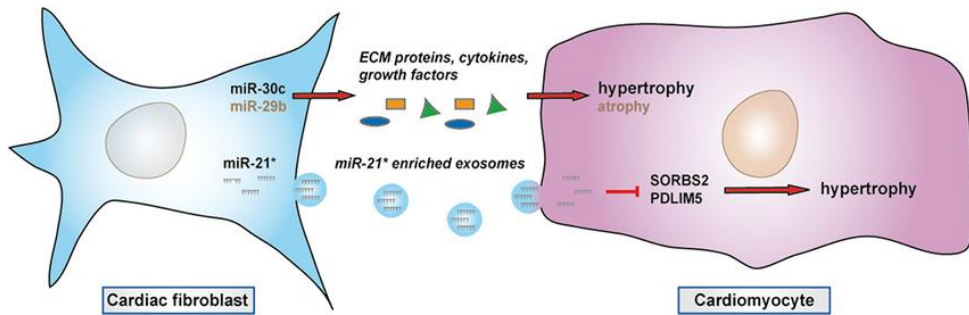
MOLEKULÁRIS ÉLETTAN ÁTTEKINTÉS

transzkriptomikai szint

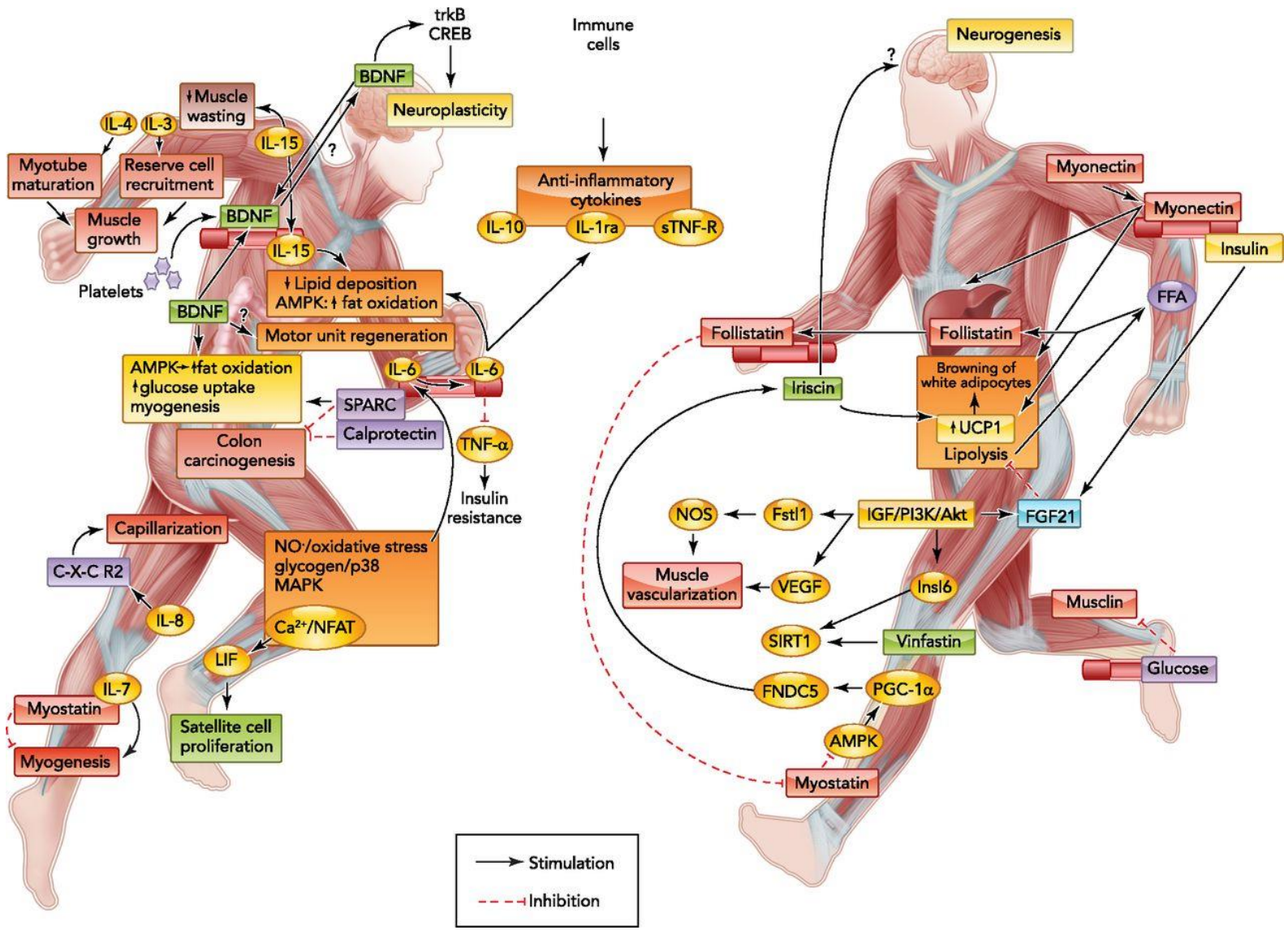
Szívizomsejt



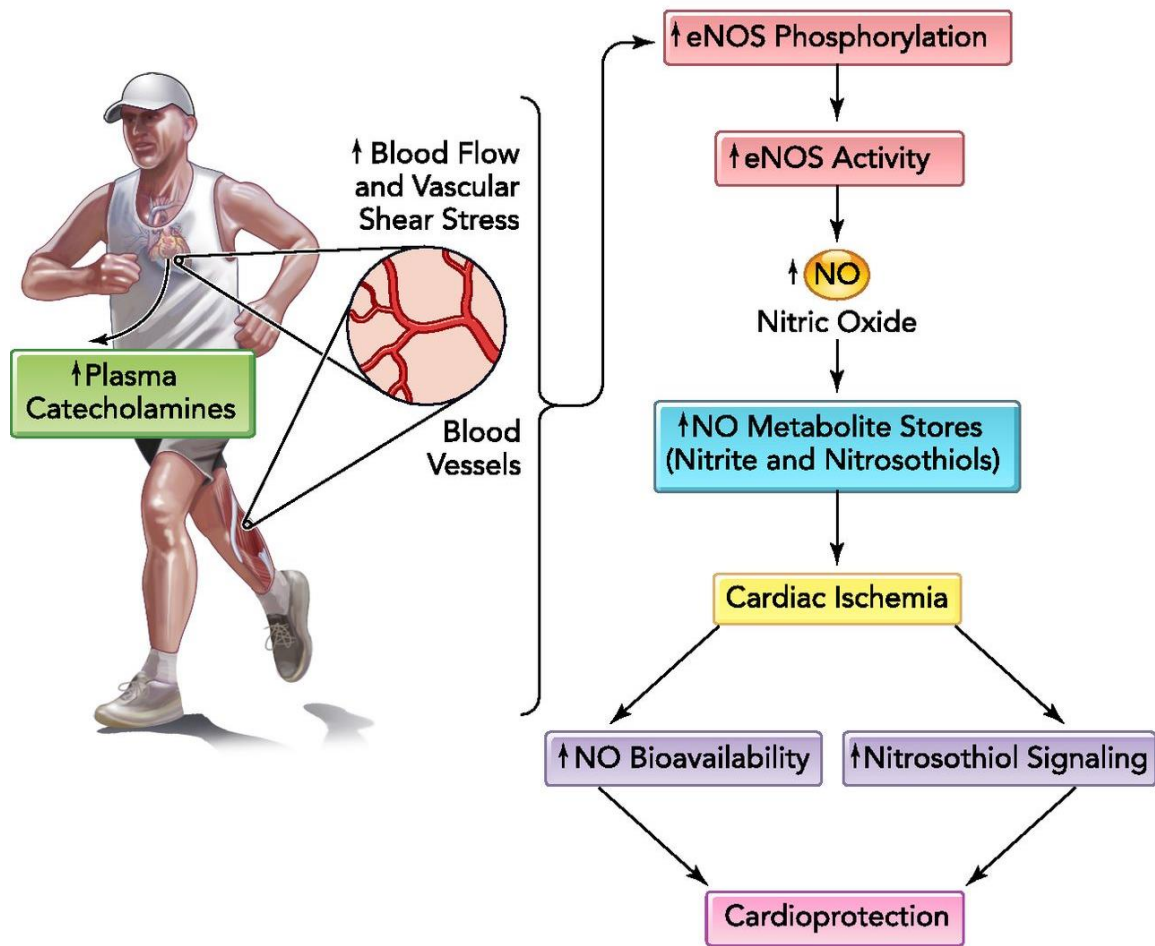
INTERCELLULÁRIS KOMMUNIKÁCIÓ



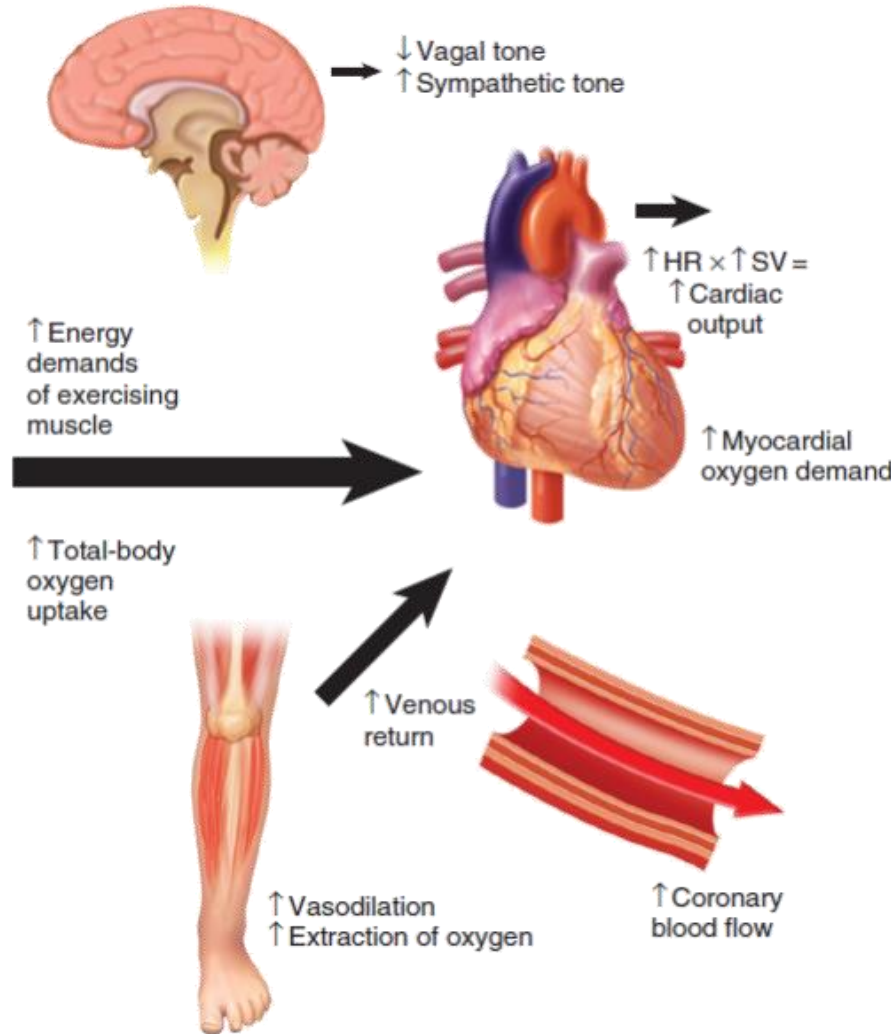
MIOKIN HÁLÓZAT



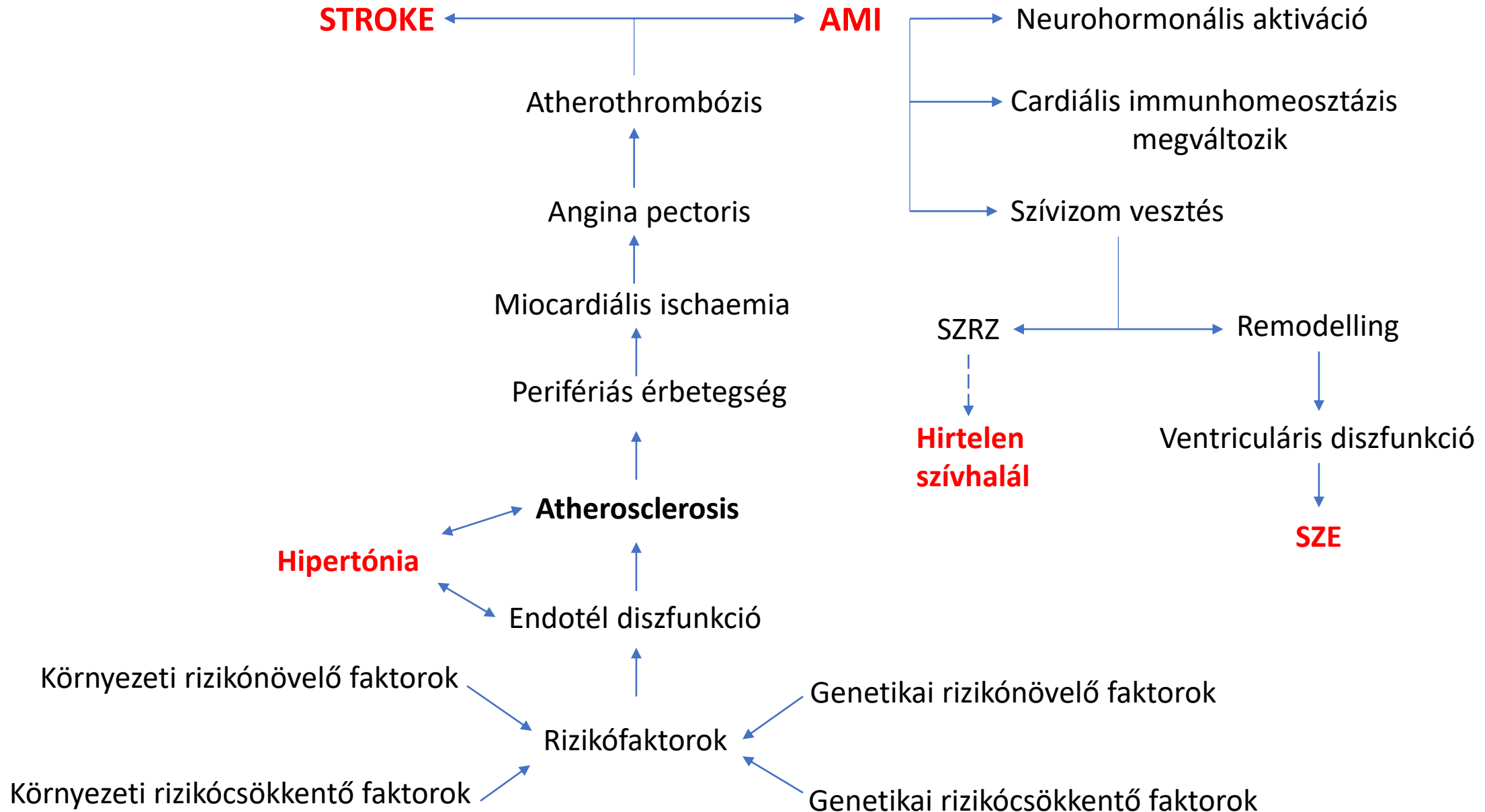
SPORT HATÁSA A SZÍVRE



DYNAMIC EXERCISE



KARDIOVASZKULÁRIS KÓRKÉPHÁLÓZAT



GENETIKAI FAKTOROK SZEREPE

ASGR1 (12 bp inaktiváló del)

APOC3

ANGPTL4

LPA

PCSK9 (inaktiváló mut),

NPCL1 (inaktiváló mut)

VÉDŐ



LDLR (5kb del)

APOB

PCSK9 (GOF)

LDLRAP1

ABCG5

ABCG8

LRP6

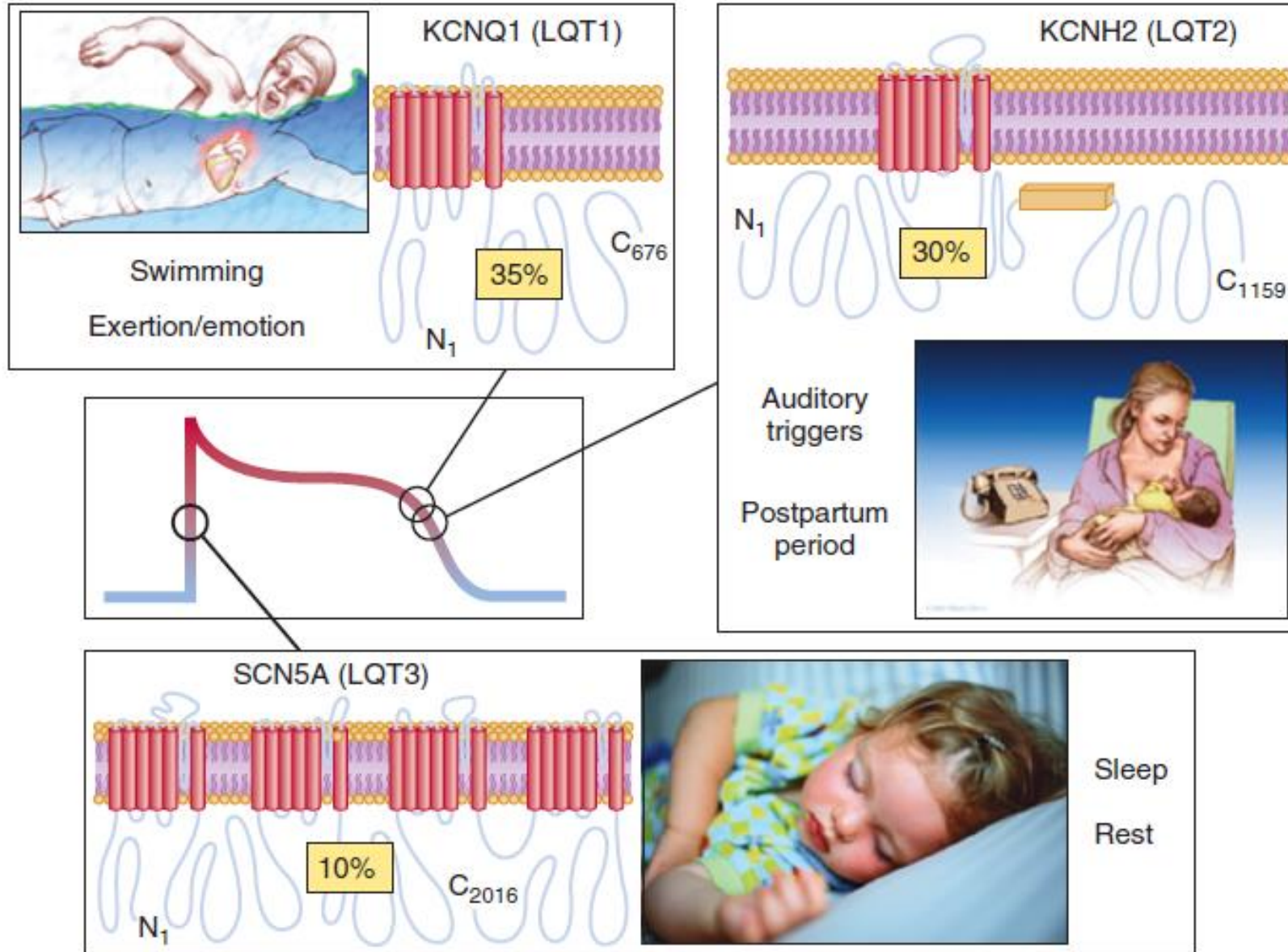
DYRK1B

GUCY1A3

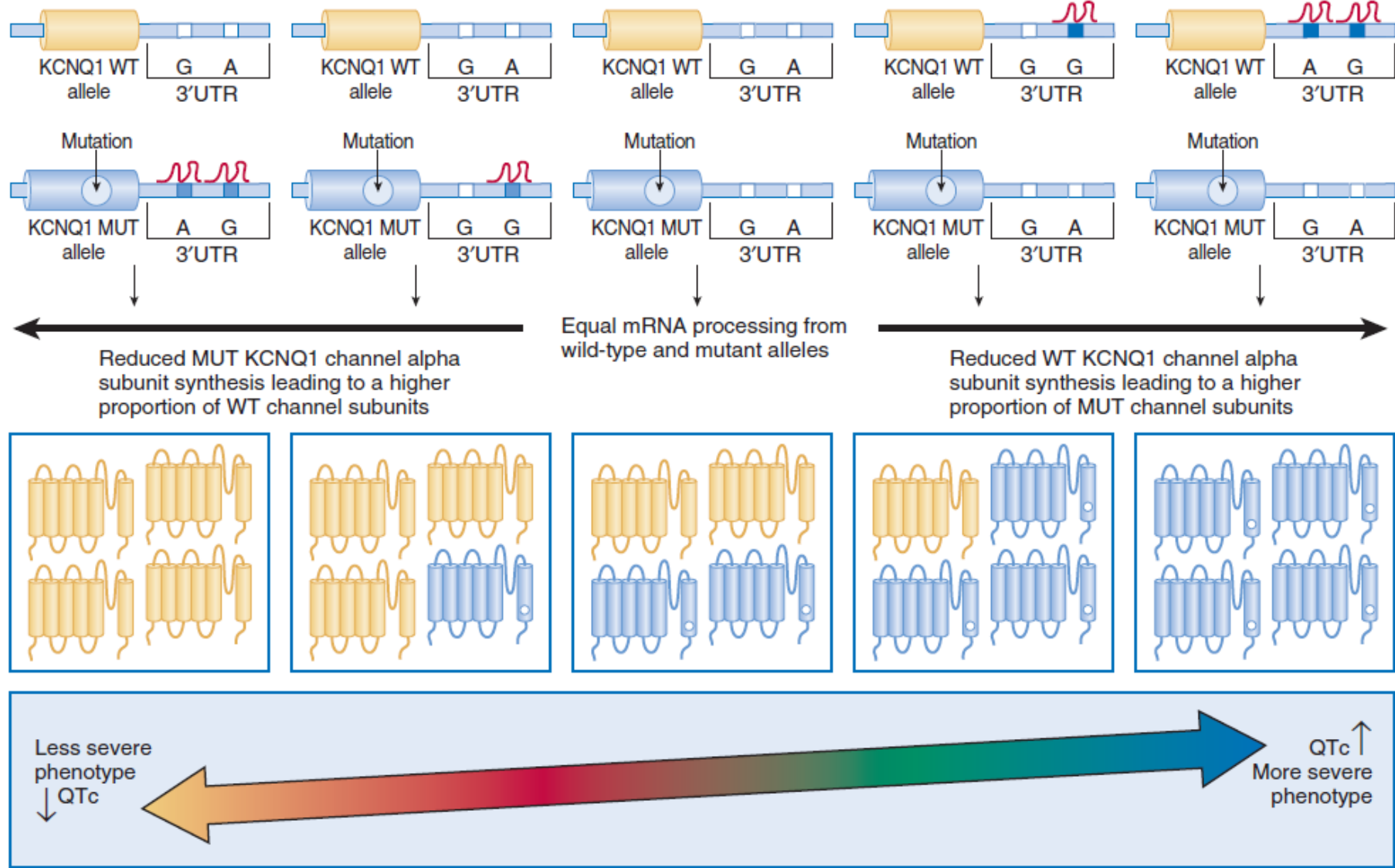
NOS3

RIZIKÓ

GENETIKAI FAKTOROK SZEREPE (2)



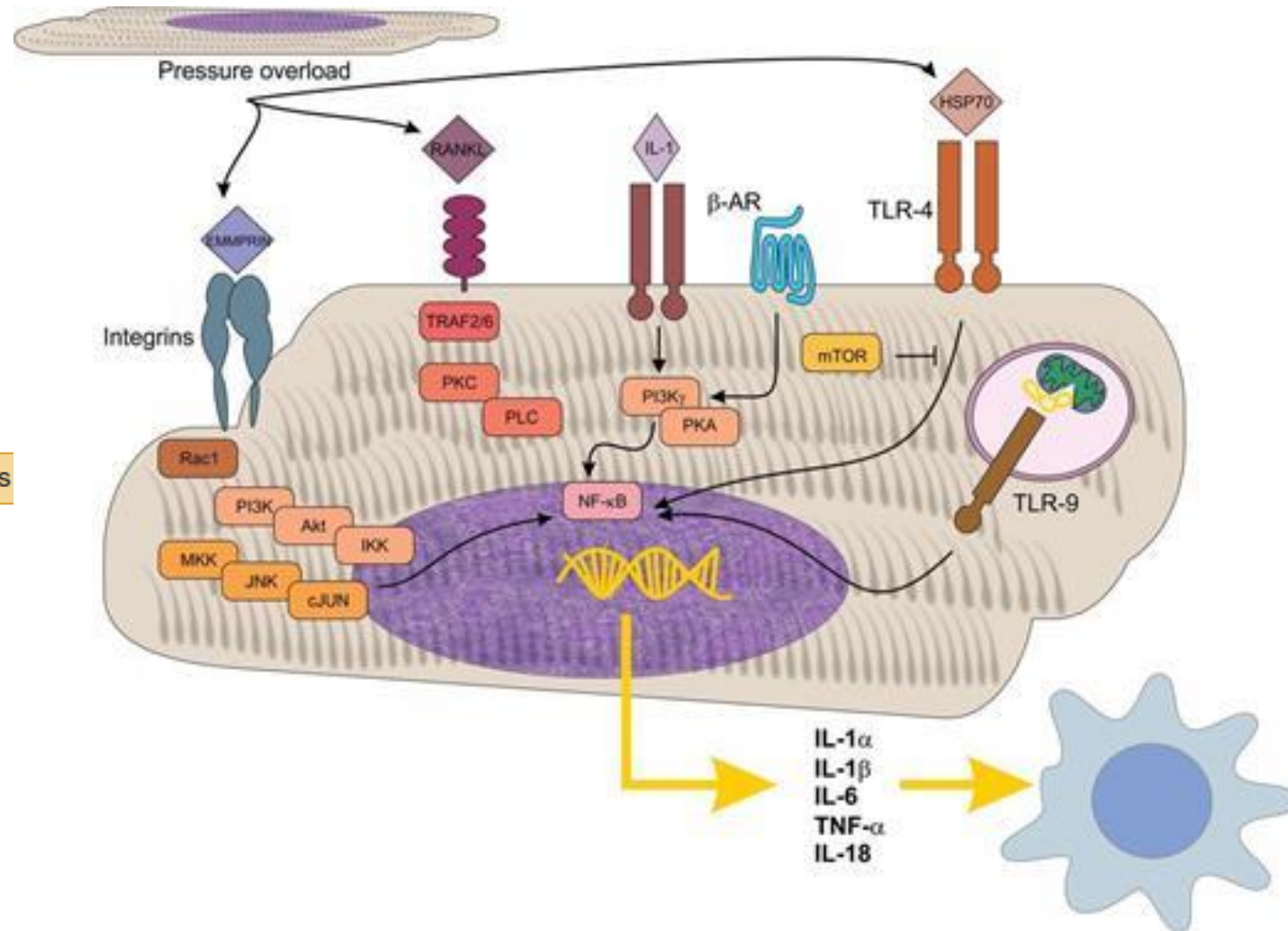
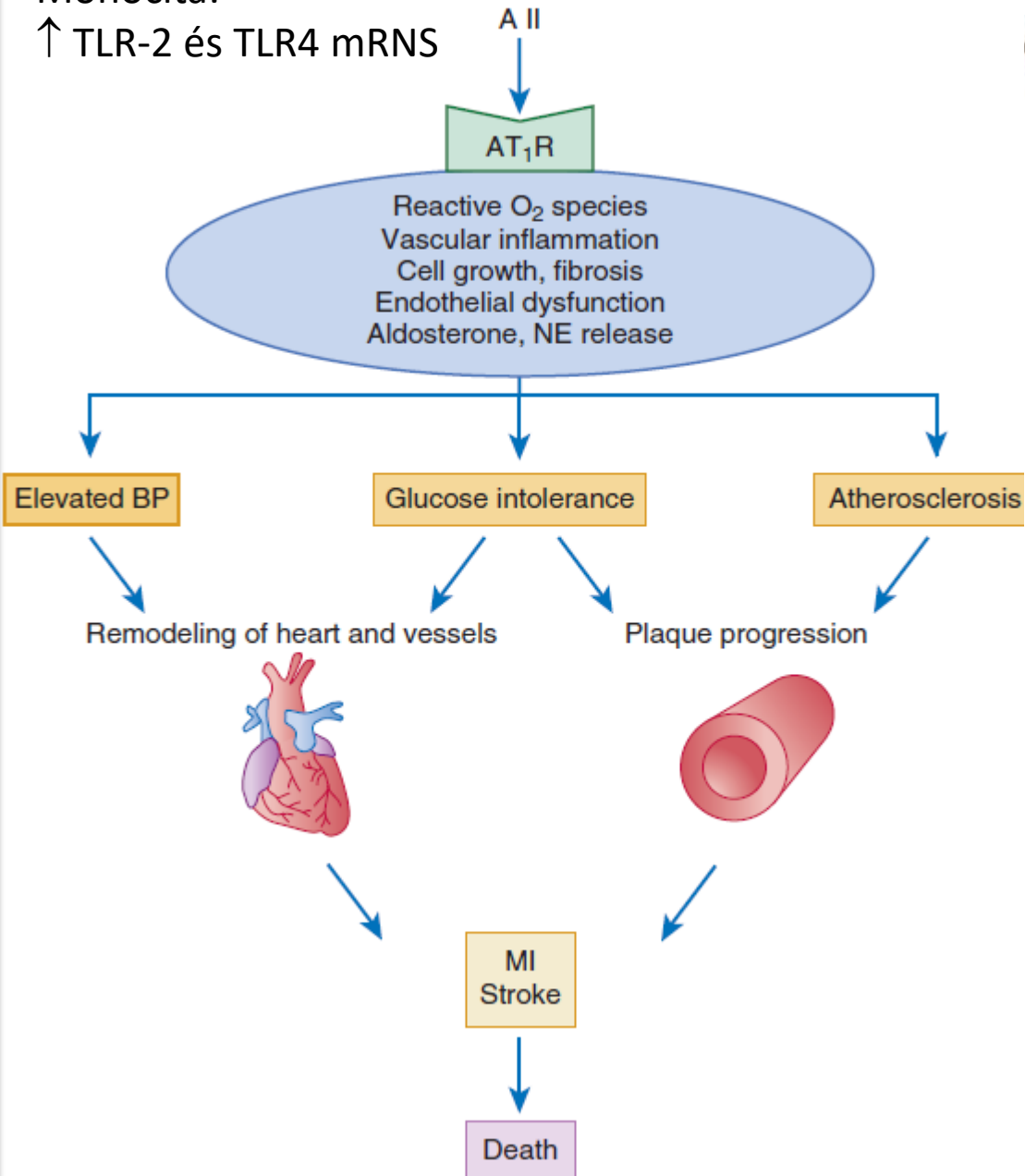
GENETIKAI FAKTOROK SZEREPE (2)



HIPERTÓNIA

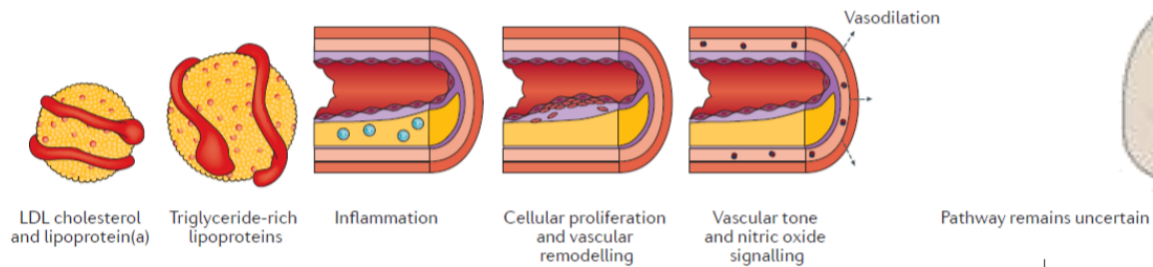
Monocita:

↑ TLR-2 és TLR4 mRNS



ISCHAEMIÁS SZÍVBETEGSÉG

REVIEWS



- SORT1
- PCSK9
- APOB
- ABCG5-ABCG8
- LPA
- LIPA
- LDLR
- APOE

- LPL
- TRIB1
- APOA5-APOA4
- APOA4-APOA1
- ANGPTL4

- IL6R
- CXCL12

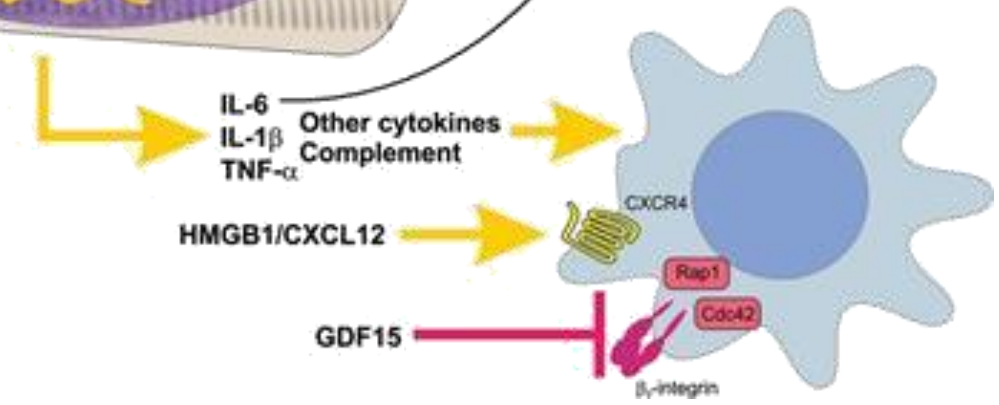
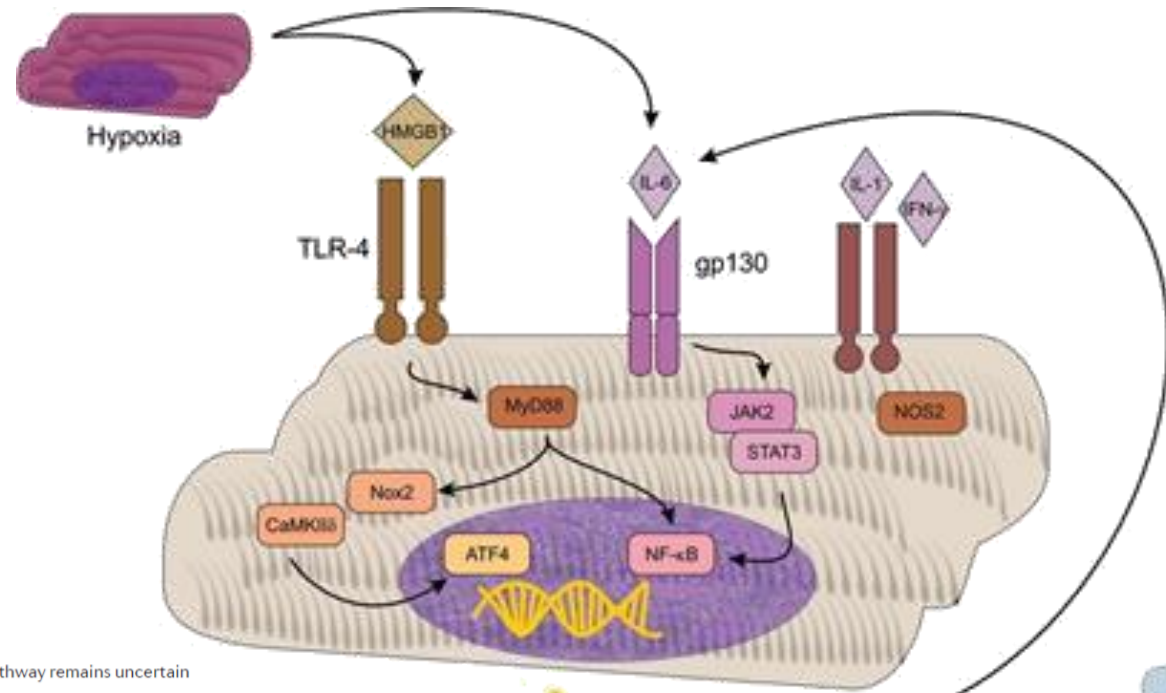
- COL4A1-COL4A2
- MIA3
- REST-NOA1
- ZC3HC1
- 9p21
- PDGFD
- SWAP70
- KSR2
- ADAMTS7
- BCAS3
- FLT1
- SMAD3

- GUCY1A3
- EDNRA
- NOS3

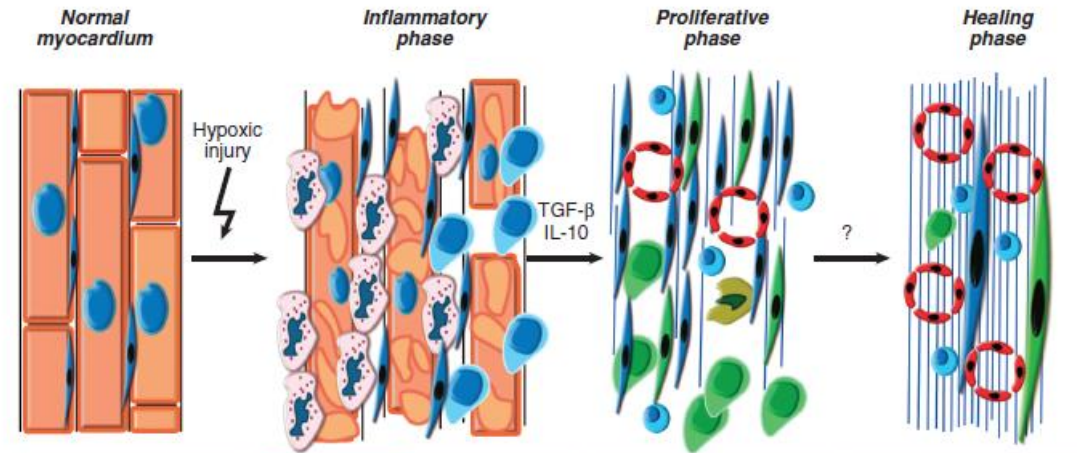
- PPAP2B
- WDR12
- VAMP5-VAMP8-GGCX
- ZEB2
- AK097927
- MRAS
- SLC22A4-SLC22A5
- ANKS1A
- PHACTR1
- TCF21
- KCNK5
- PLG
- HDAC9
- ABO
- SVEP1
- SH2B3

- CYP17A1-CNNM2-NT5C2
- KIAA1462
- ATP2B1
- HHIPL1
- MFGE8-ABHD2-SMG6-SRR
- RASD1-SMCR3-PENT
- UBE2Z-GIP-ATP5G1-SNF8
- PMAIP1-MC4R
- ZNF507
- SLC5A3-MRPS6-KCNE2
- POM121L9P-ADORA2A
- FURIN-FES

Pathway remains uncertain

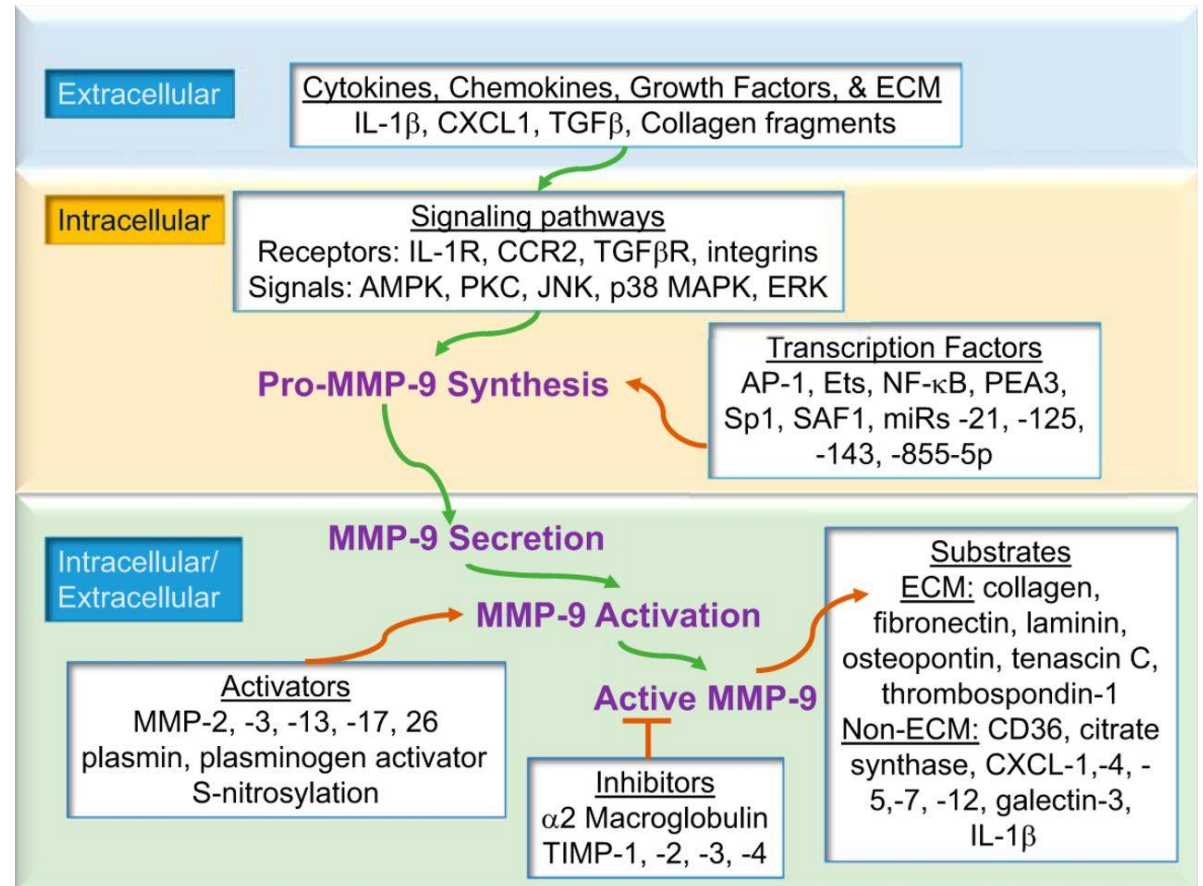
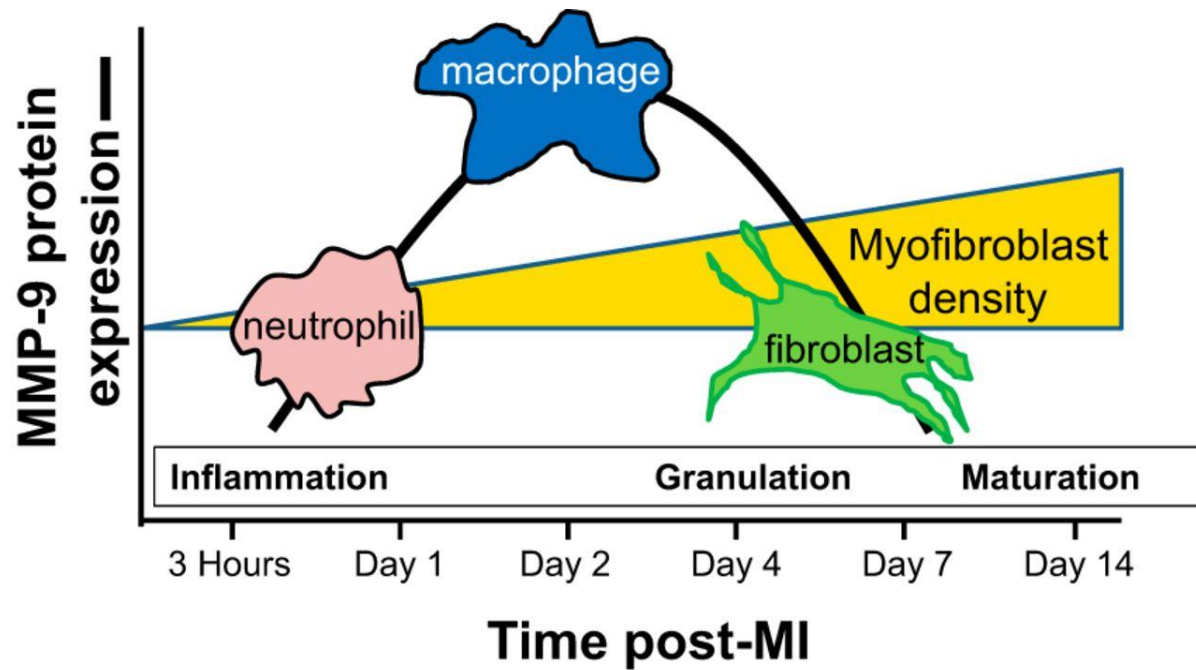


SZÍVINFARKTUS (1)



<ul style="list-style-type: none"> • Contraction • Self-regeneration 	<ul style="list-style-type: none"> • Cardiomyocyte death • Chemokine/cytokine synthesis • Neutrophil infiltration • $Gr-1^{high}$ monocyte recruitment • Debris clearance • Preconditioning 	<ul style="list-style-type: none"> • Inhibition of inflammation • $Gr-1^{low}$ monocyte infiltration • Lymphocyte recruitment • Angiogenesis • Myofibroblast differentiation • Collagen synthesis • MSC recruitment • Cardiac cell regeneration 	<ul style="list-style-type: none"> • Myofibroblast apoptosis • Formation of mature scar
	0-4 days	0 to 3-4 weeks	2-3 to 4-6 weeks
<ul style="list-style-type: none"> • Cardiomyocytes • $Gr-1^{low}$ monocytes • Fibroblasts • Cardiac progenitor cells 	<ul style="list-style-type: none"> • Dead cardiomyocytes • Neutrophils • $Gr-1^{high}$ monocytes • Fibroblasts 	<ul style="list-style-type: none"> • $Gr-1^{low}$ monocytes • EPCs • Lymphocytes • Fibroblasts • Cardiac progenitor cells • MSCs 	<ul style="list-style-type: none"> • $Gr-1^{low}$ monocytes • Lymphocytes • Fibroblasts
ECM	Fibrin-based provisional matrix	Collagen-based matrix	Mature and dense collagen-based matrix

SZÍVINFARKTUS (2)



miRNS EXPRESSZIÓS MINTÁZAT

Cardiac Development

↑ miRNA 1-2	—	Irx4, Hrt2, Hand1 and Gata6
miRNA 1	—	MyoD
miRNA 133	—	Mef2
miRNA 133a	—	SRF and cyclin D2
miRNA 17~92	—	STAT3

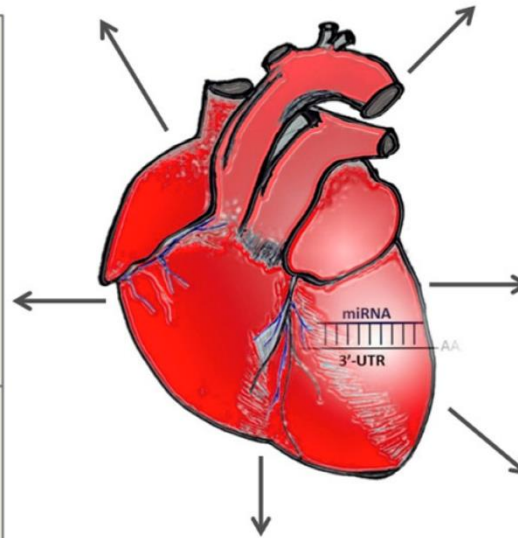
Stem/Progenitor Cells differentiation

↑ miRNA 21	—	SPRY2
miRNA 221	—	Bim
↓ miRNA 34a	—	Sirt1
miRNA 126	—	Spred1

Cardiac Hypertrophy

↑ miRNA 150	—	ACVR2A, c-myb
miRNA 208	—	THRAP1, Myostatin
miRNA 23a	—	MuRF1
miRNA 24	—	NLK
miRNA 21	—	SPRY2
miRNA 195	—	MO25
miRNA 199	—	Dyrk1a, Hif-1a, Sirt1

↓ miRNA 1	—	RASGAP, MEF2A, GATA4
miRNA 26b	—	GSK3β
miRNA 27a	—	Foxo3a
miRNA 143	—	ACE2
miRNA 29	—	TGFB3
miRNA 133	—	Nelf-A/WHSC2, Rho



Cardiac Regeneration

↑ miRNA 15a	—	Chek1
miRNA 17-92	—	PTEN
miRNA 195	—	Chek1

↓ miRNA 133	—	mps1, cdc37, PA2G4
miRNA 208	—	βMHC
miRNA 499	—	Sox6 and Rod1
miRNA 24	—	eNOS

Cardiac Arrhythmia

↑ miRNA 1	—	KCNJ2 GJA1
miRNA 133	—	KCNQ1 and SRF
miRNA 133a	—	Cx43
miRNA 212	—	Kir2.1
miRNA 17~92	—	Pitx2
miRNA 106b-25	—	Pitx2

↓ miRNA 150	—	AT1R
-------------	---	------

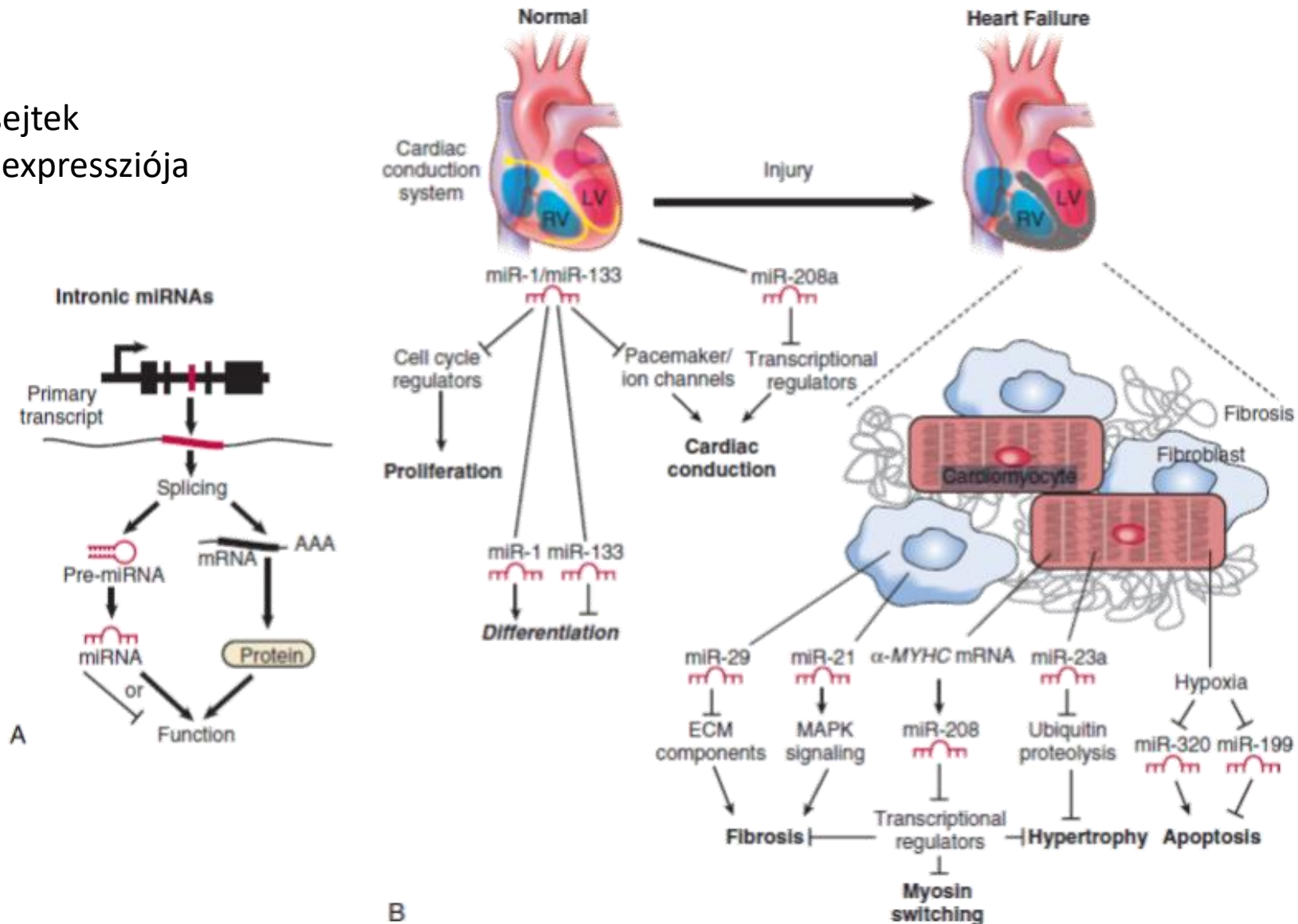
Cardiac Fibrosis

↑ miRNA 21	—	Spry1, PTEN
miRNA 133	—	CTGF

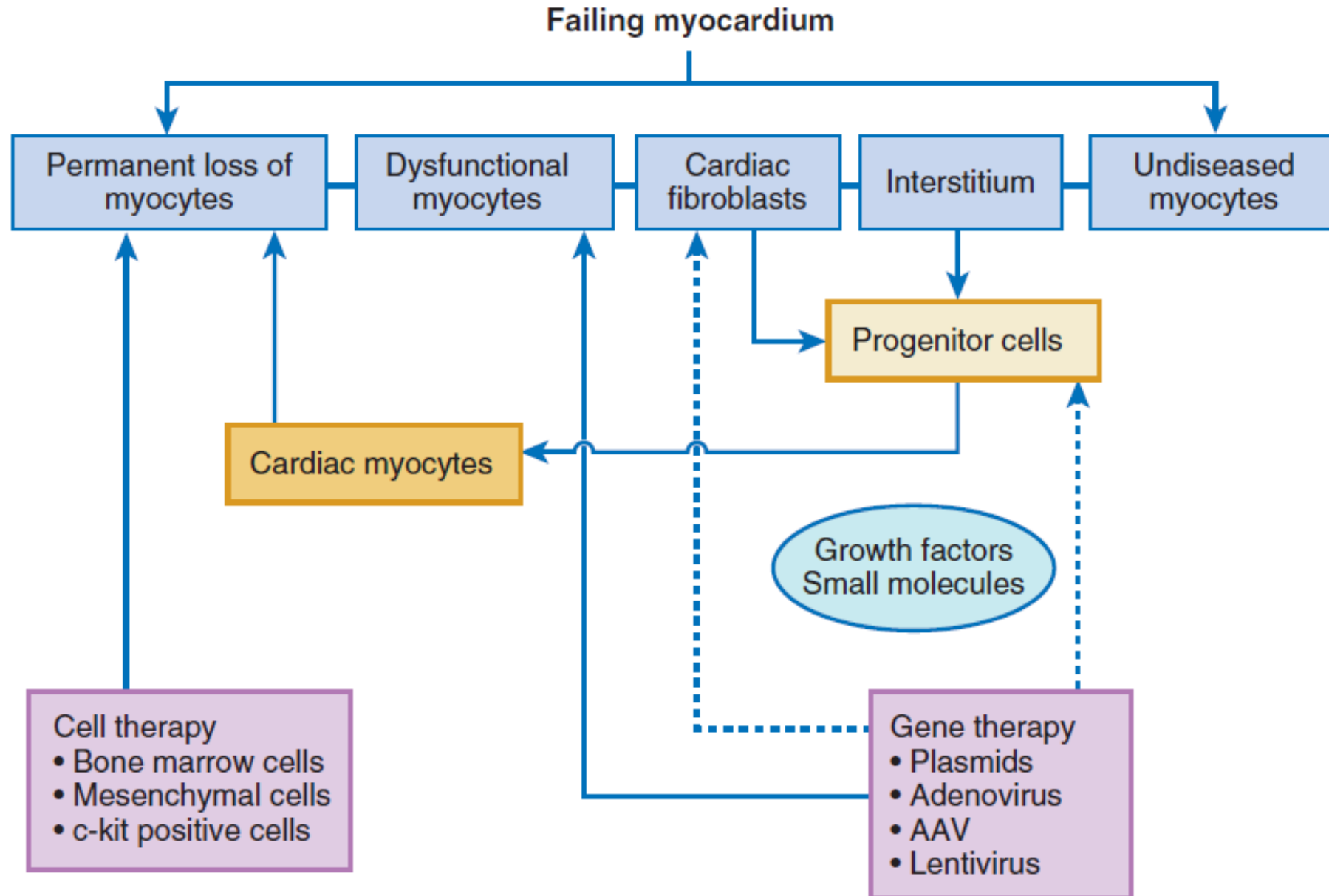
↓ miRNA 29	—	COL4A5
------------	---	--------

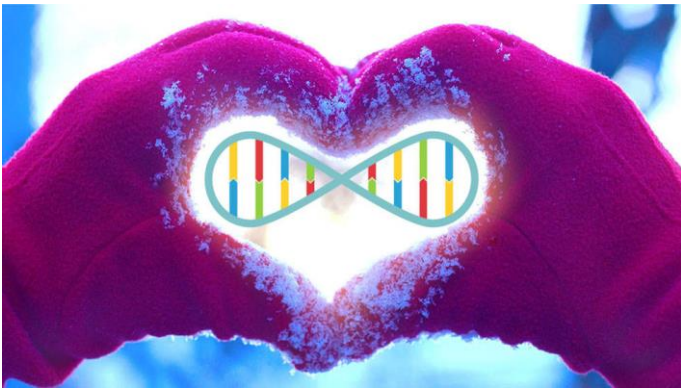
SZÍVELÉGTELENSÉG (1)

- ↑ pericardiális Treg sejtek
- ↑ embrionális gének expressziója

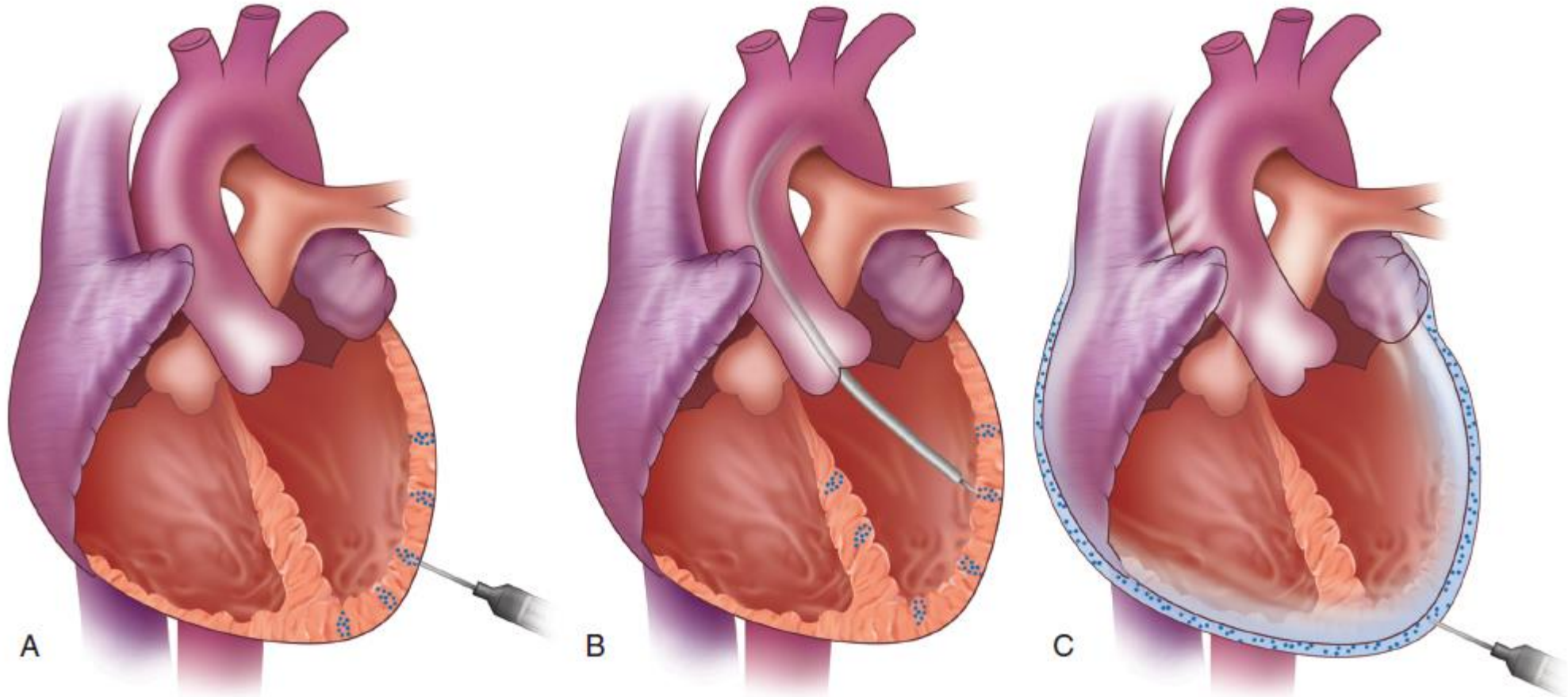


SZÍVELÉGTELENSÉG (2)





TERÁPIÁS LEHETŐSÉGEK (őssejt, EV, nanomedicina)





WRAP UP

Annual Meeting - ISEV2017
Toronto, Canada
18-21 May 2017
www.isev.org

ISEV 2017

tRNAs are increased in primary cardiomyocytes derived EVs

↑VCAM1+ EVs

↑↑TNF+ EVs

EC-EVs mobilize the monocytes from spleen in vivo mice

In human: Monocytes from spleen are mobilized after AMI

AMI modulates EV miRNA: ↑ miR:126-3p, 126-5p, 26b-5p, 1472, 23a-3p, 151a-3p, 374b-5p

CABG diabetes pericardial fluid EVs (CABG non diabetes, MVR)

Exosomes: CD63, Alix, TSG101 + Beltrami et al, 2017

RNA:

→ Proangiogenic response: let-7b-5p; hsa-mir-21-5p; has-mir126-3p (relative to cel-miR-39)

→ increase apoptosis in EC

→ comparing microRNA signature with the miRNA pattern in piece of atrium and piece of aortic tissues

MS:

→ ↑expression of apoptotic proteins in CABG DM PF

→ APAF1 protein (under control by let-7b-5p; protein presence validated by WB)

WB

CD63 APAF1 double positive EVs



KÖSZÖNÖM SZÉPEN A FIGYELMET!