

A fibrosis molekuláris pathogenezise

Szűcs Gabriella

Debreceni Egyetem

ÁOK Reumatológiai Tanszék

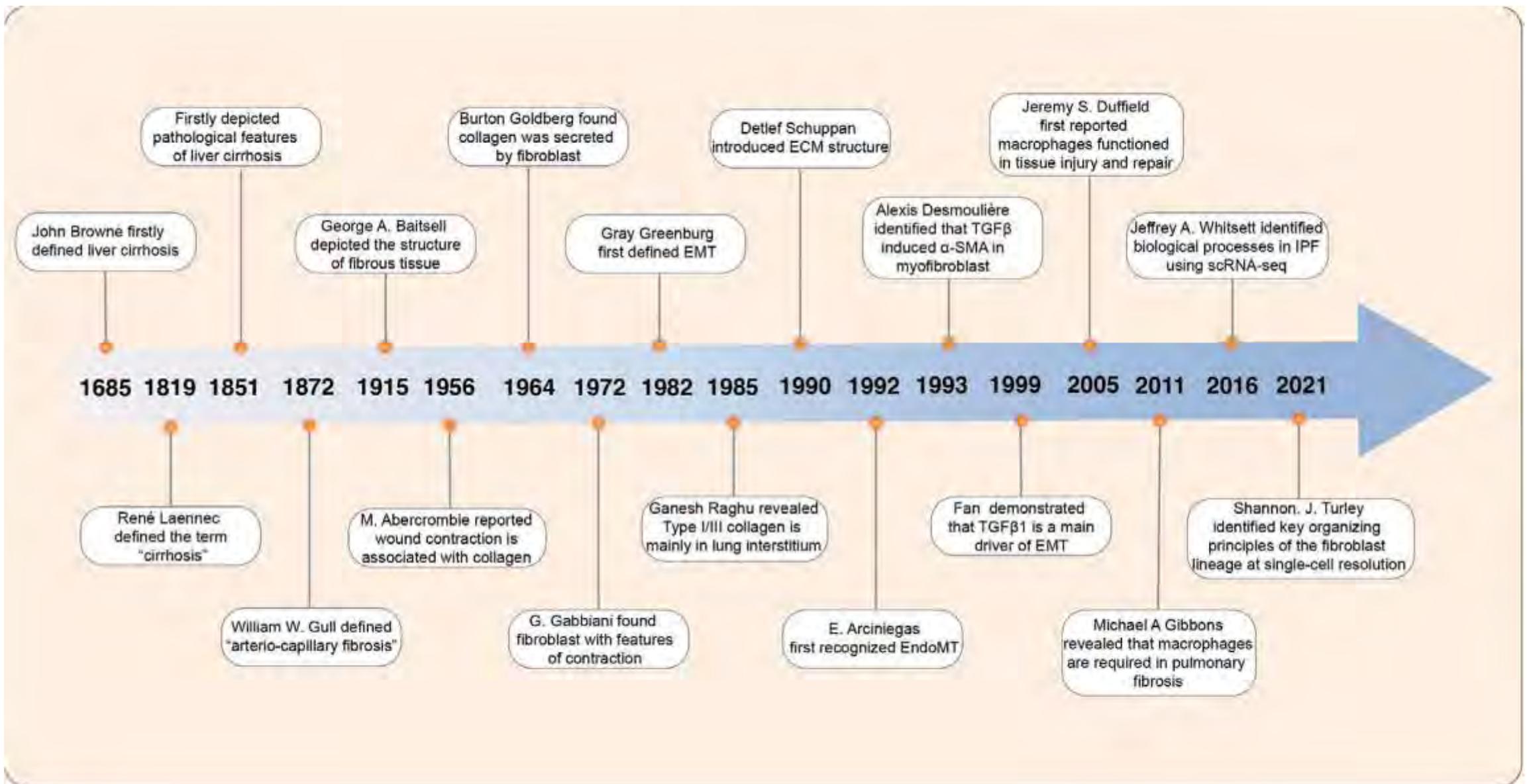
KK Reumatológiai és Immunológiai Klinika



**DEBRECENI
EGYETEM**



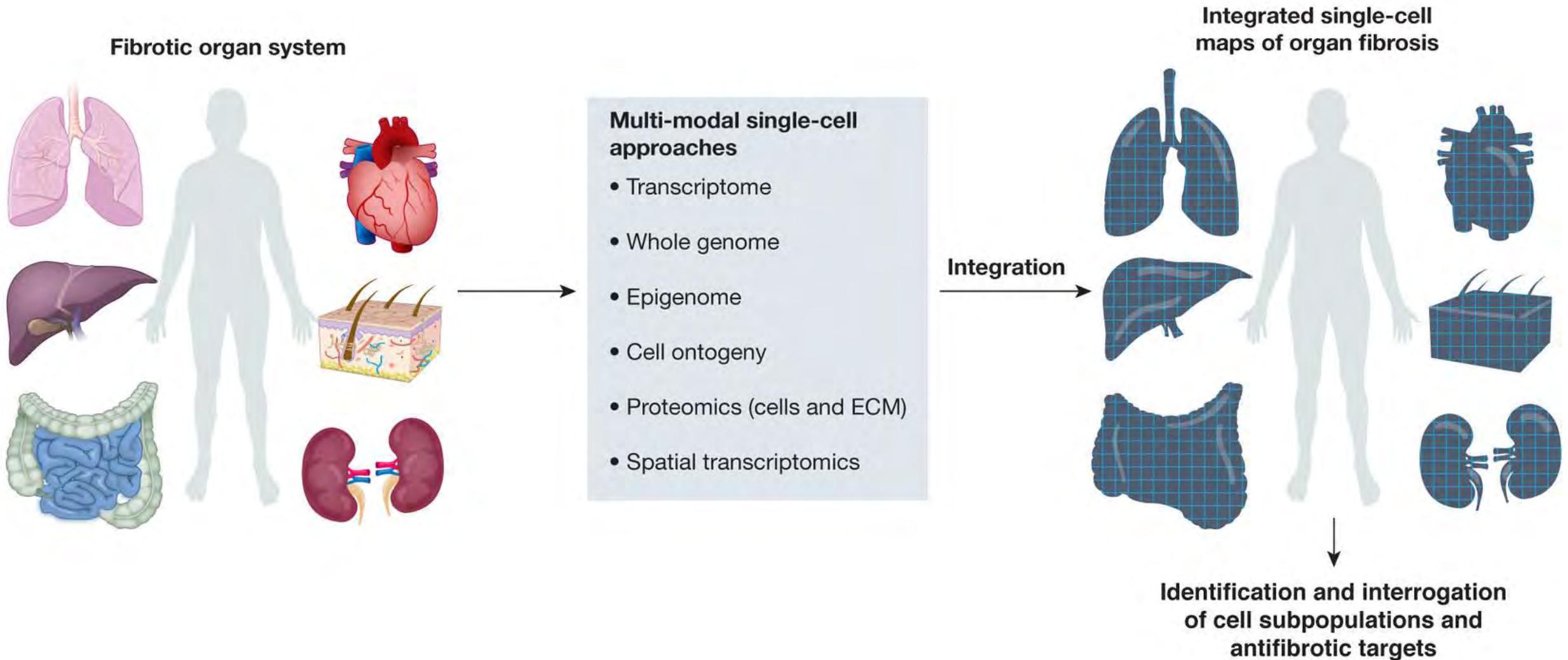
**Klinikai immunológia és allergológia I. Elmélet Tanfolyam 2026. március 09-17.
SE, Reumatológiai és Klinikai Immunológiai Klinika**



Timeline of the milestones in the investigation of fibrosis over the past 300 years

FIBROSIS: FROM MECHANISMS TO MEDICINES

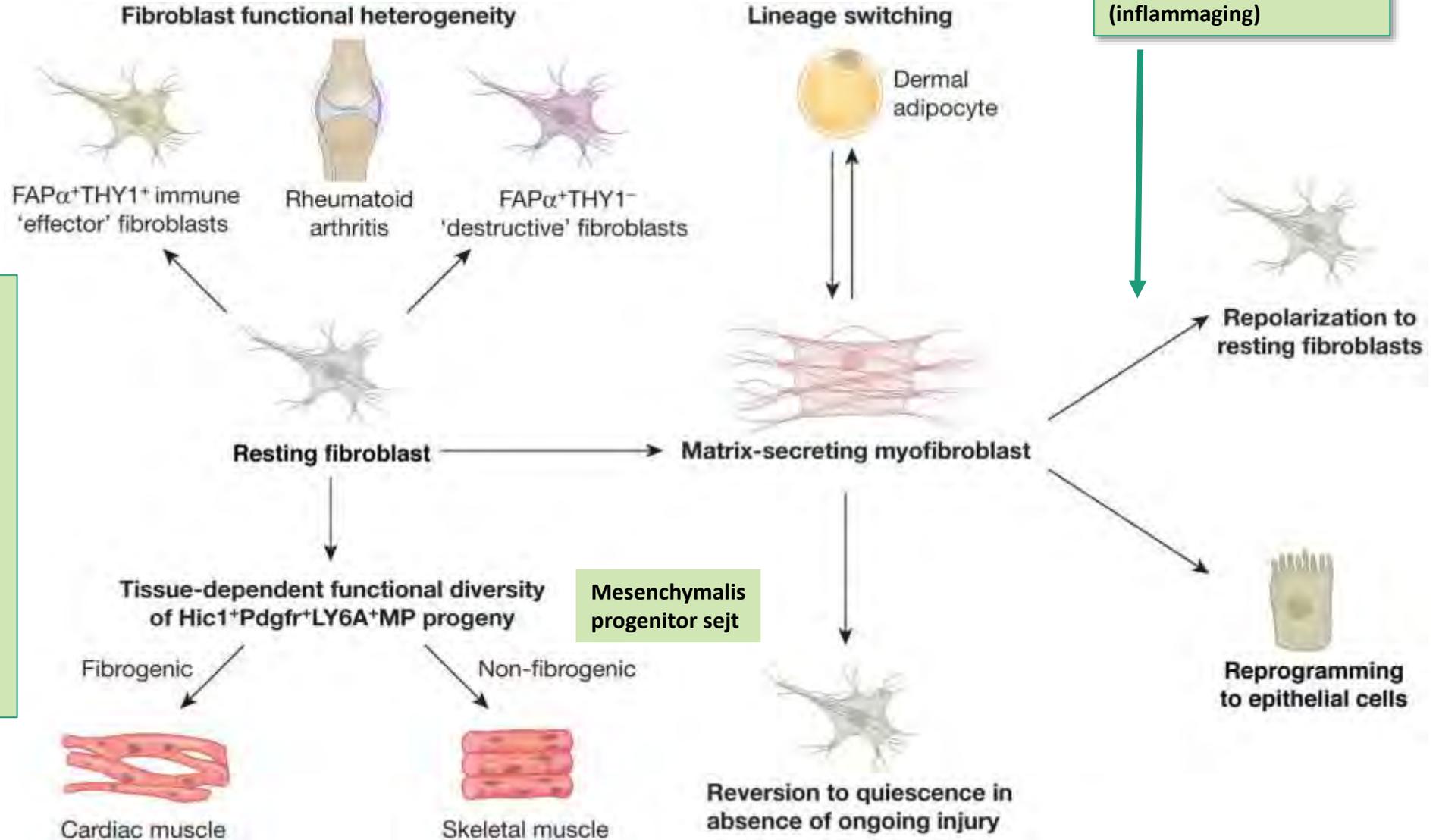
Henderson NC et al. Nature. 2020 November ; 587(7835): 555–566.



Az ipari világ halálzásának 45%-a

FIBROSIS: FROM MECHANISMS TO MEDICINES

Henderson NC et al. Nature. 2020 November ; 587(7835): 555–566.



Fibrotikus szövet kialakulása –
sérülés utáni normál repair

extracellular matrix (collagen,
fibronectin stb) accumulatio

Pl. bőrben a fascia fibroblastok
+ a környező egységek (erek,
macrophagok, perifériás erek)

Gyógyulás

Funkcionális fibroblast heterogenitás és plaszticitás

Senescence and tissue fibrosis: opportunities for therapeutic targeting

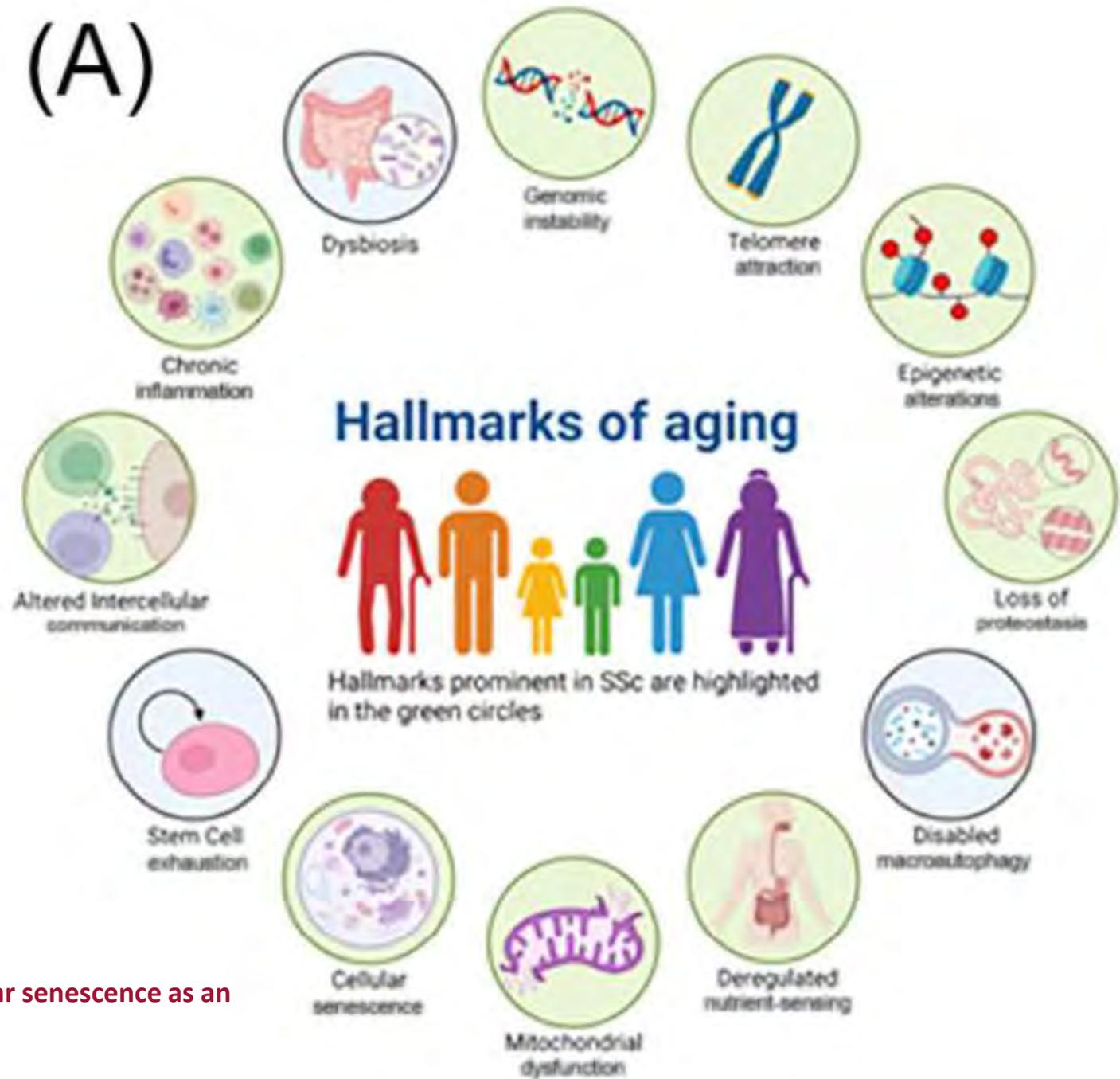
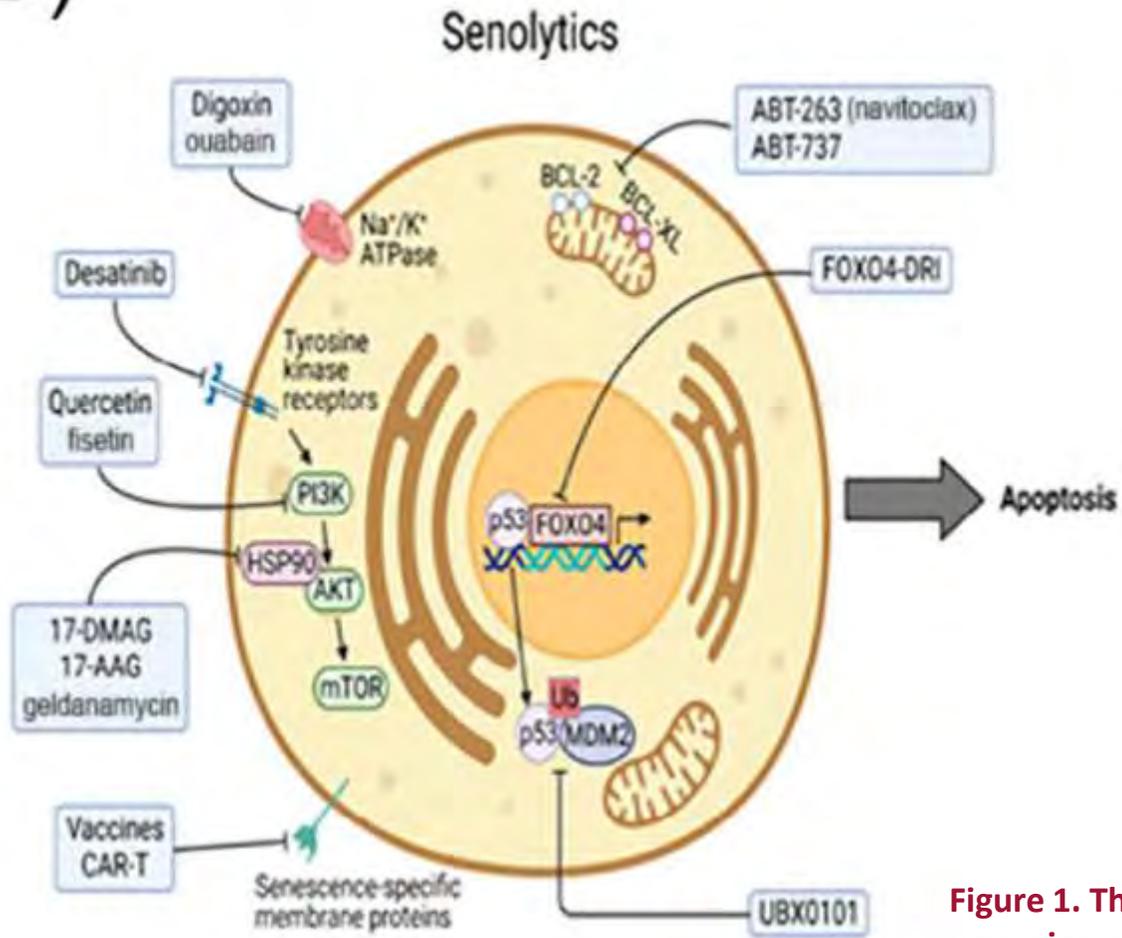


Figure 1. The 12 hallmarks of aging and targeting cellular senescence as an emerging novel therapeutic strategy for fibrosis

Senescence and tissue fibrosis: opportunities for therapeutic targeting

(B)



(C)

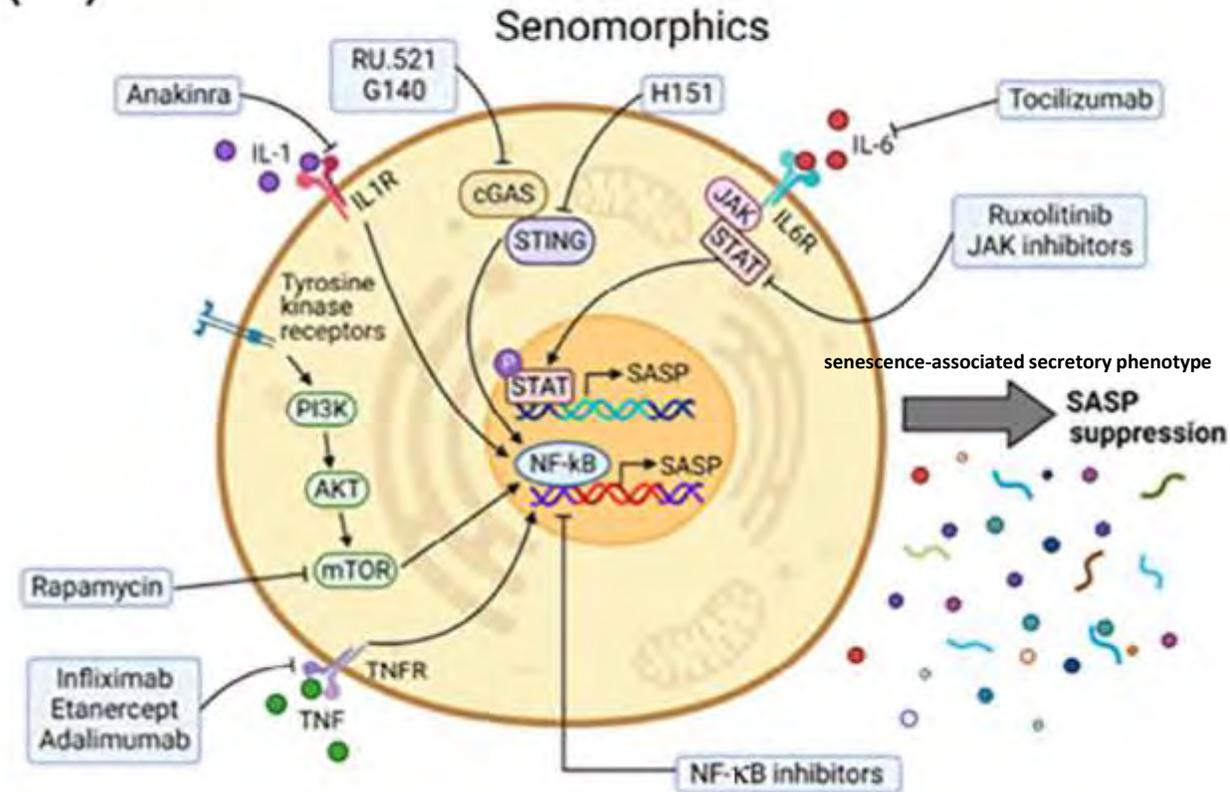
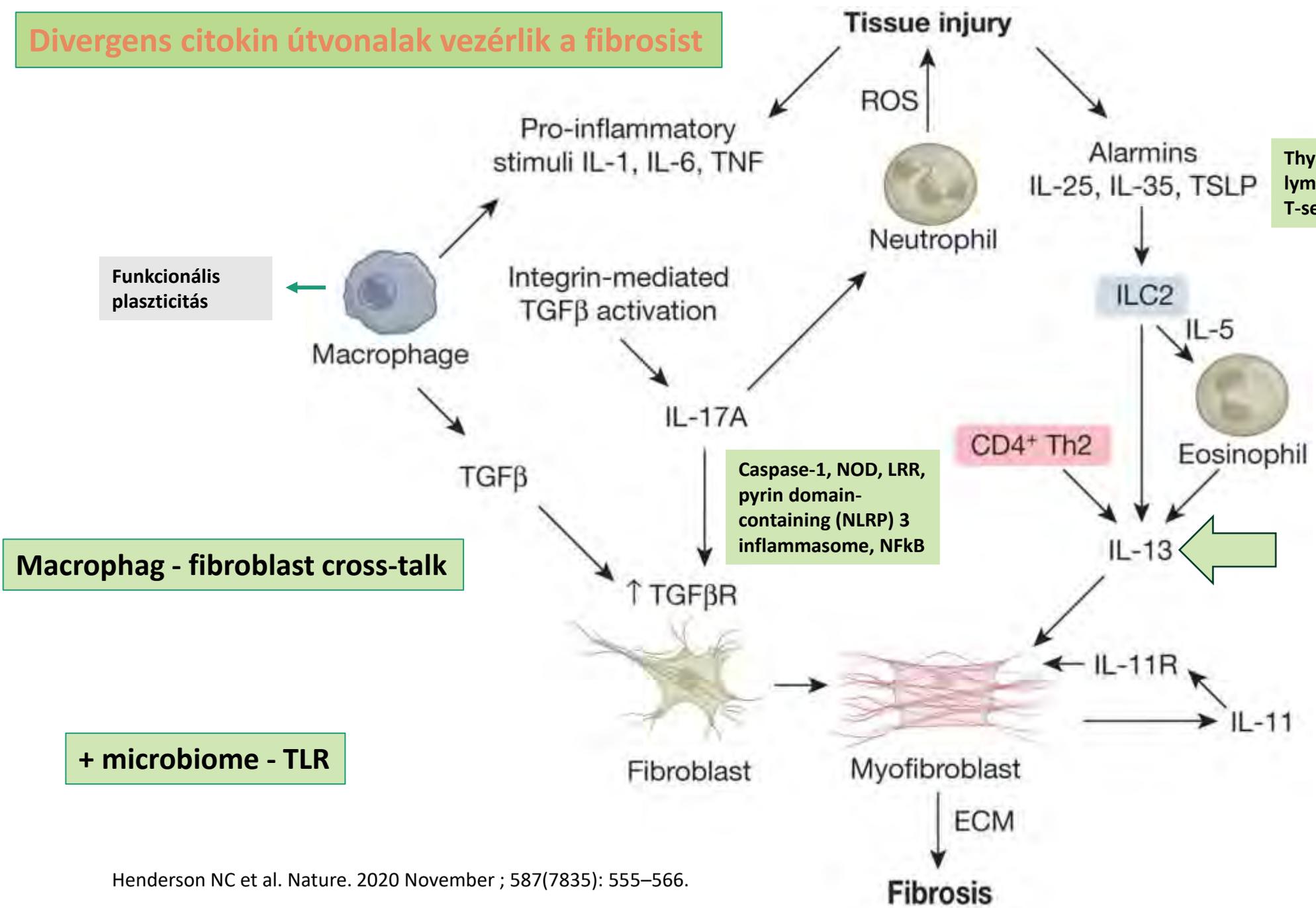
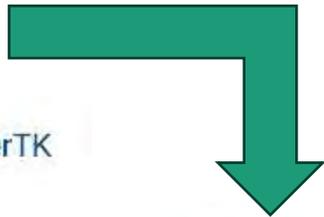
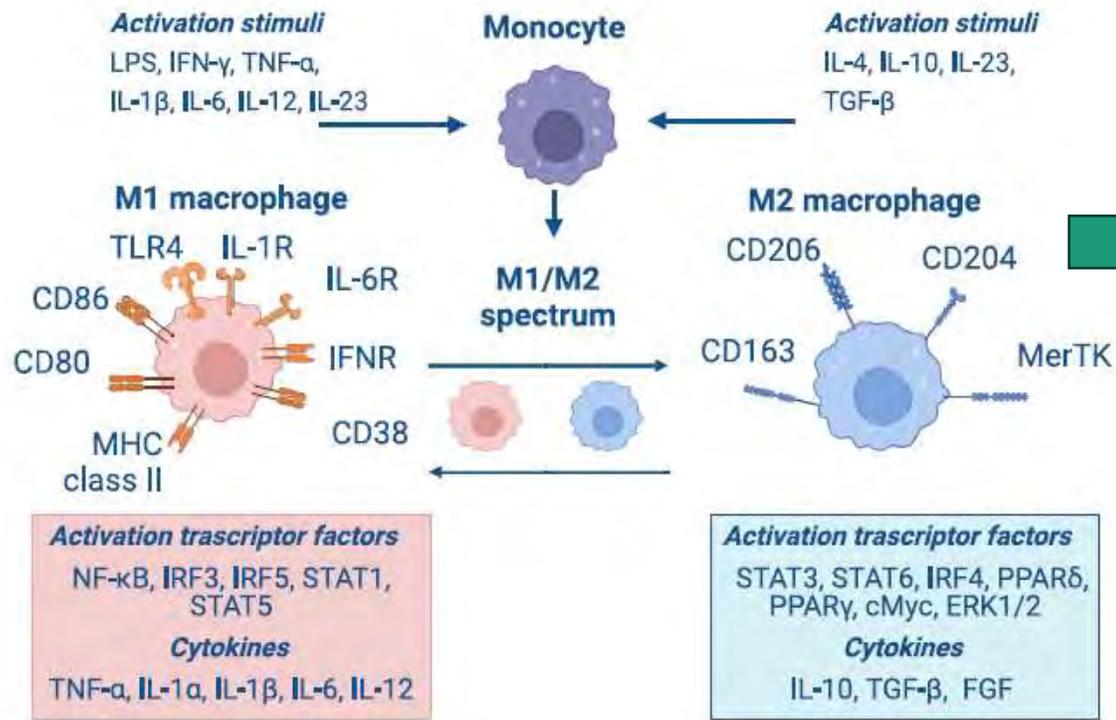


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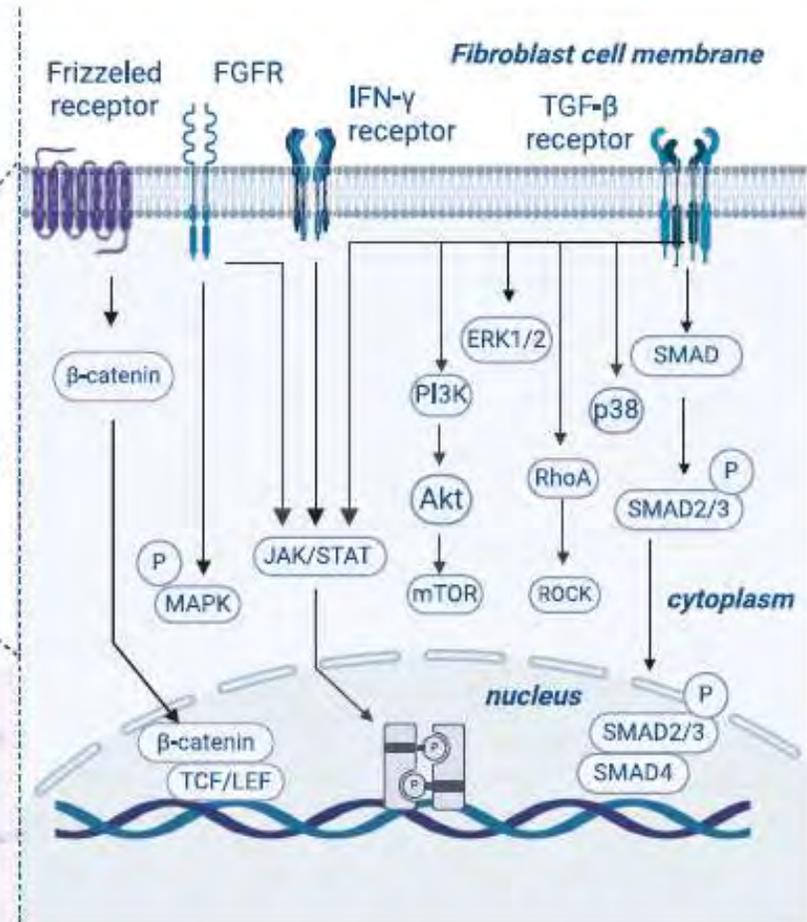
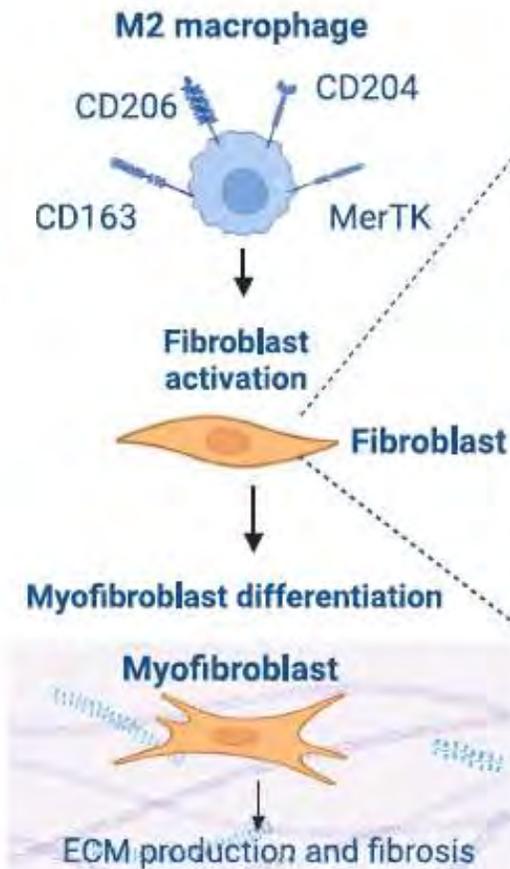
Divergens citokin útvonalak vezérik a fibrosist



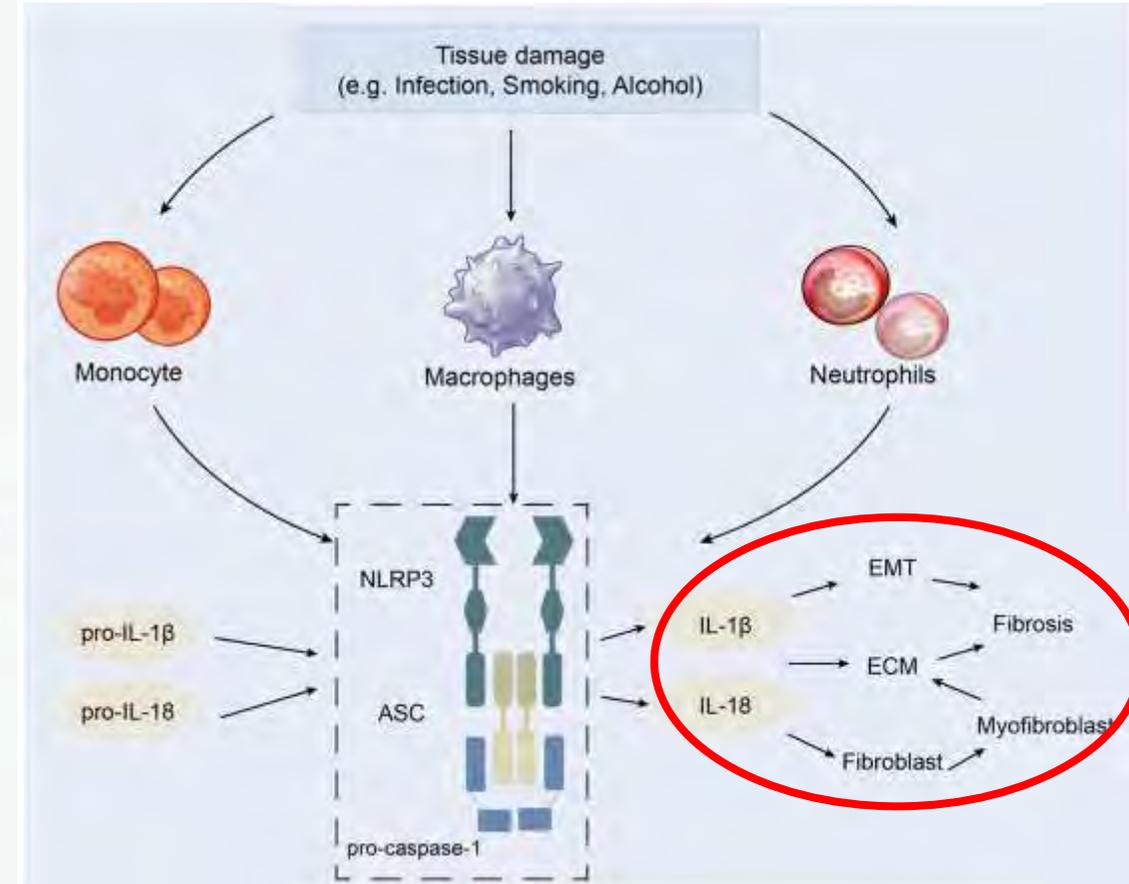
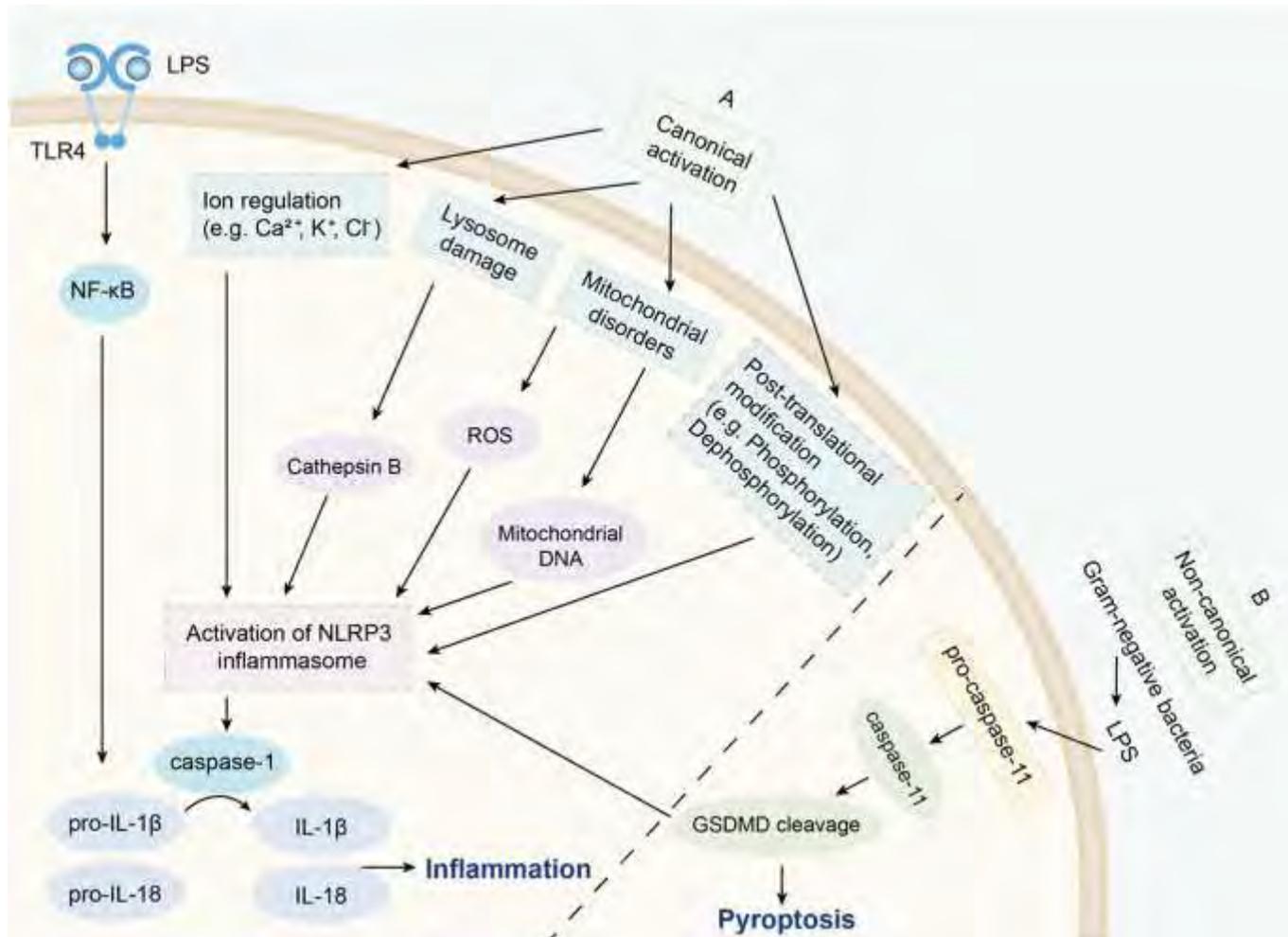
Monocyte-derived-macrophages



Macrophag - fibroblast cross-talk



The NLRP3 inflammasome in fibrosis and aging: The known unknowns



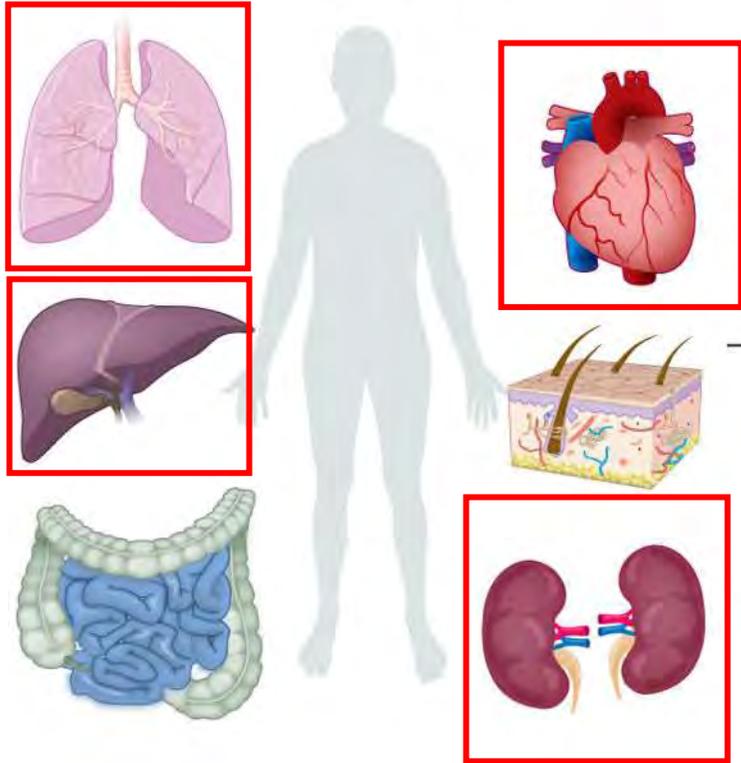
ASC: apoptosis-associated speck-like protein

Fig. 1. Regulatory mechanism of the NLRP3 inflammasome.

FIBROSIS: FROM MECHANISMS TO MEDICINES

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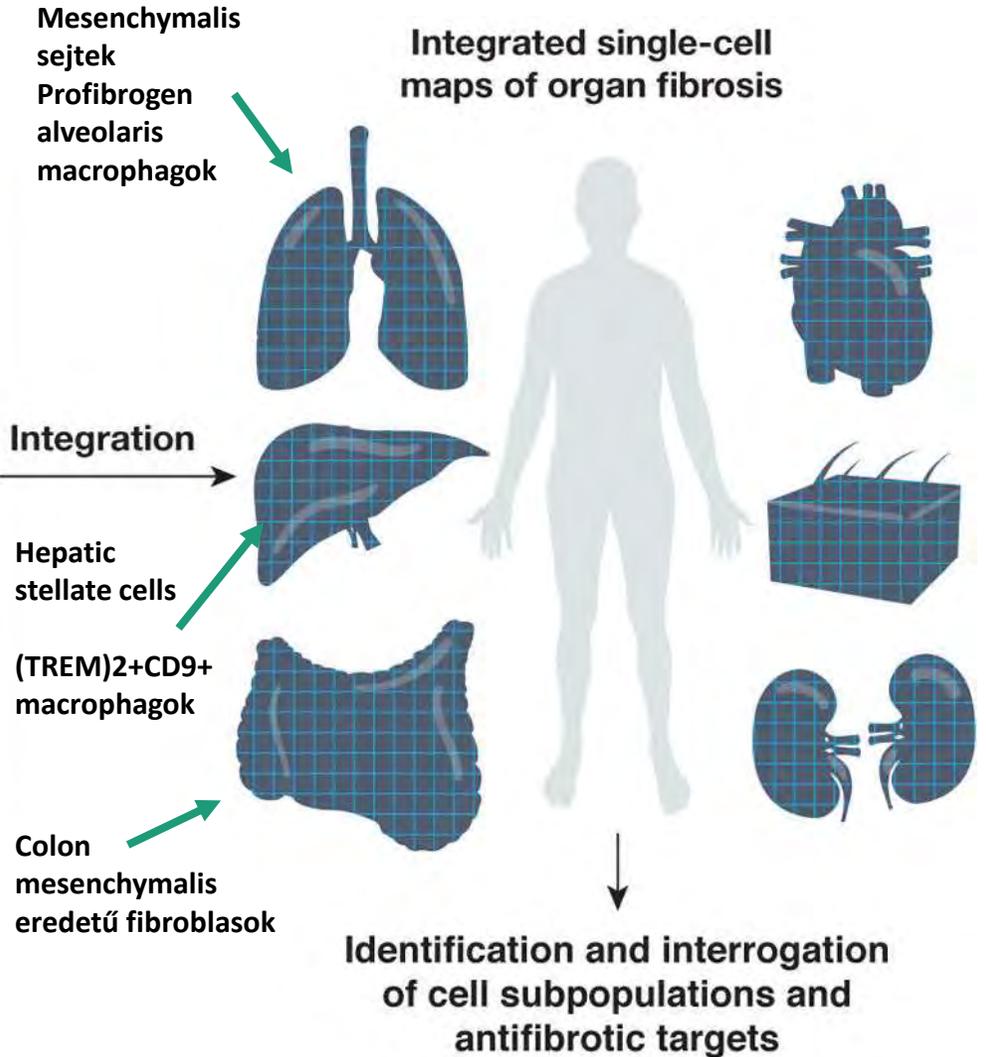
Fibrotic organ system



Szisztémás sclerosis
IgG4-related betegség

Multi-modal single-cell approaches

- Transcriptome
- Whole genome
- Epigenome
- Cell ontogeny
- Proteomics (cells and ECM)
- Spatial transcriptomics



Az ipari világ halálozásának 45%-a

Inflammation and immunity in IPF pathogenesis and treatment

Heukels P et al. Respiratory Medicine 147 (2019) 79–91.

Incidencia: 3-9/100 000
>65 év: 94/100 000,
prevalencia 494/100 000

Repetitív alveolaris epithelialis sérülés

+

Repair mechanizmusok diszregulációja

+

fibroblast diszfunkció



fibrosis

Genetikai vizsgálatok vizsgálatok:

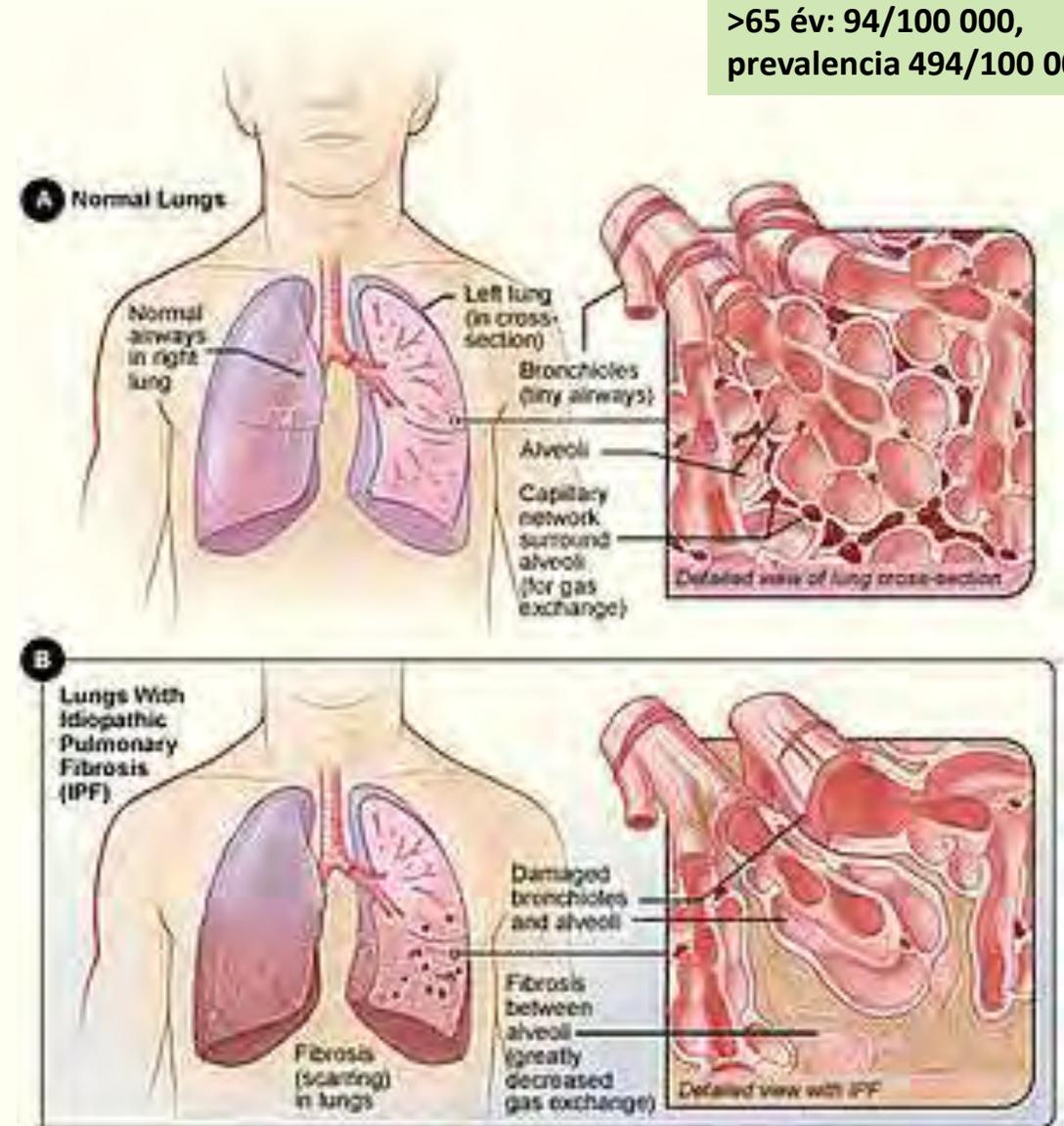
FAM13A (4q22), *DSP* (6p24), *OBFC1* (10q24)

WNT, TGF, NOTCH, sonic hedgehog (SHH)

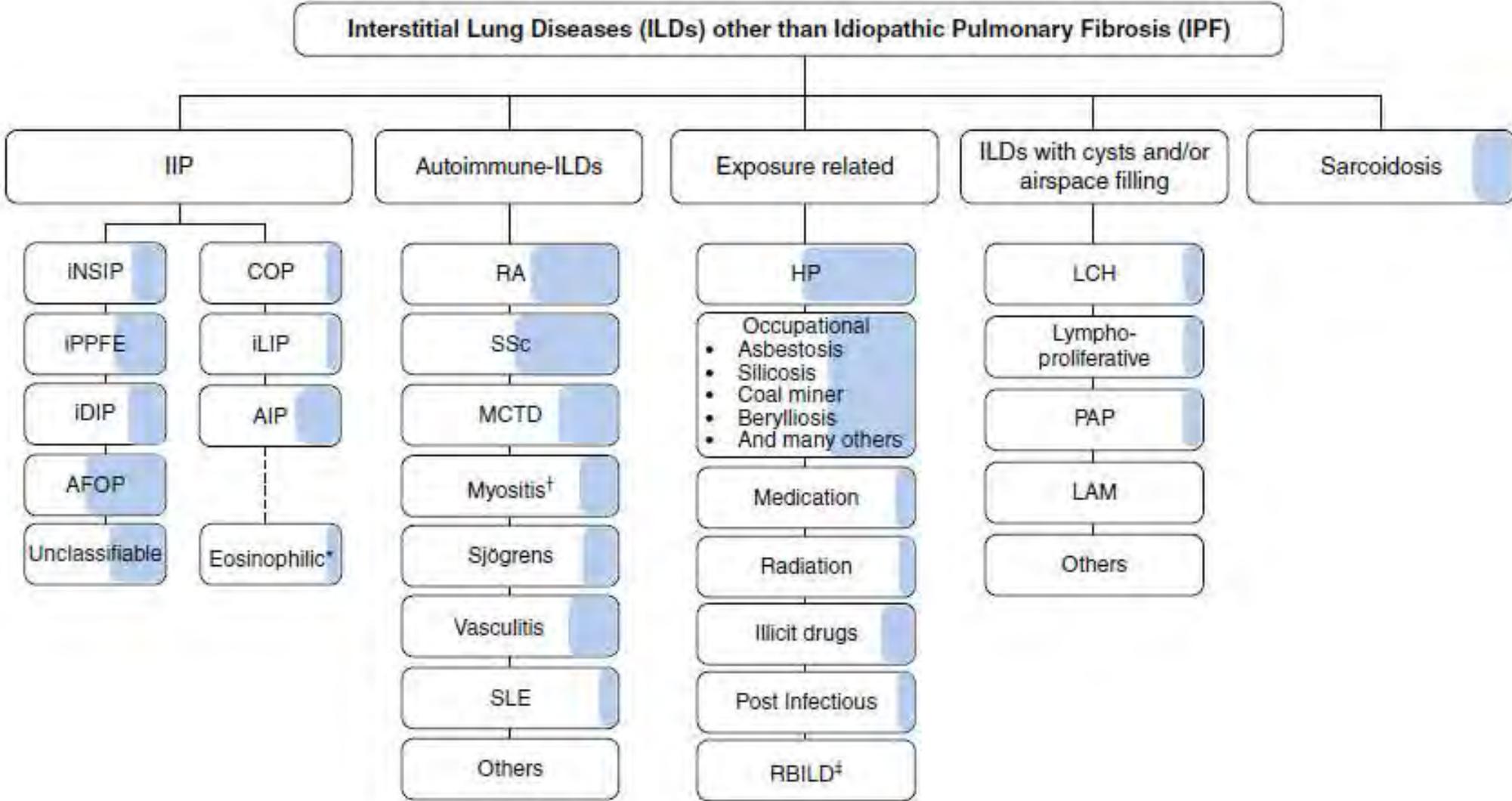
TOLLIP (Toll-interacting protein), the inhibitory protein of the Toll-like receptor (TLR)

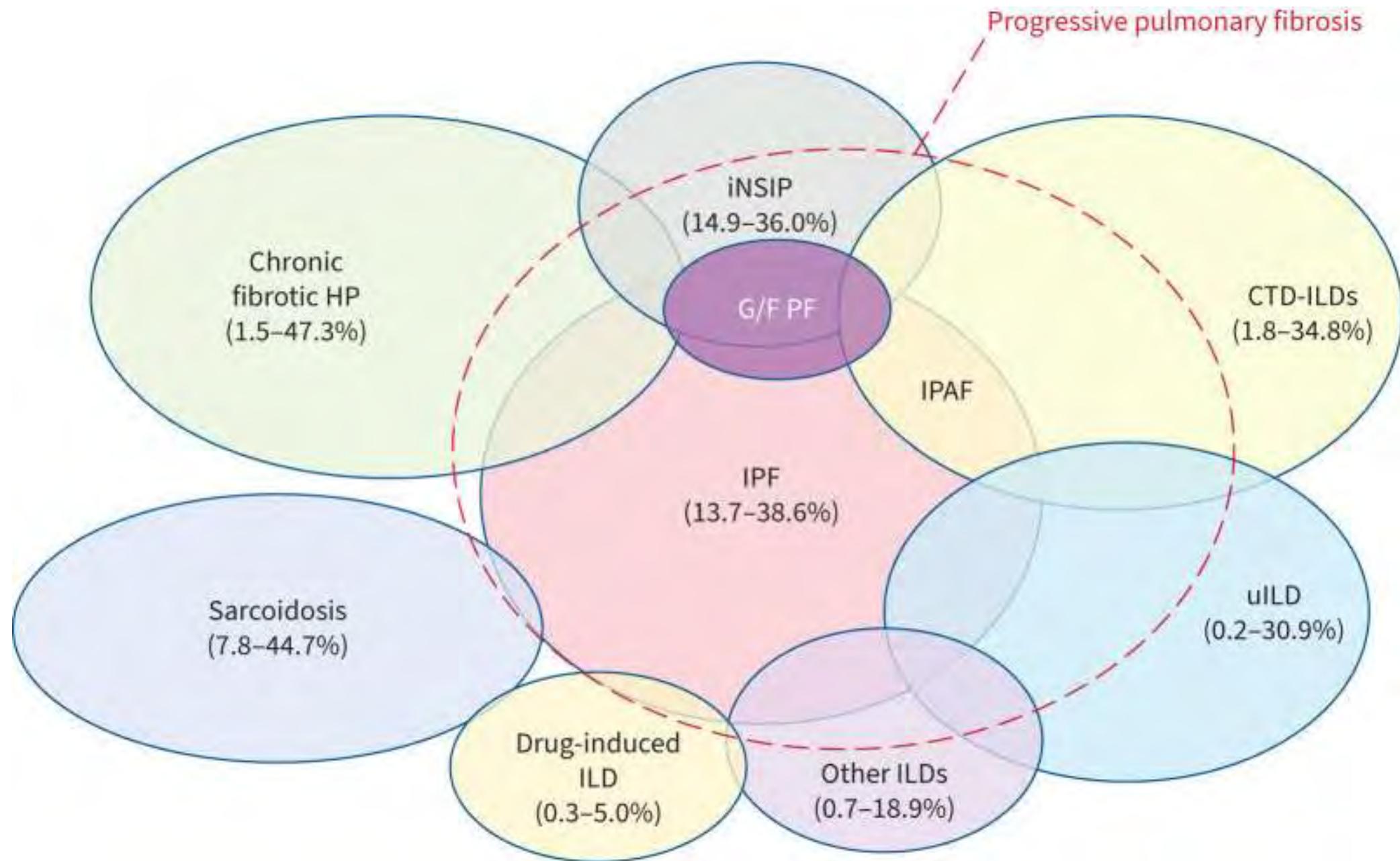
*DRB1*15:01* and *DQB1*06:02*

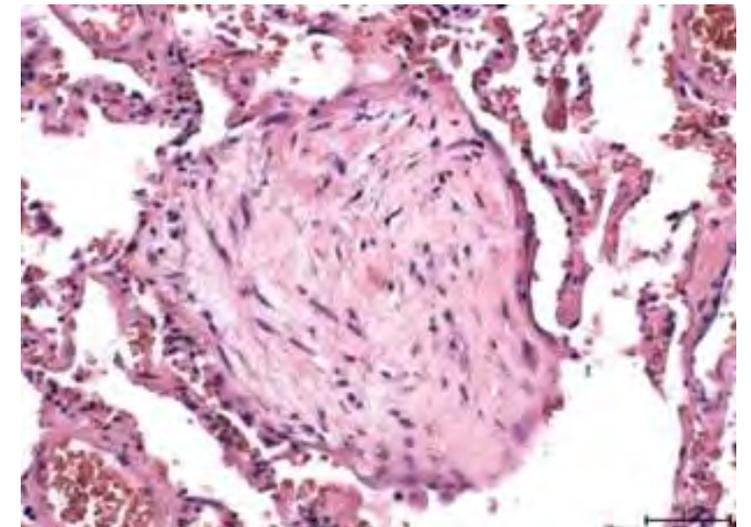
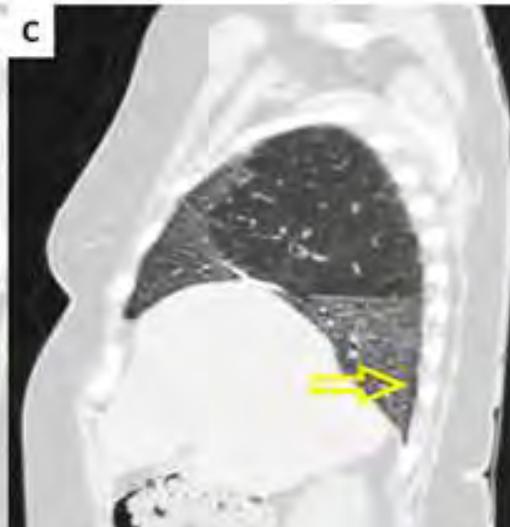
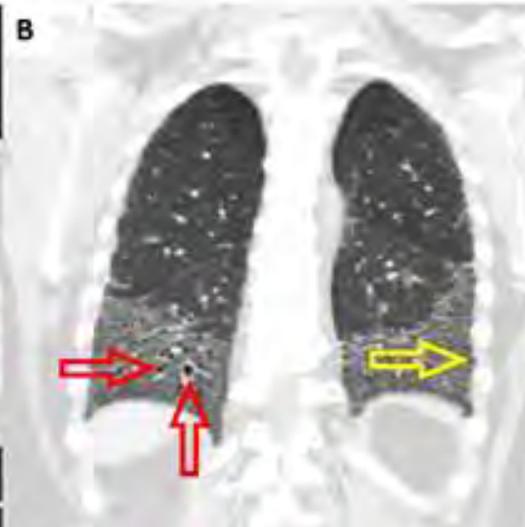
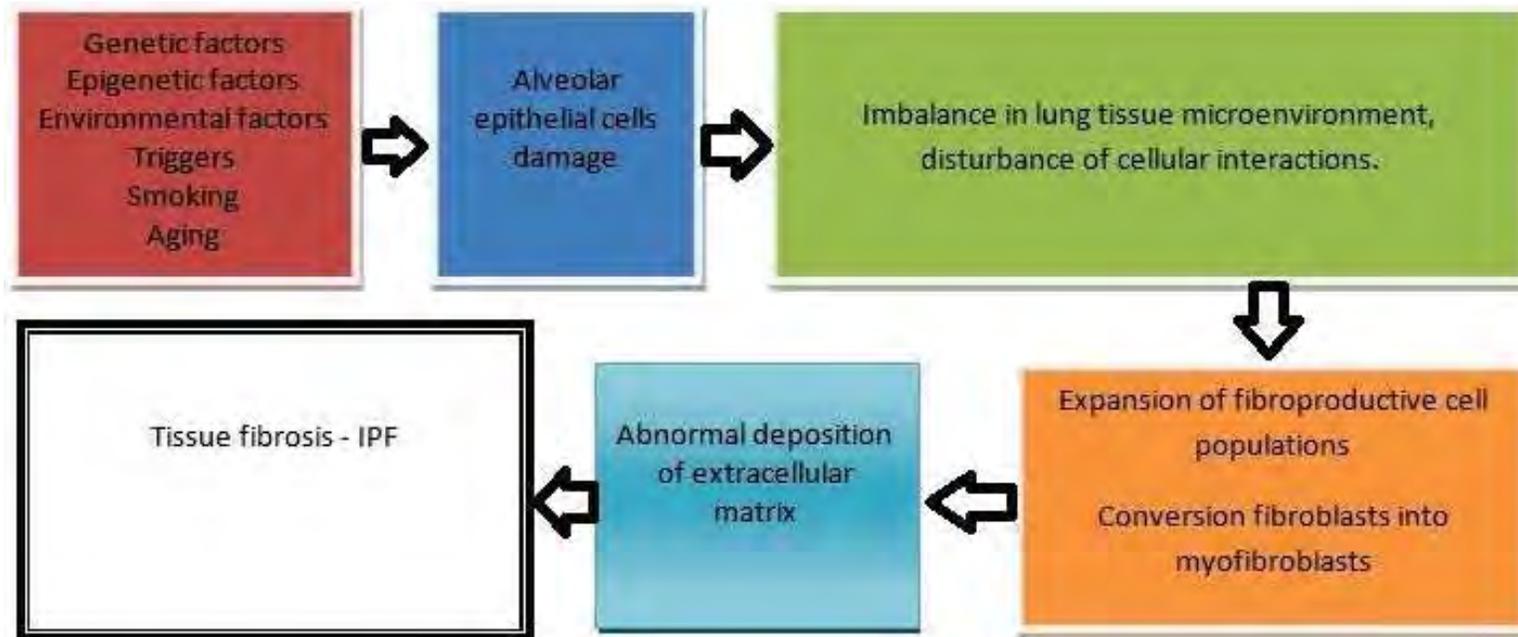
MUC5B gén



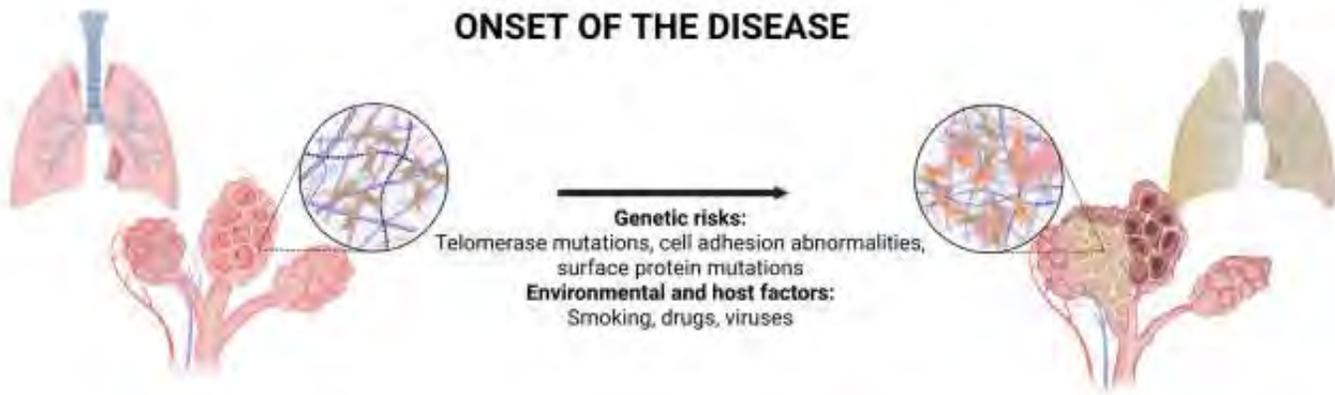
Az ILD klasszifikációja



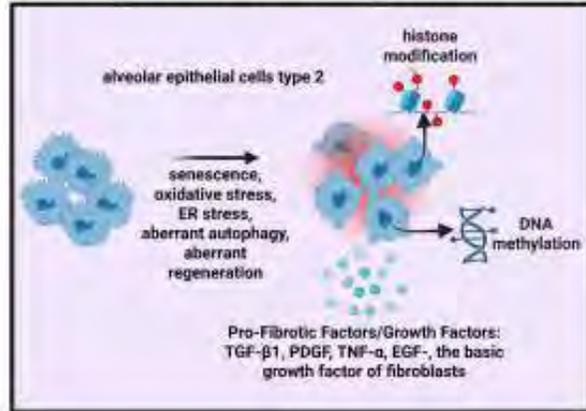




ONSET OF THE DISEASE



Epithelial Driven Lung Fibrosis



Inflammation Driven Lung Fibrosis

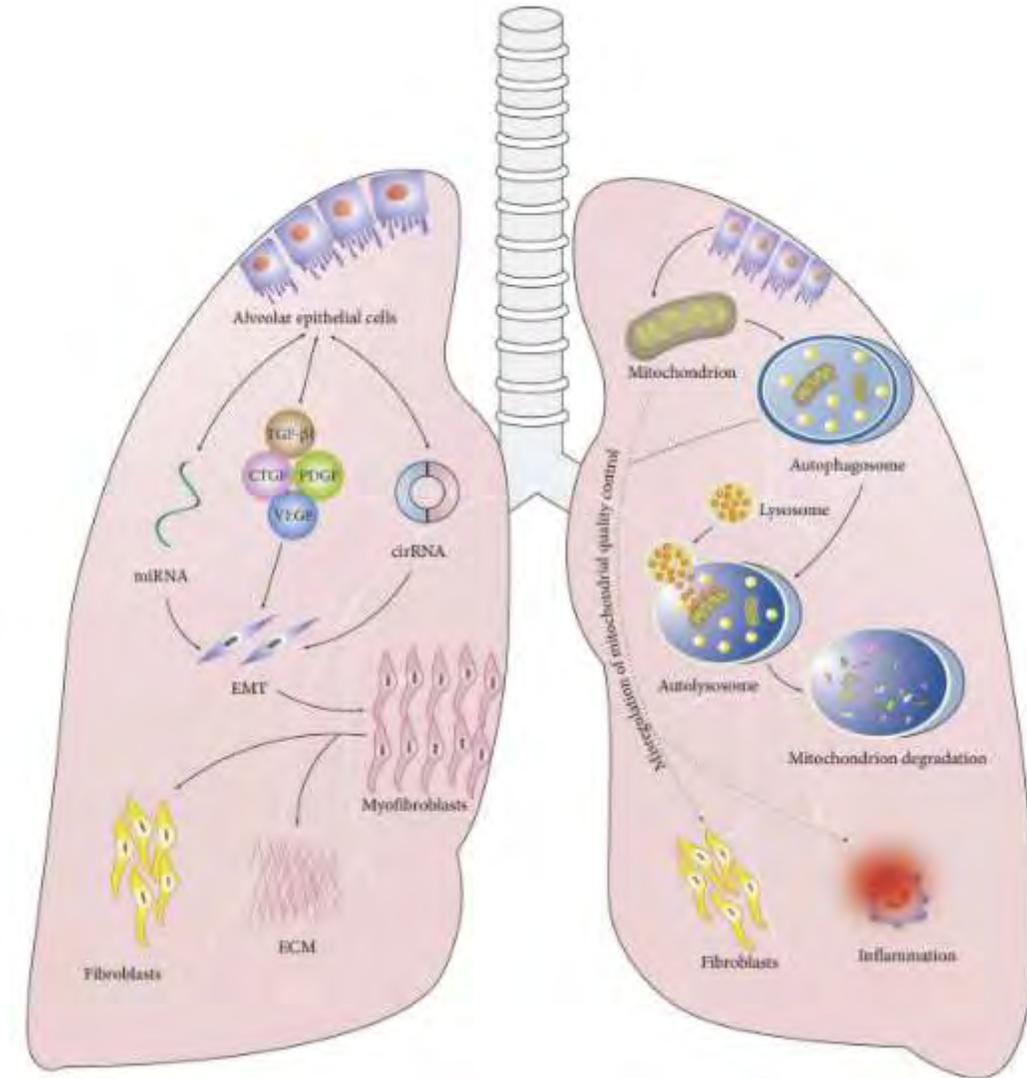
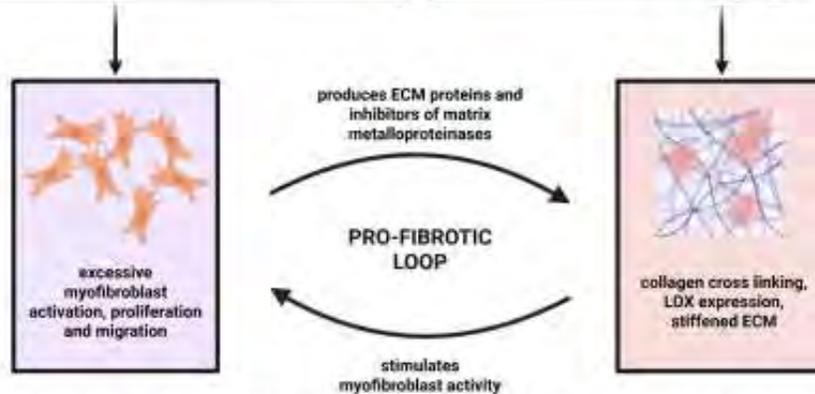
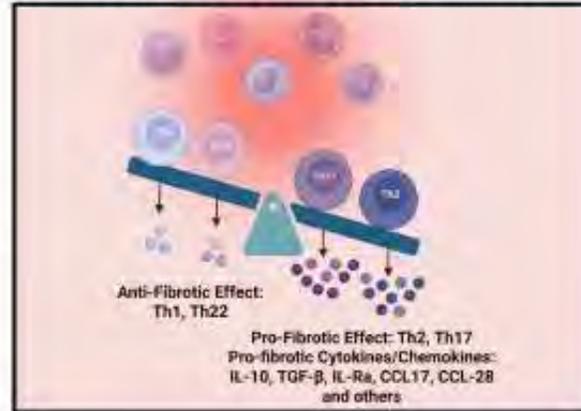


Fig. 1 Pathogenesis of lung fibrosis [27]. The scheme shows epithelia-driven lung fibrosis pathway and inflammation-driven lung fibrosis pathway

Fibrocyta – myofibroblast átalakulás

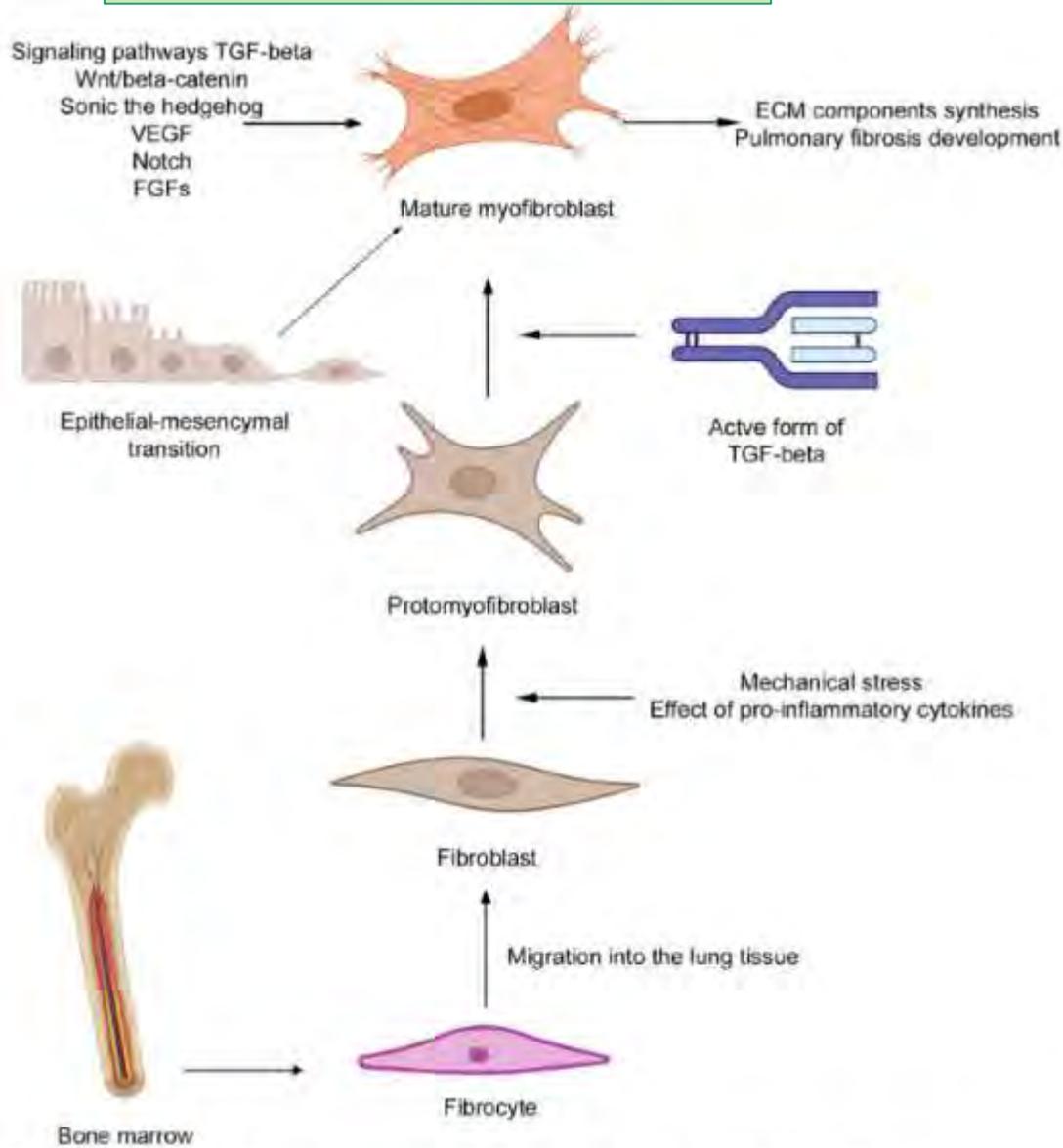


Figure 2. Evolution of fibrocyte to myofibroblast—main effector cell in pulmonary fibrosis development.

Szignál-transzdukció folyamata

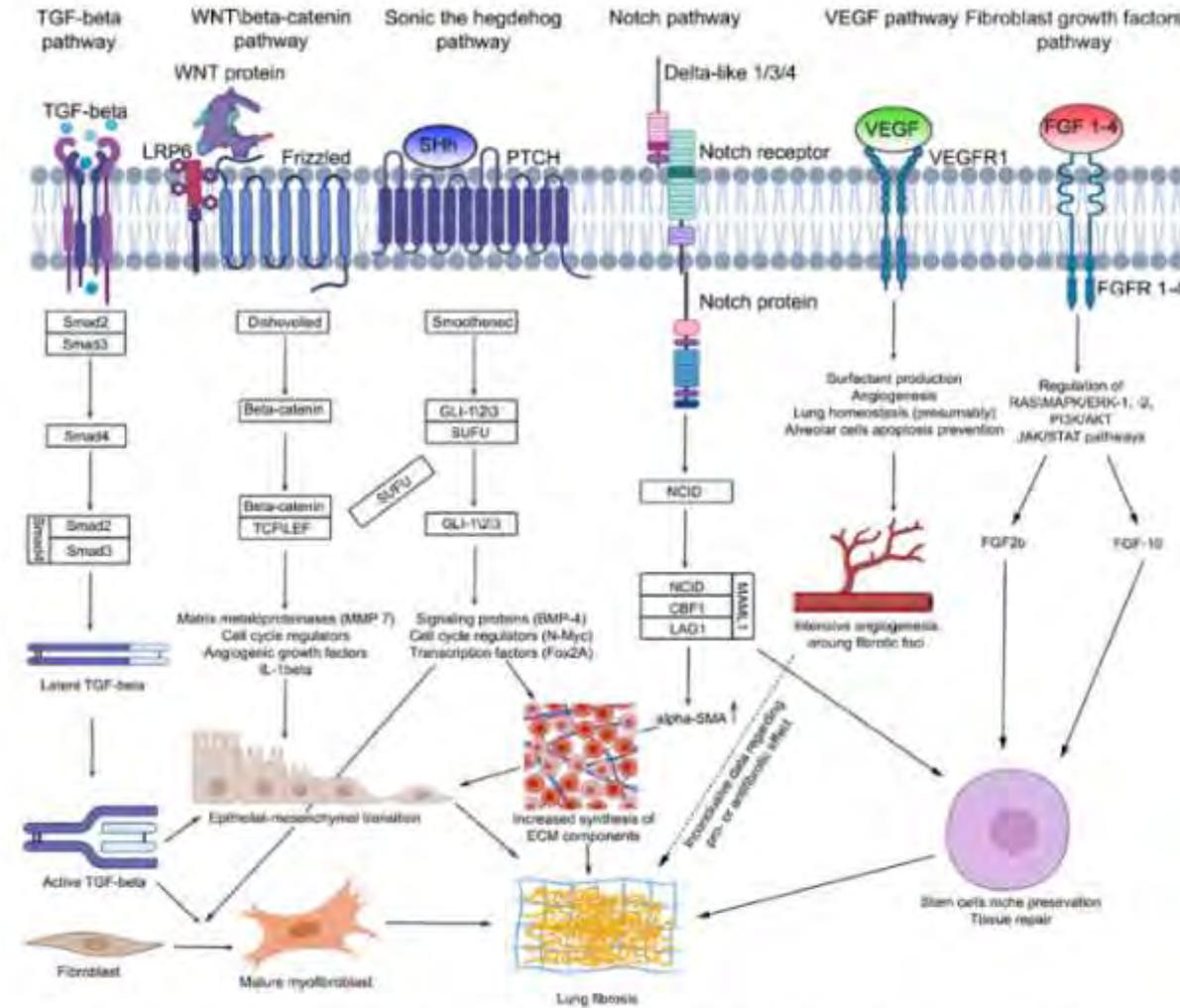


Figure 3. Overview of particular signaling pathways regulating pulmonary fibrosis development.

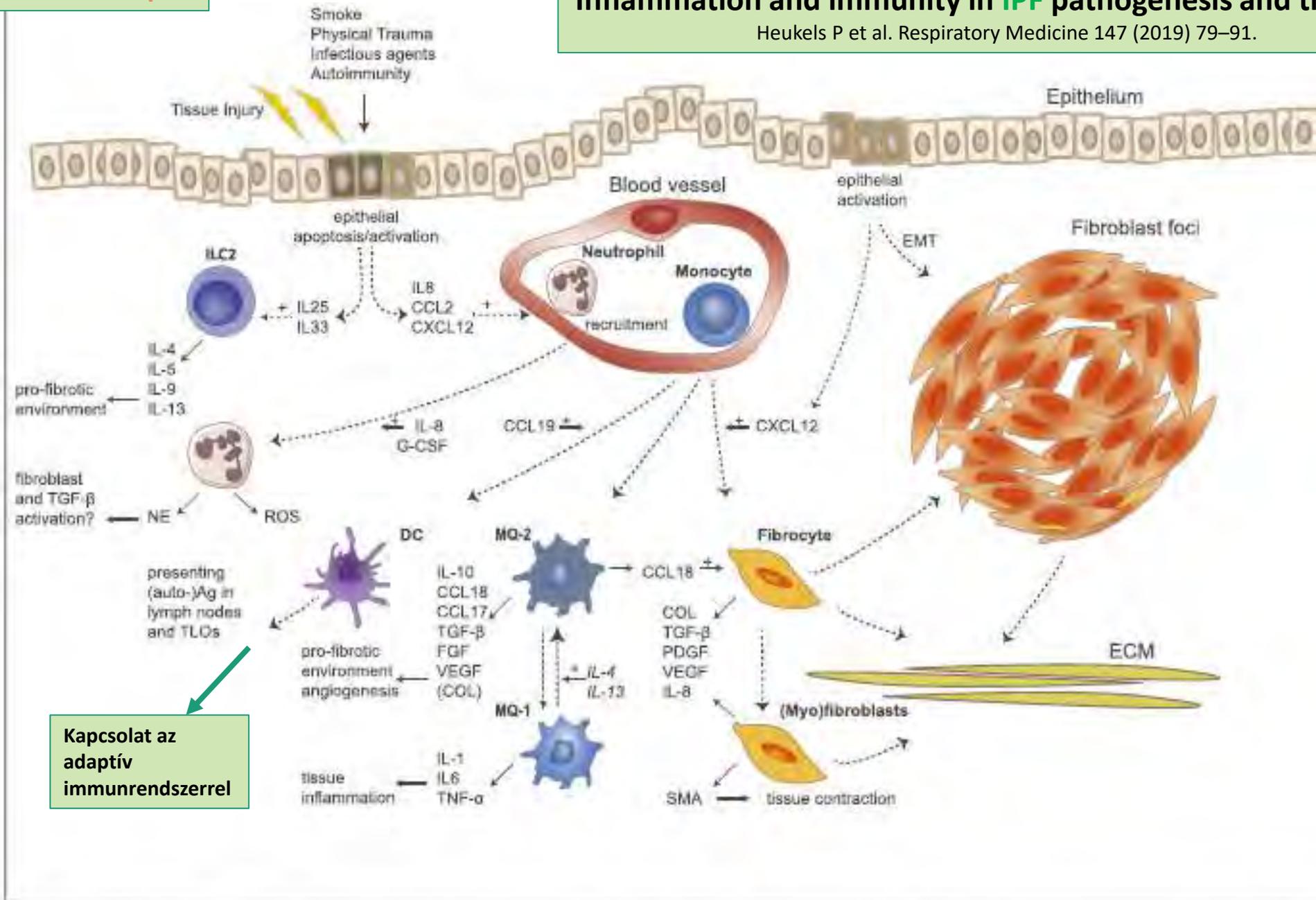


Fig. 1. Schematic overview of the role of the innate immune system in IPF pathogenesis. Abbreviations: EMT = epithelial–mesenchymal transition, II

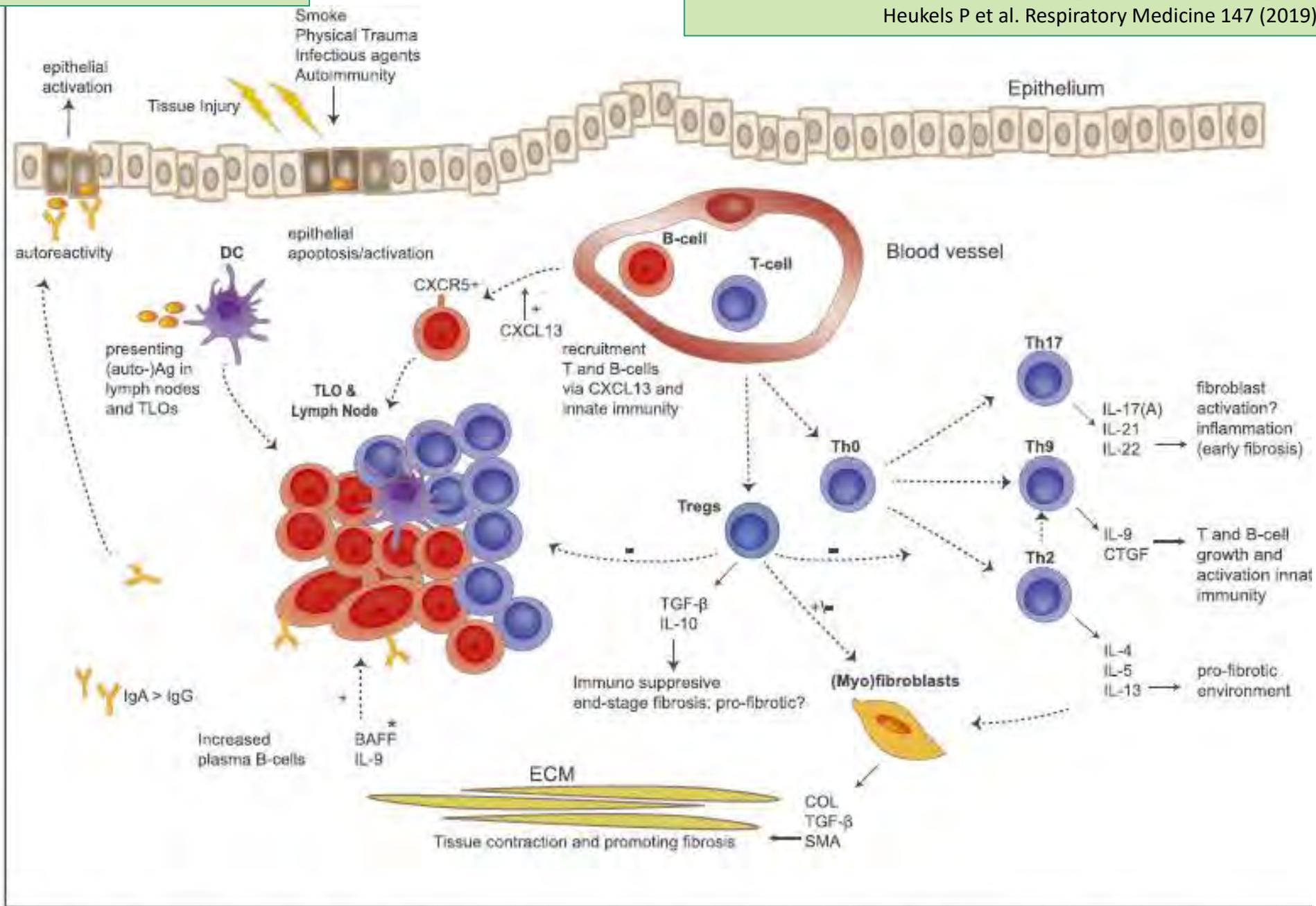
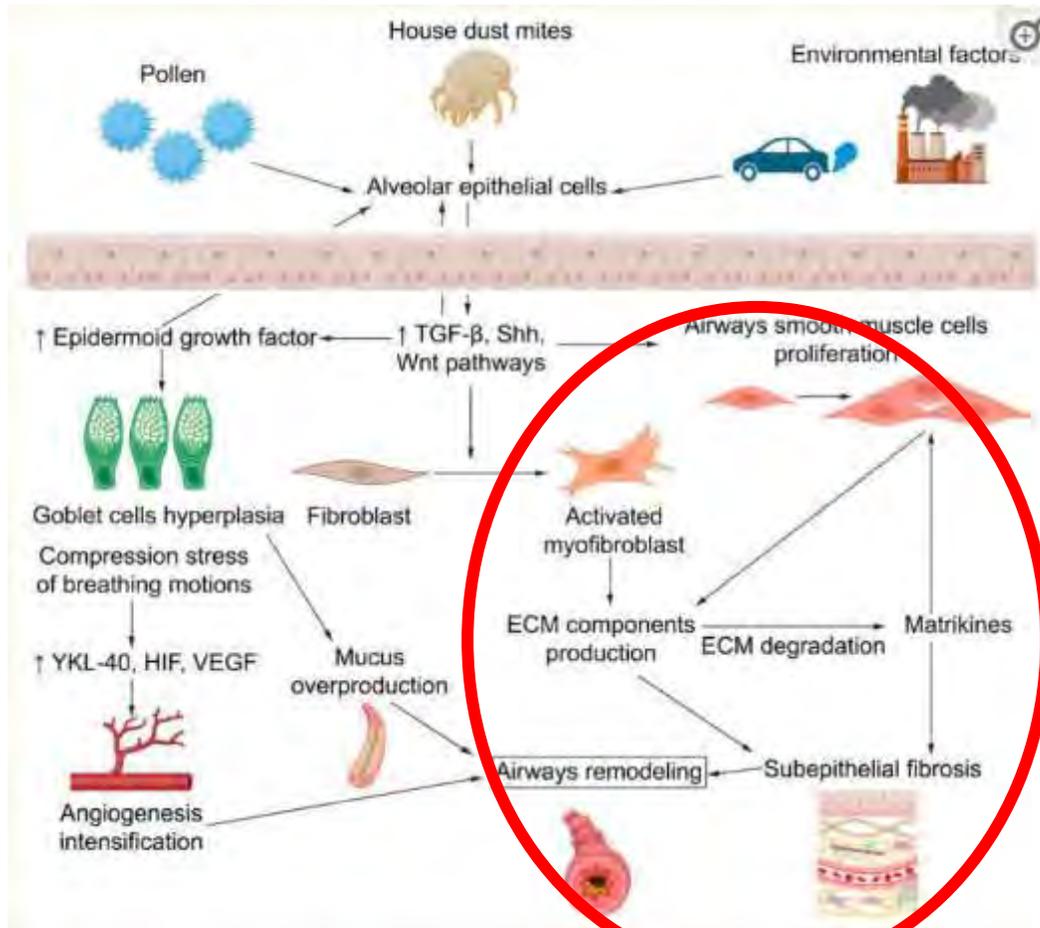


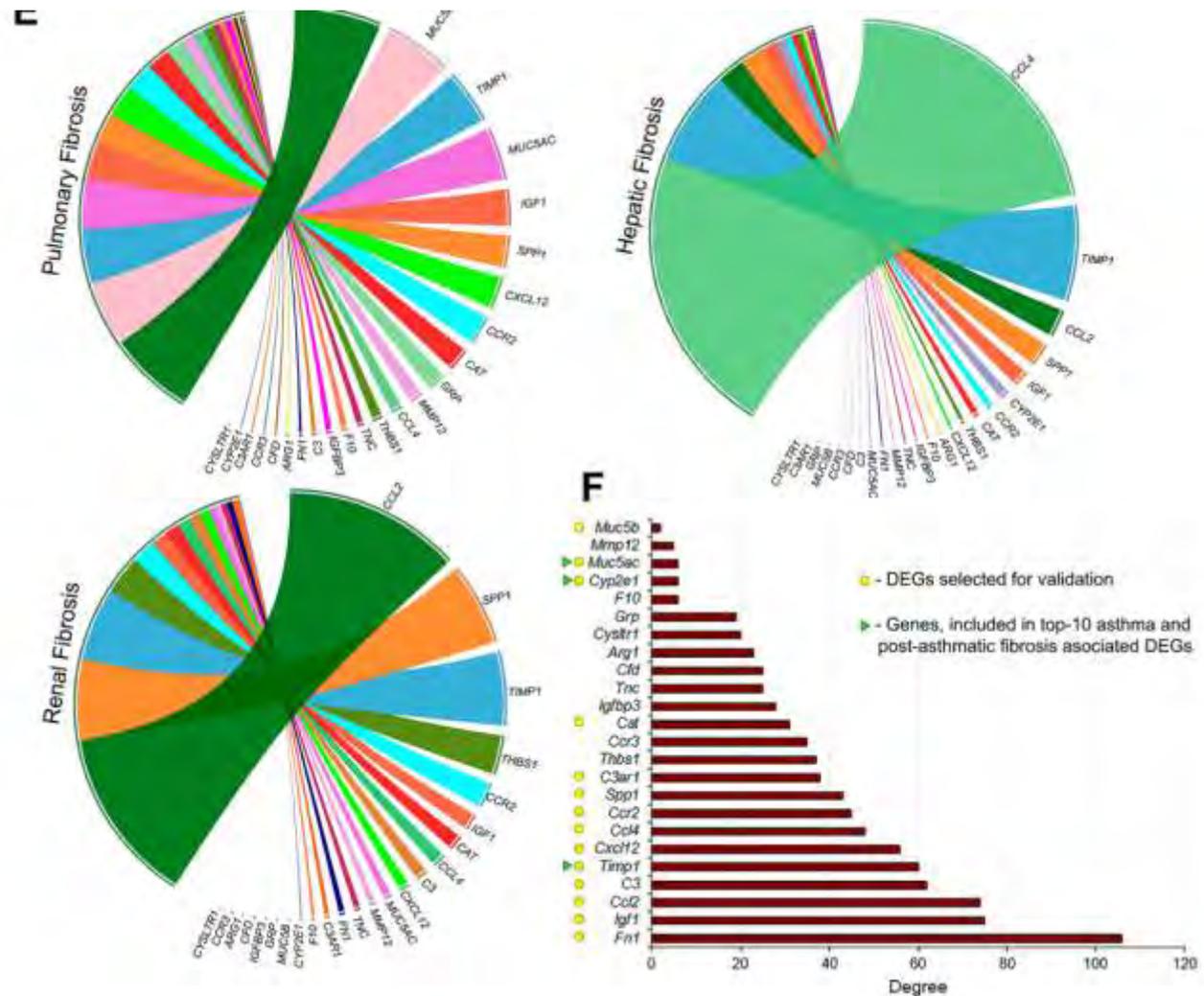
Fig. 2. Schematic overview of the role of the **adaptive immune system** in IPF pathogenesis. * also known as B lymphocyte stimulator (BL)

Asthma és fibrosis



Principal pathophysiological components of airway remodeling emergence in allergic asthma.

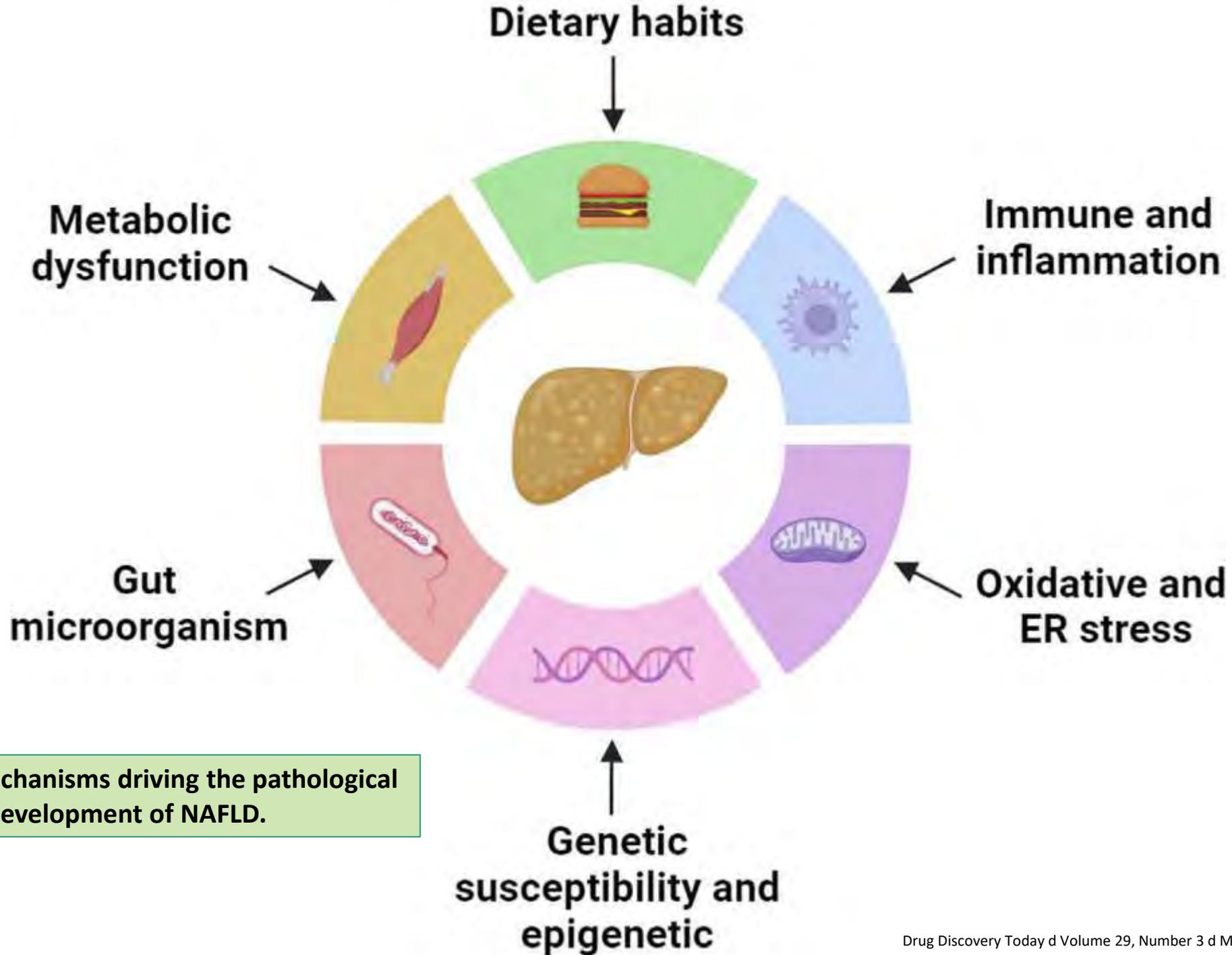
• 2023 Nov 7;24(22):16042. doi: 10.3390/ijms242216042.



Asthma and Post-Asthmatic Fibrosis

Biomedicines 2022, 10, 17.





Immune mechanisms linking metabolic injury to inflammation and fibrosis in fatty liver disease – novel insights into cellular communication circuits

Peiseler M et al. Journal of Hepatology 2022 vol. 77 j 1136–1160.

Előfordulás: 6-35%/populáció

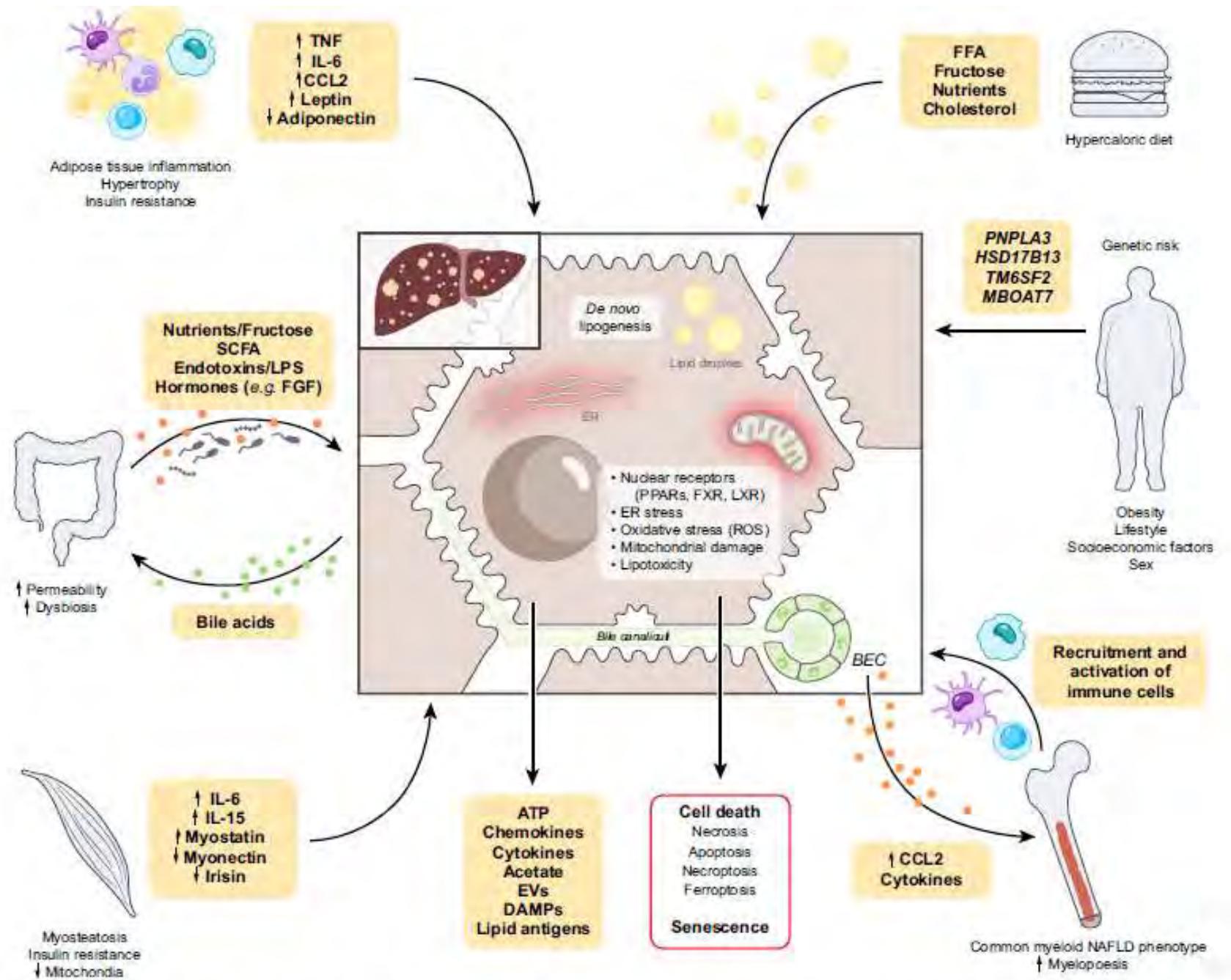


Fig. 1. Triggers of inflammation in NAFLD. Intra- and extrahepatic factors trigger inflammation in NAFLD. Hypercaloric diet, obesity, lifestyle, and genetic risk

Metabolic reprogramming in liver fibrosis

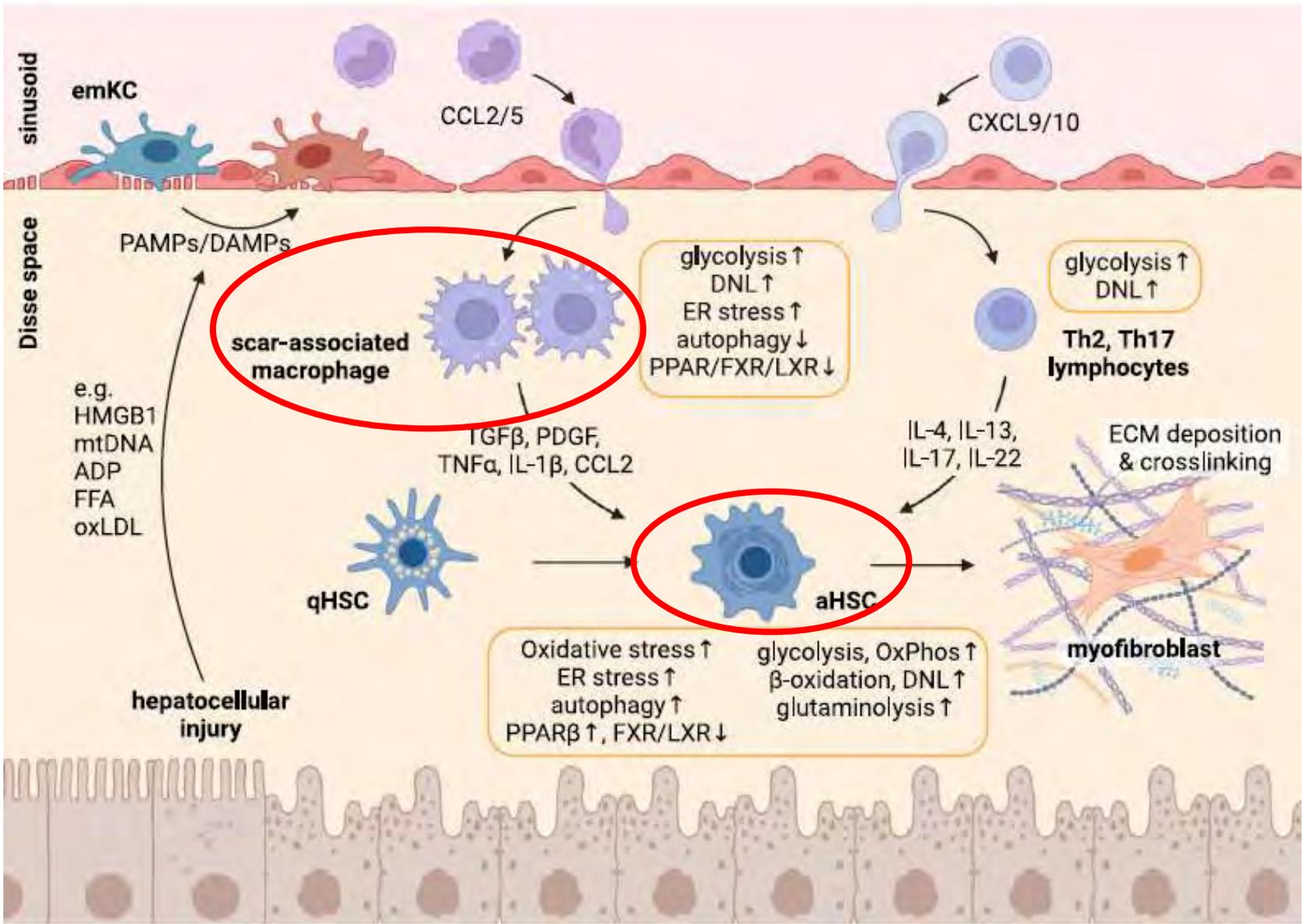


Figure 1. General mechanisms of liver fibrosis and main metabolic adaptations in macrophages, lymphocytes, and activated hepatic stellate cells

Metabolic reprogramming in liver fibrosis

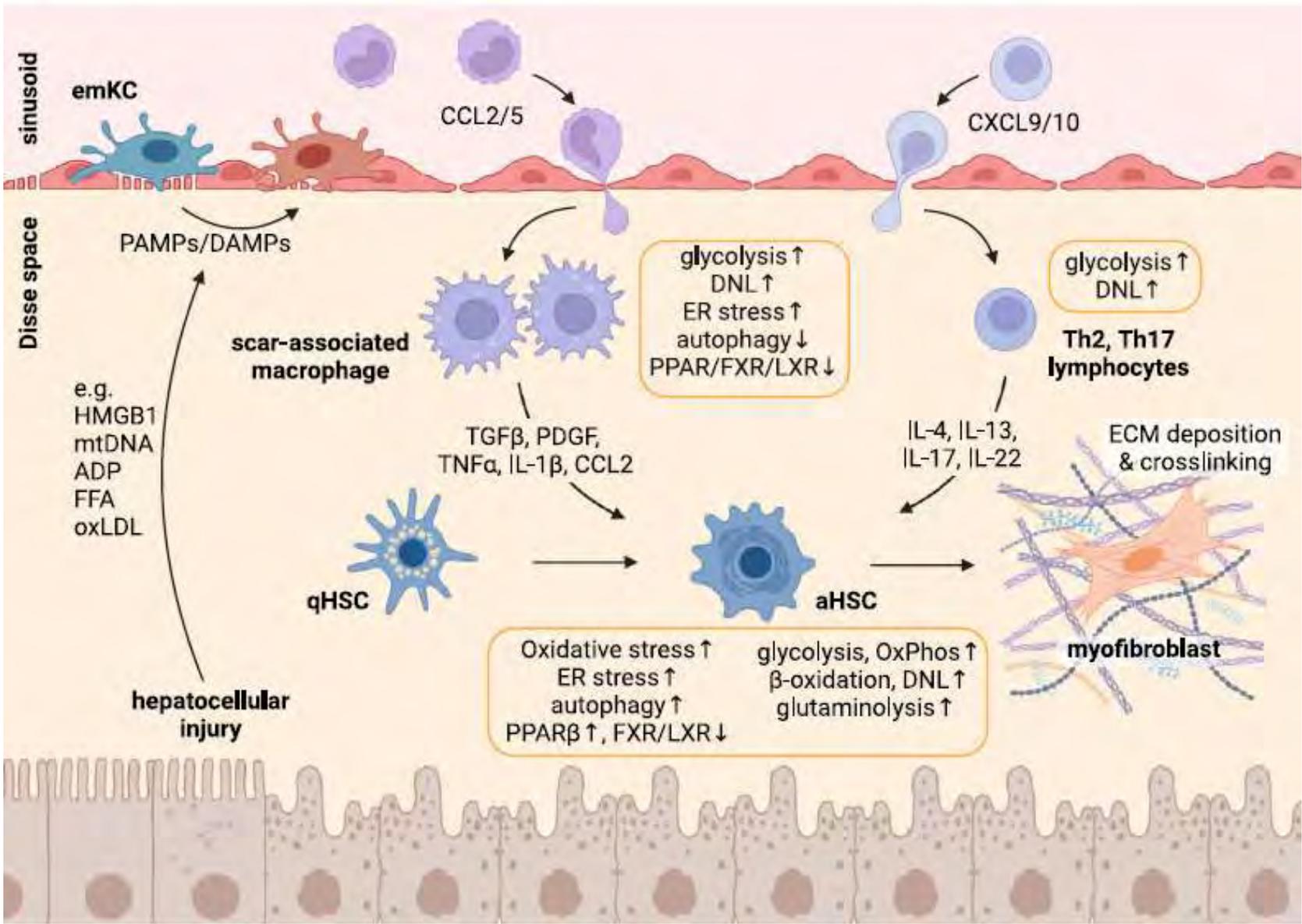


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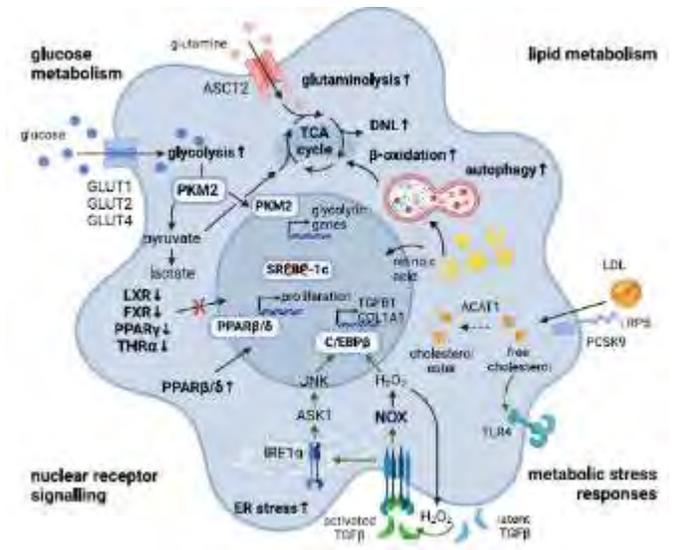


Figure 3. Metabolic reprogramming in fibrogenic hepatic stellate cell activation

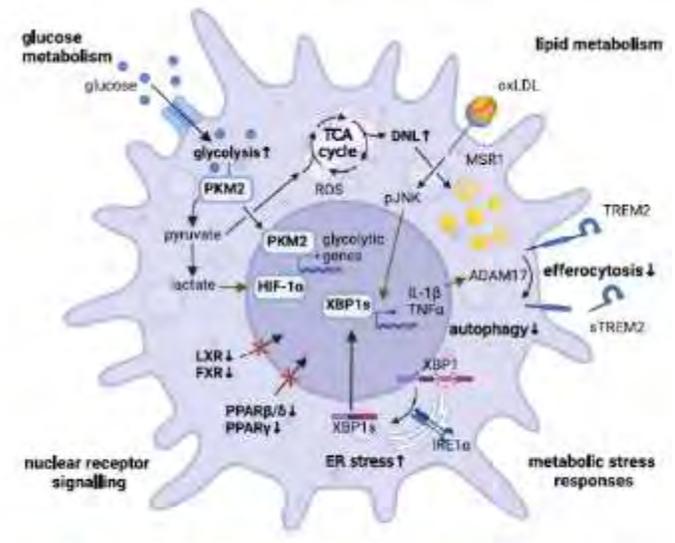


Figure 2. Metabolic reprogramming in hepatic macrophage activation during liver fibrogenesis

Autoimmun májbetegségek és fibrosis

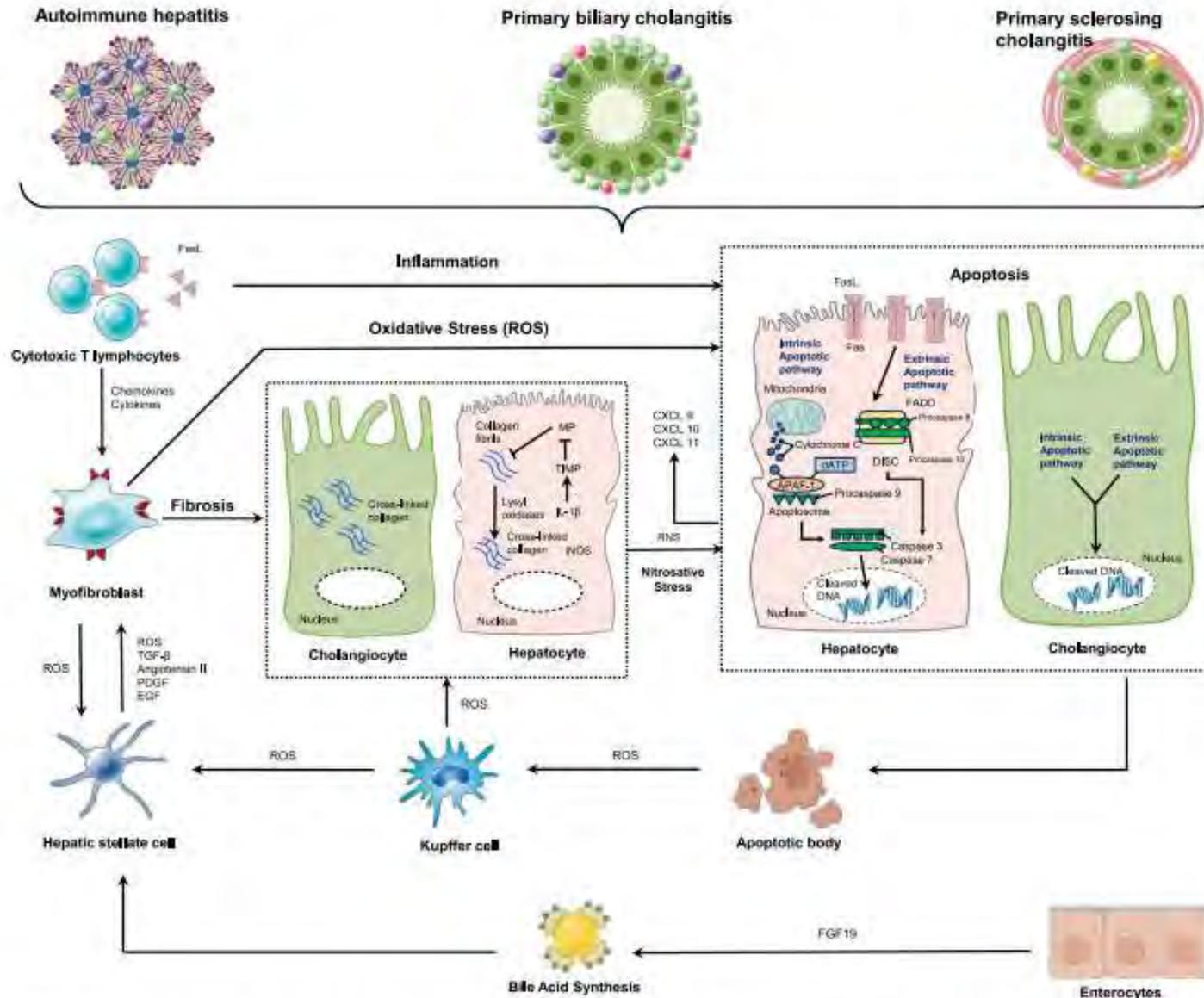


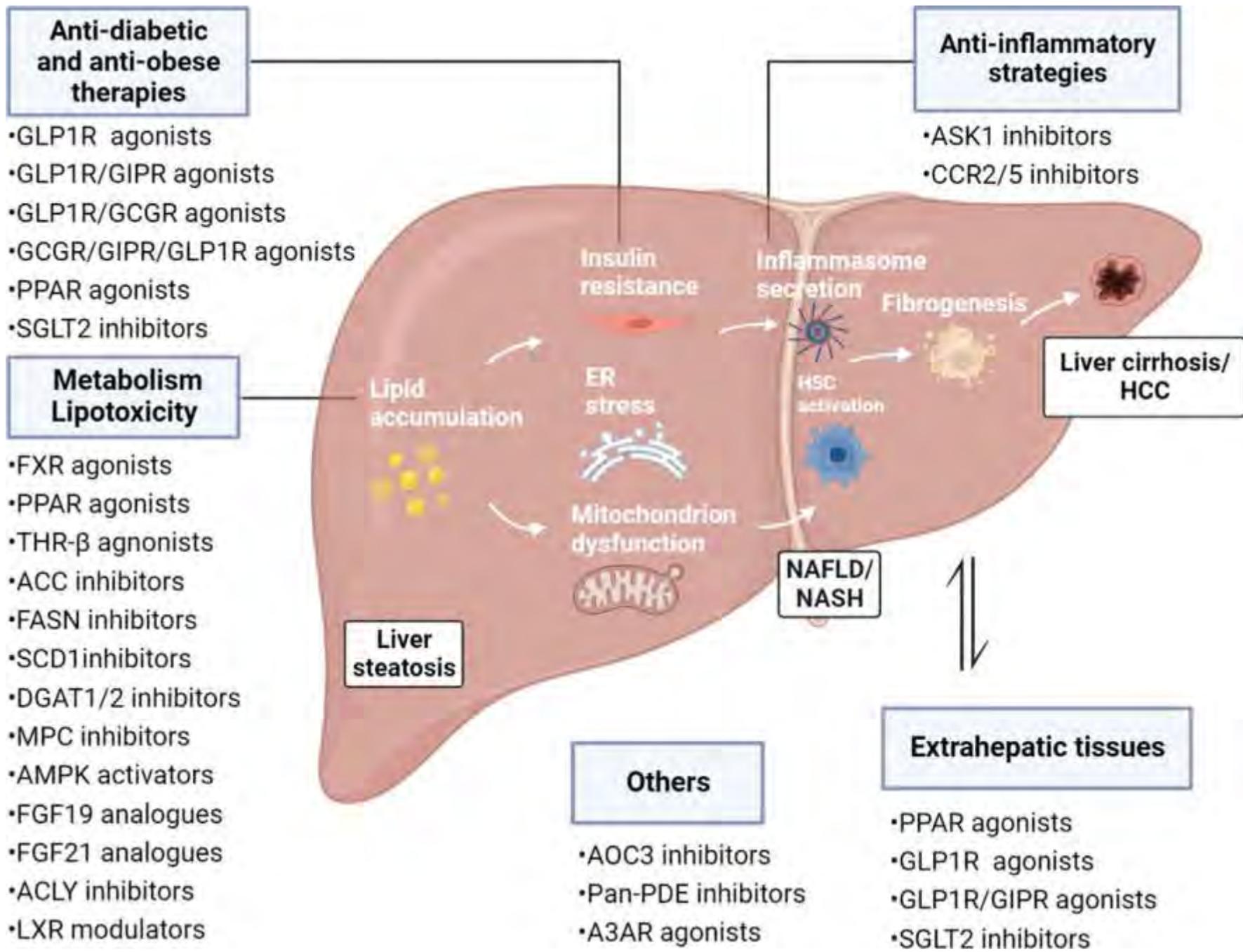
FIGURE 1 | Mechanisms of hepatic fibrosis associated with liver inflammation, oxidative stress, nitrosative stress and apoptosis in AILD.

Autoimmun májbetegségek és fibrosis

TABLE 1 | Non-invasive biomarker-based scores for liver fibrosis and parameters required for their calculation.

Score	Age	Sex	ALT	AST	GGT	Platelet count	RDW	INR	PT	Albumin	Total bilirubin	Urea	HA	Hyaluronate	PIIINP	TIMP-1	α -2-macroglobulin
APRI				X		X											
FIB-4 score	X		X	X		X											
AAR			X	X													
GPR					X	X											
ELF score													X		X	X	
ALBI grade										X	X						
FibroQ	X		X	X		X		X									
Fibrometer	X			X		X			X			X		X			X
Hepascore	X	X			X						X		X				X
RPR						X	X										

Abbreviations: AAR, AST/ALT ratio; ALBI grade, Albumin-Bilirubin grade; ALT, alanine transaminase; APRI, AST/platelet ratio index; AST, aspartate transaminase; ELF score, Enhanced Liver Fibrosis score; FIB-4 score, Fibrosis-4; GGT, gamma-glutamyl transferase; GPR, GGT to platelet ratio; HA, hyaluronic acid; INR, international normalised ratio; PIIINP, propeptide of type III procollagen; PT, prothrombin time; RDW, red cell distribution width; RPR, RDW to platelet count ratio; TIMP-1, tissue inhibitor of metalloproteinase type 1; α -2-macroglobulin, alpha-2-macroglobulin.





Diffuse myocardial fibrosis: mechanisms, diagnosis and therapeutic approaches

Begoña López^{1,2,4}, Susana Ravassa^{1,2,4}, María U. Moreno^{1,2,4}, Gorka San José^{1,2}, Javier Beaumont^{1,2}, Arantxa González^{1,2} and Javier Díez^{1,2,3}

Box 1 | Conditions associated with diffuse myocardial fibrosis

Ischaemic heart disease

- Coronary artery disease¹
- Alterations of the coronary microcirculation caused by hypertension⁷ or diabetes mellitus⁸

Cardiac pressure overload

- Systemic arterial hypertension⁹
- Aortic stenosis¹⁰
- Coarctation of the aorta¹¹
- Pulmonary arterial hypertension^{4,12}

Cardiac volume overload

- Obesity^{4,13}
- Aortic regurgitation¹⁴
- Mitral regurgitation^{4,15}

Cardiac inflammation

- Myocarditis¹⁶
- Sarcoidosis^{4,17}

Genetic cardiac diseases

- Hypertrophic cardiomyopathy¹⁸

Cardiac metabolic alterations

- Obesity^{4,13}

- Diabetes mellitus¹⁹

- Chronic kidney disease²⁰

Infiltrative cardiac alterations

- Amyloidosis²¹

Cardiac storage diseases

- Anderson–Fabry disease^{4,22}

Congenital heart diseases

- Tetralogy of Fallot²³
- Ebstein anomaly^{4,24}
- Transposition of the great arteries^{4,25}

Other conditions

- Ageing²⁶
- Non-ischaemic dilated cardiomyopathy²⁷
- Atrial fibrillation-mediated cardiomyopathy²⁸
- Exposure to pharmacological cardiotoxic agents²⁹

*Conditions in which diffuse myocardial fibrosis was identified by cardiovascular MRI instead of endomyocardial biopsy, which was performed in the other conditions.

Diffuse myocardial fibrosis: mechanisms, diagnosis and therapeutic approaches

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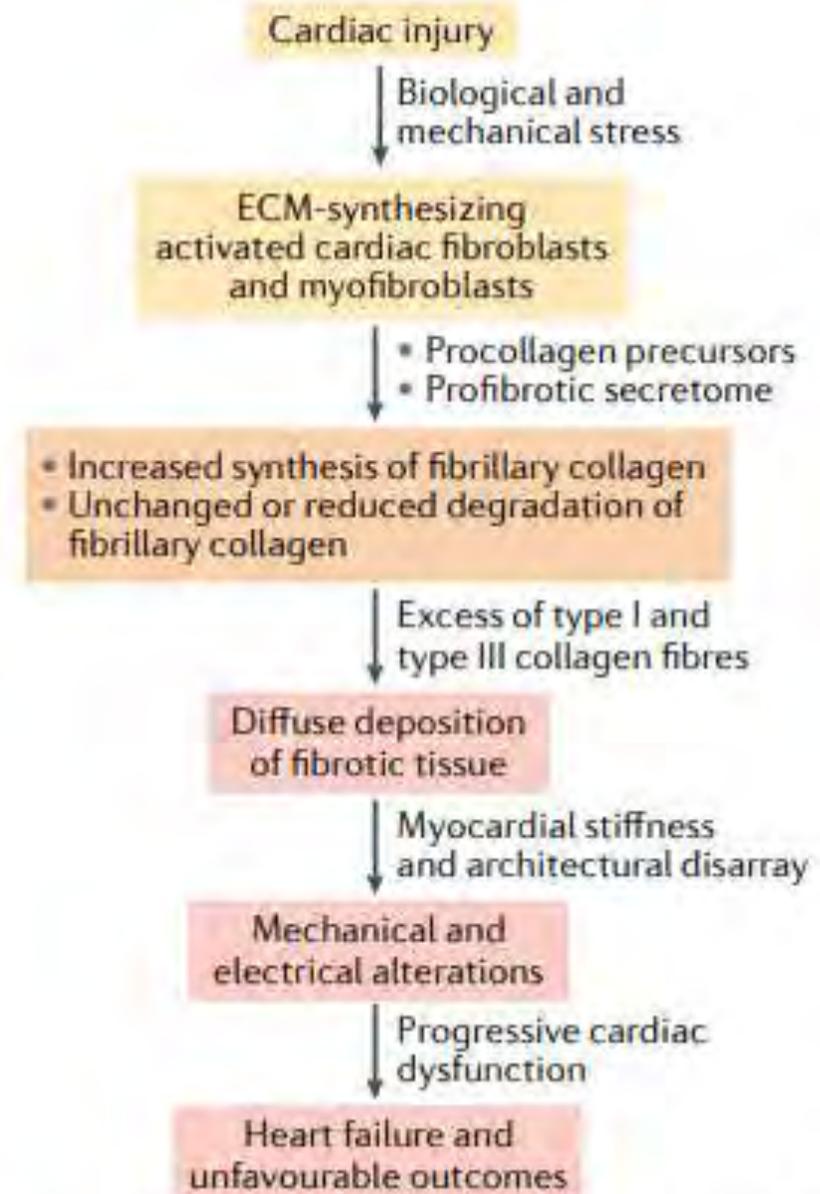


Fig. 1 | Pathogenesis and consequences of diffuse myocardial fibrosis. In response to cardiac injury,

Diffuse myocardial fibrosis: mechanisms, diagnosis and therapeutic approaches

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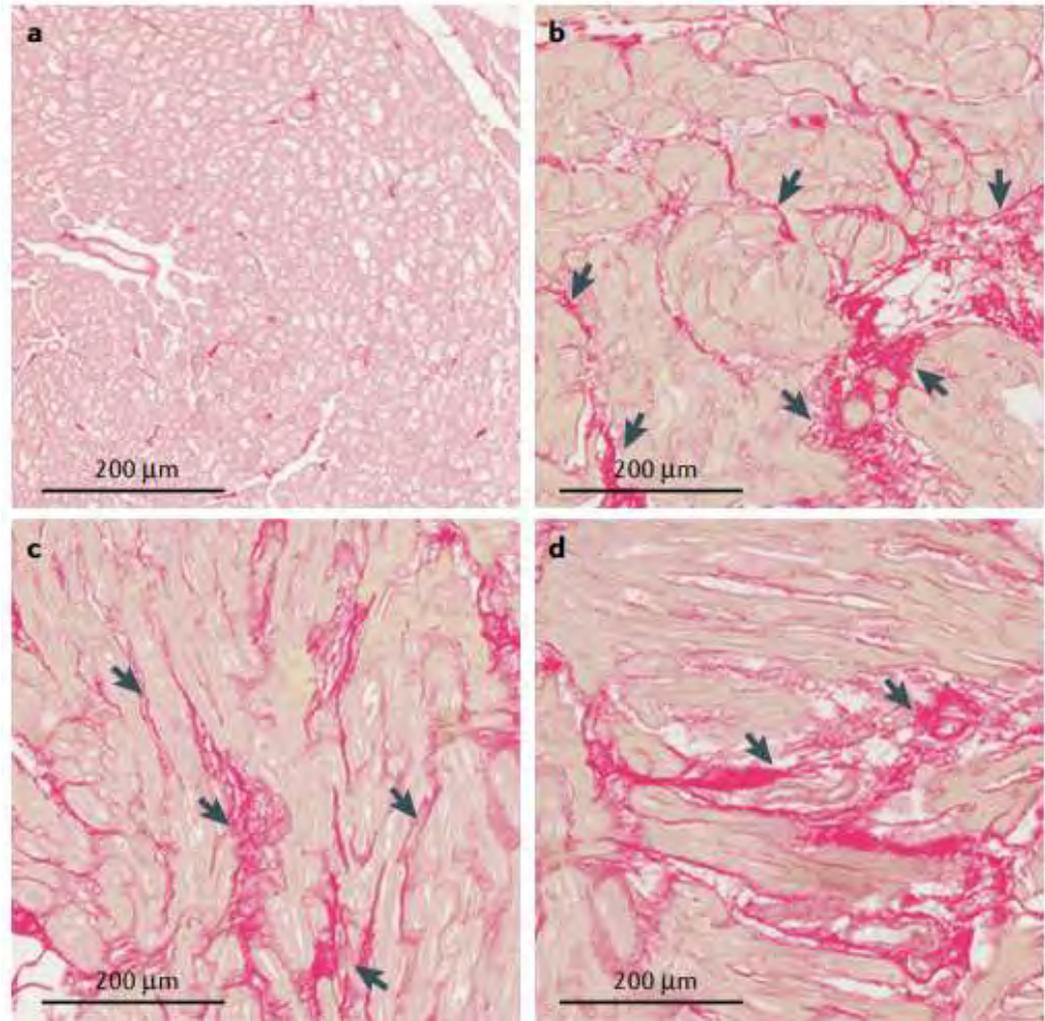
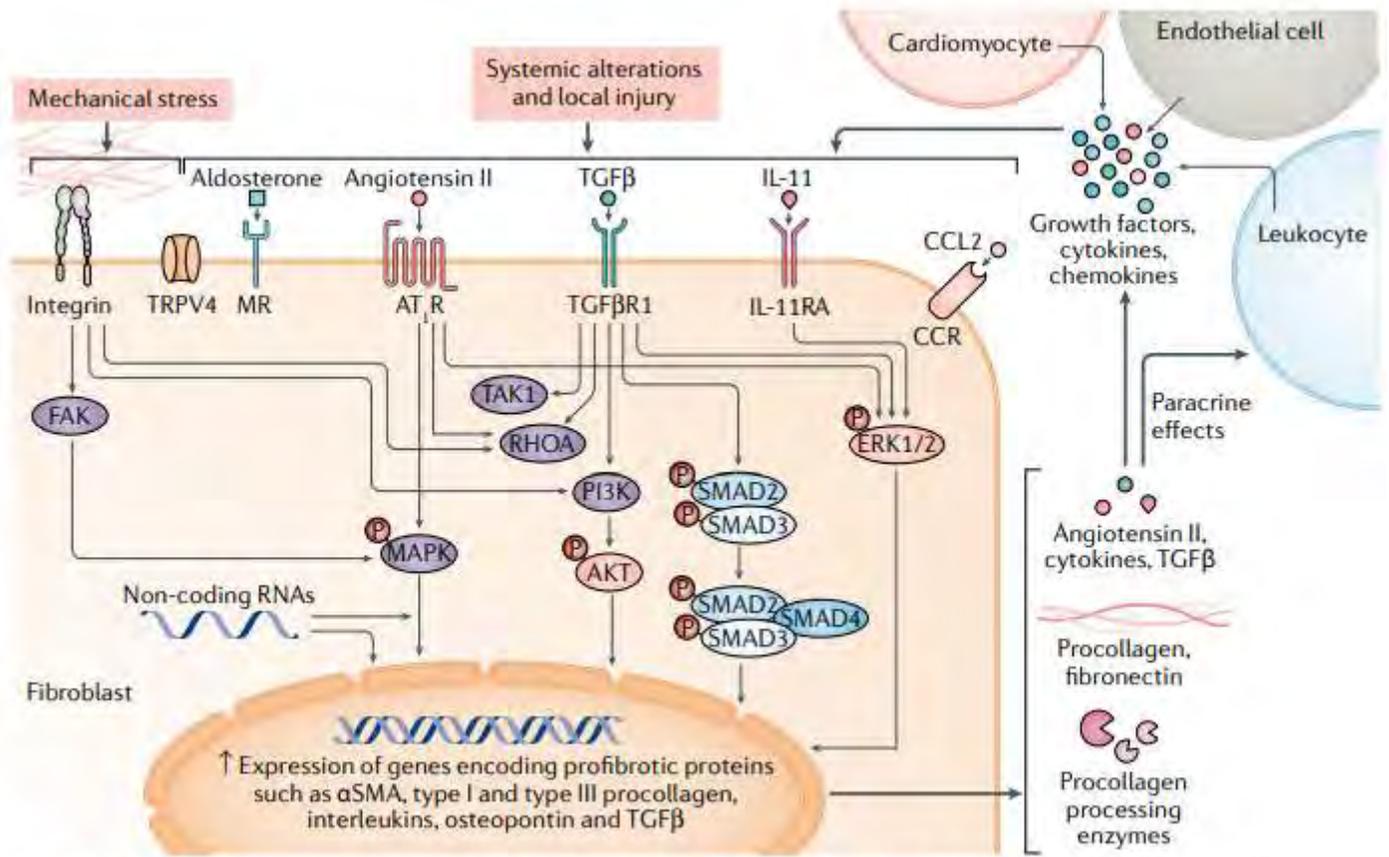
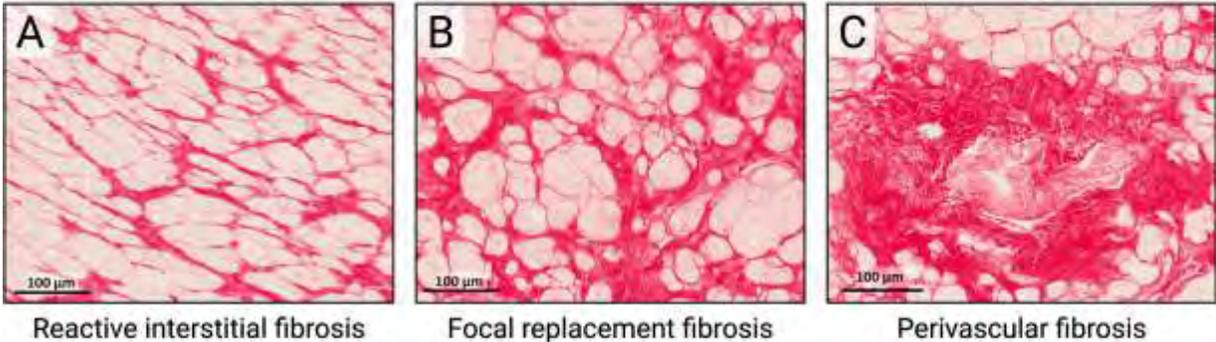


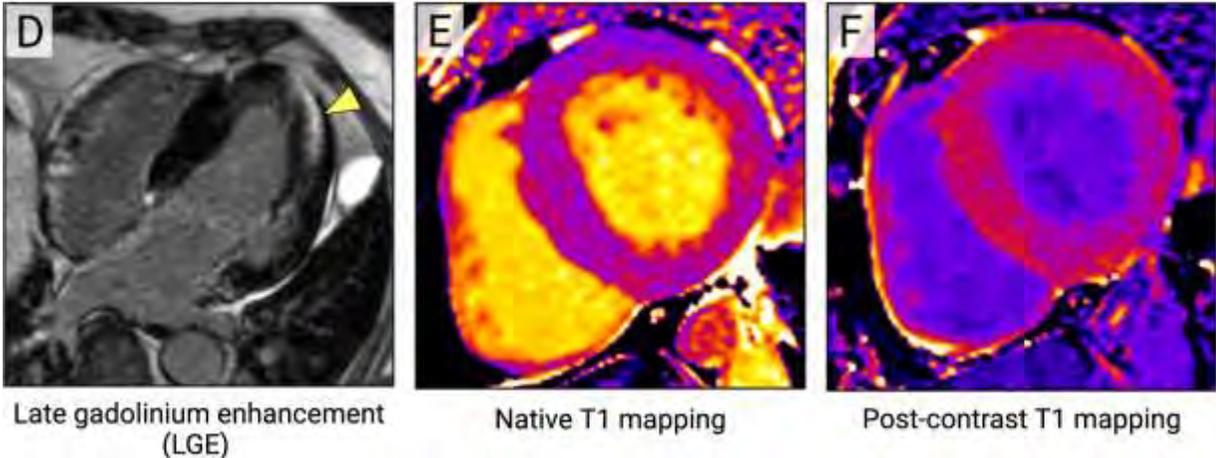
Fig. 3 | Major signalling pathways involved in the activation of **cardiac fibroblasts** in response to increased

Myocardial fibrosis from the perspective of the extracellular matrix: Mechanisms to clinical impact

Endomyocardial biopsy (EMB)



Cardiac magnetic resonance (CMR) imaging



Biomarkers of cardiac fibrosis

<p>Endomyocardial biopsy (EMB)</p> <p>Pro</p> <ul style="list-style-type: none"> • Direct and specific assessment of myocardial collagen <p>Contra</p> <ul style="list-style-type: none"> • Invasive procedure • Vulnerable to sampling bias • Screening is logistically challenging 	<p>Cardiac MRI or CT</p> <p>Pro</p> <ul style="list-style-type: none"> • Repeatable, non-invasive procedure • Whole-heart visualisation <p>Contra</p> <ul style="list-style-type: none"> • Low resolution (0.5 - 2.0 mm) • Limited ability to discriminate tissues • Mostly detects focal fibrosis
<p>Clinical</p>	
<p>Preclinical</p> <p>Circulating biomarkers</p> <p>Pro</p> <ul style="list-style-type: none"> • Easy to assess and up-scale • Inexpensive, reproducible • Operator independent <p>Contra</p> <ul style="list-style-type: none"> • Not cardiac specific 	

Myocardial fibrosis from the perspective of the extracellular matrix: Mechanisms to clinical impact

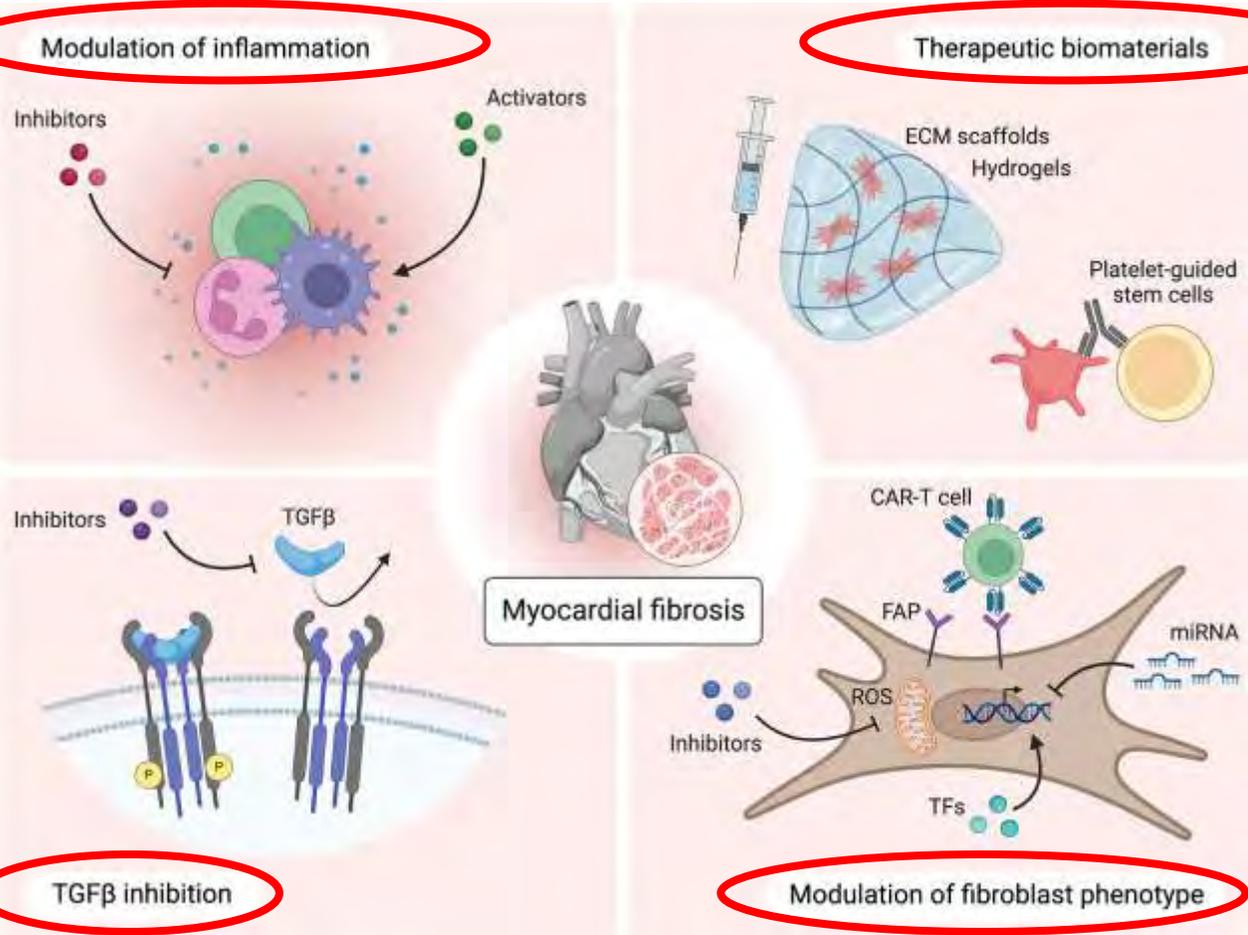


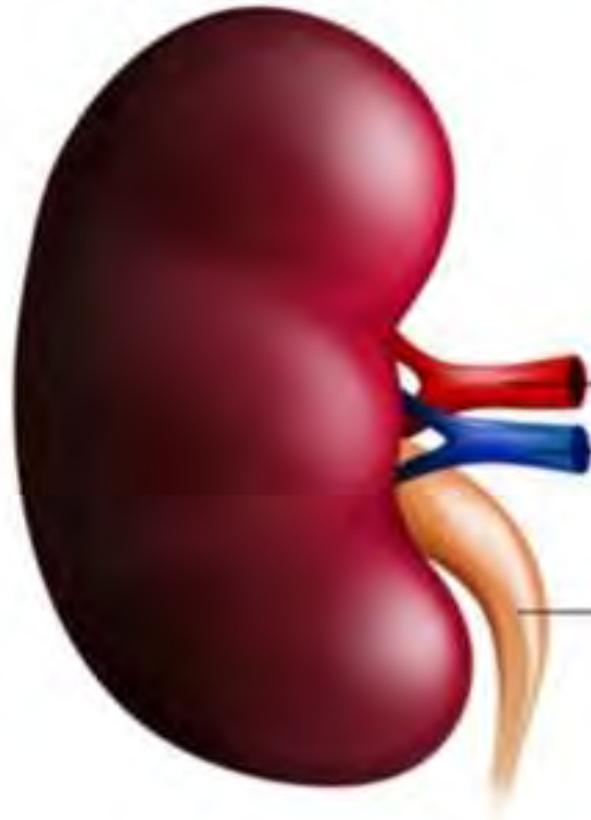
Table 3 | Novel therapies potentially applicable to reverse diffuse myocardial fibrosis

Target	Therapeutic strategy	Study stage	Status	Ref.
TGFβ1 signalling	Inhibiting connective tissue growth factor activity with the monoclonal antibody pamrevlumab	Phase II trial in patients with idiopathic pulmonary fibrosis	Completed	211
		Phase III trial in patients with idiopathic pulmonary fibrosis	Ongoing	212
Non-coding RNAs	Inhibiting miR-21 with RG-012	Phase I trials in patients with Alport syndrome	Completed	211
		Phase II trials in patients with Alport syndrome	Ongoing	212
	Mimicking miR-29a with remlarsen	Phase I trial in healthy volunteers	Completed	213
		Phase II trial in patients with cutaneous fibrosis	Ongoing	214
Metabolic pathways	Omega-3 fatty acid supplementation	Phase III clinical trial in patients with myocardial infarction	Completed	215
Extracellular collagen processing	LOXL2 inhibition with simtuzumab	Phase II clinical trial in patients with idiopathic pulmonary fibrosis	Completed	214
		Matrix metalloproteinase inhibition with low-dose doxycycline	Completed	215
	Phase II trial in patients with myocardial infarction	Ongoing	216	
Inflammation	Therapy with modified citrus pectin (a galectin 3 inhibitor)	Phase I trial in patients with chronic kidney disease	Ongoing	217
	Therapy with BLD-2660 (a calpain inhibitor)	Phase IIa trial in patients with idiopathic pulmonary fibrosis	Ongoing	218
	Therapy with sodium thiosulfate (a hydrogen sulfide-releasing agent)	Phase II trial in patients with myocardial infarction	Ongoing	219

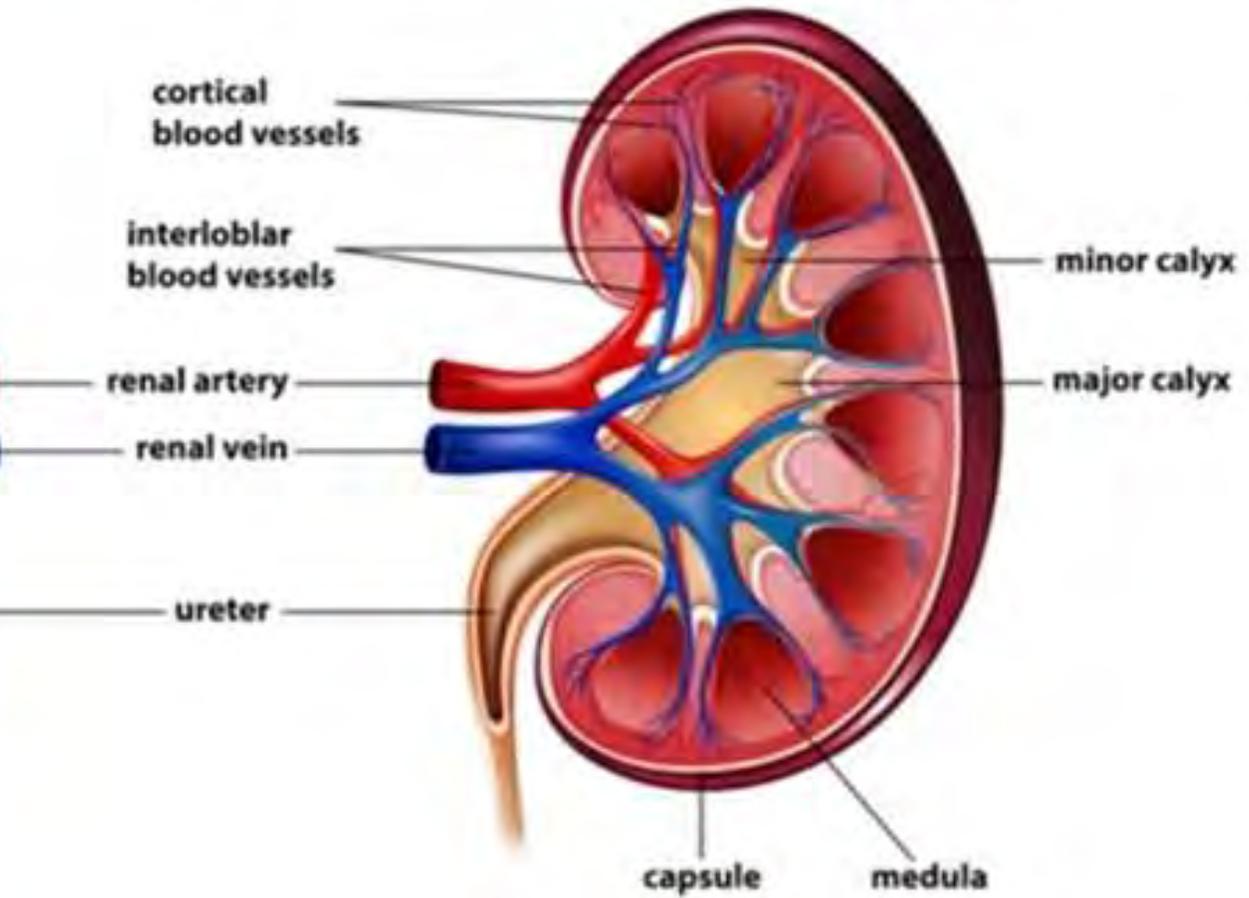
LOXL2, lysyl oxidase homologue 2; TGFβ1, transforming growth factor-β1.

Human Kidney Anatomy

External View



Internal View



cortical
blood vessels

interlobular
blood vessels

renal artery

renal vein

ureter

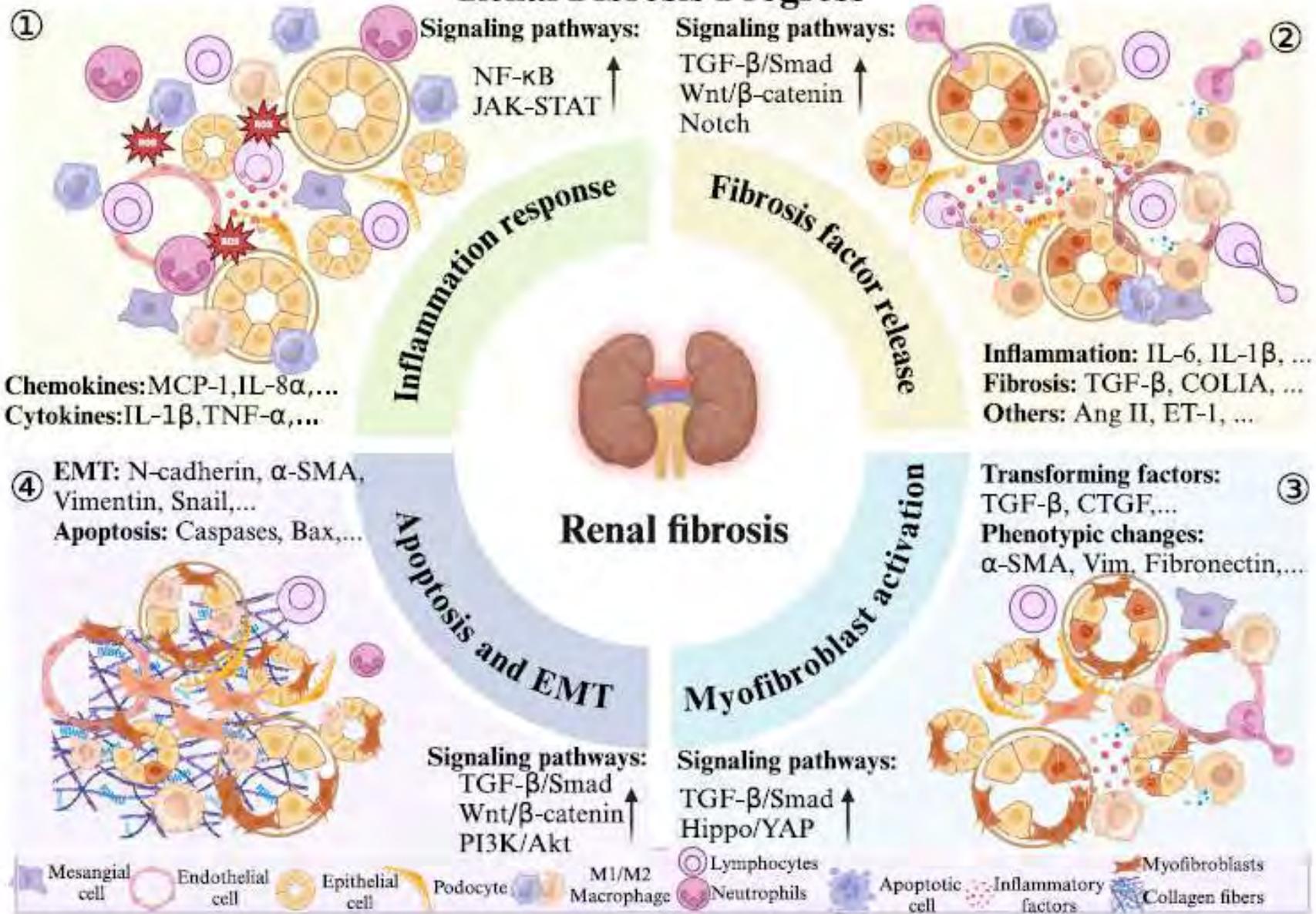
minor calyx

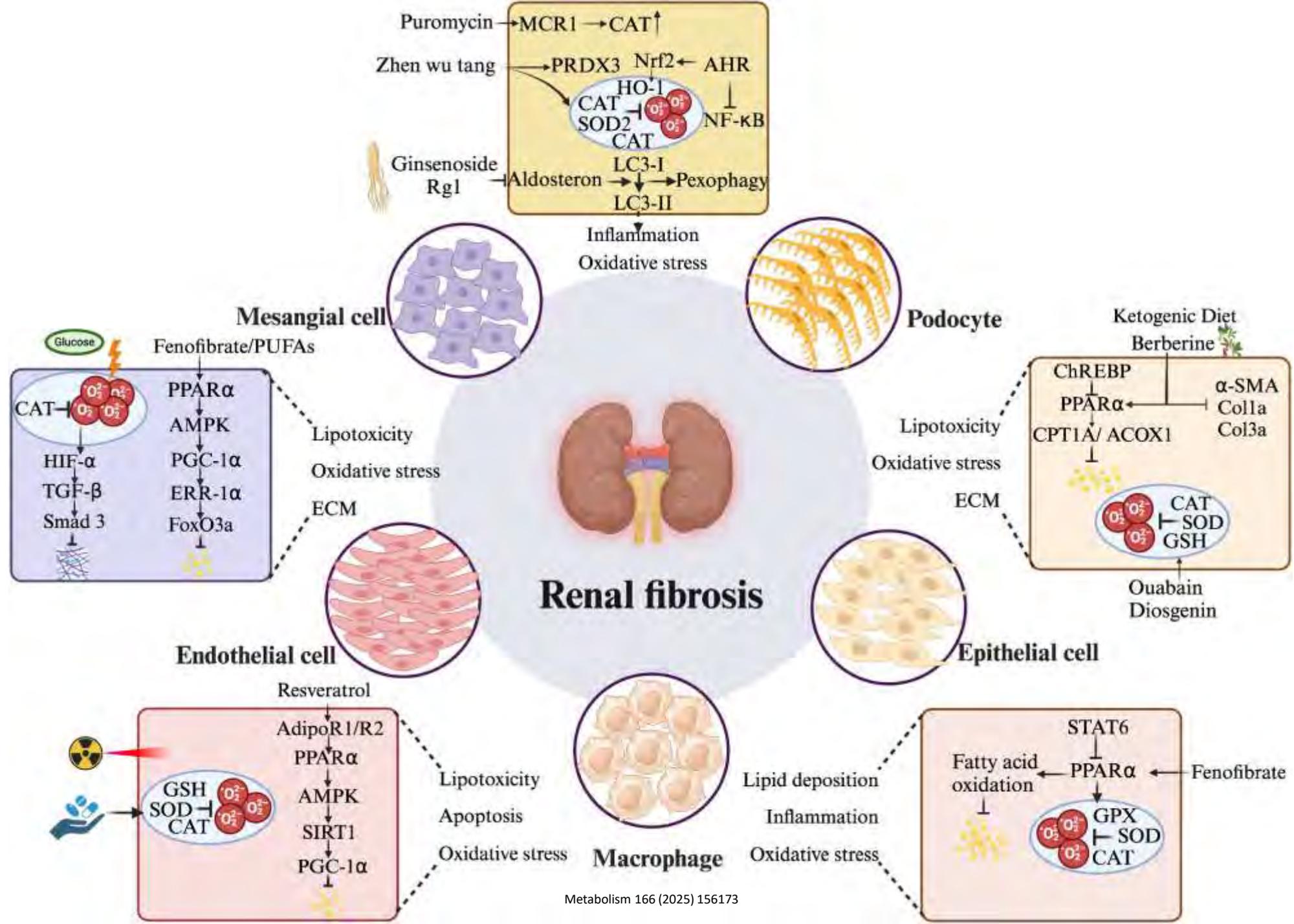
major calyx

capsule

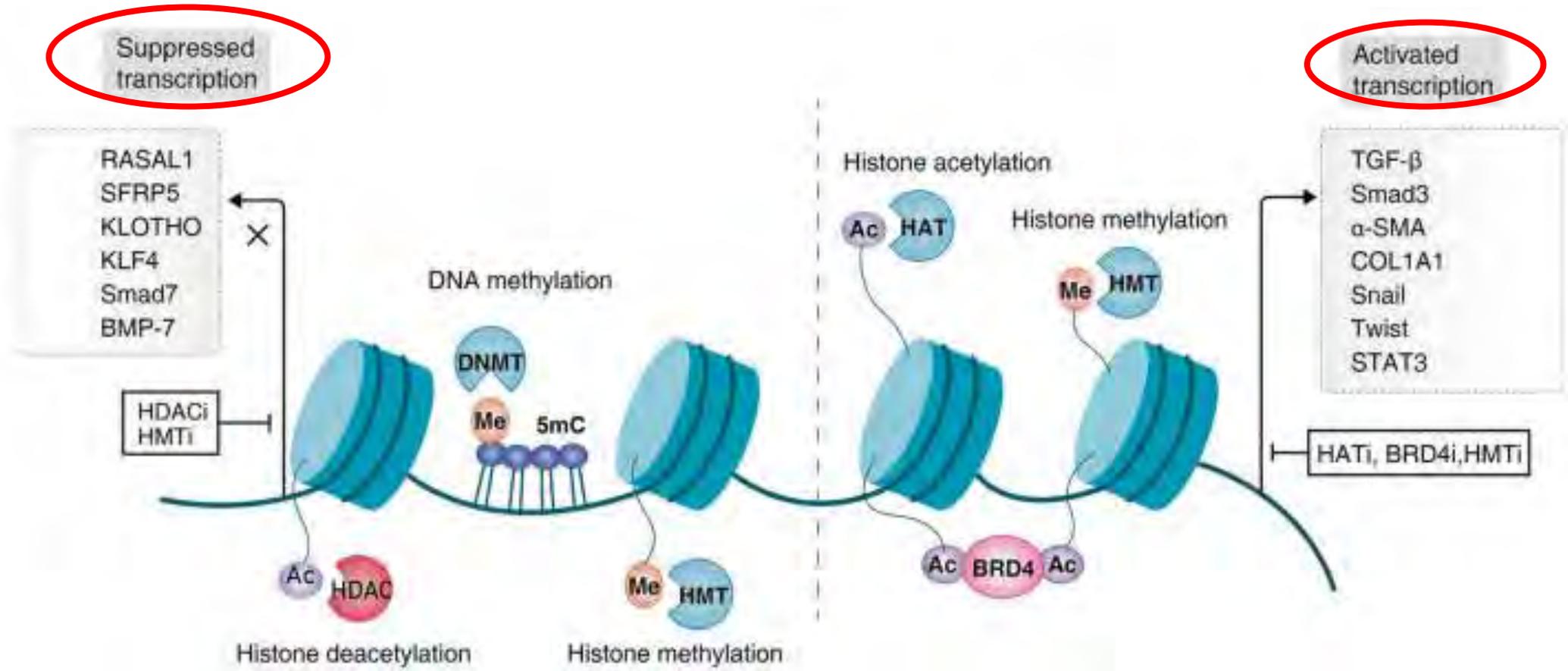
medula

Renal Fibrosis Progress





Kidney fibrosis: from mechanisms to therapeutic medicines



Histone modification and DNA methylation in kidney fibrosis. Suppression of antifibrotic genes

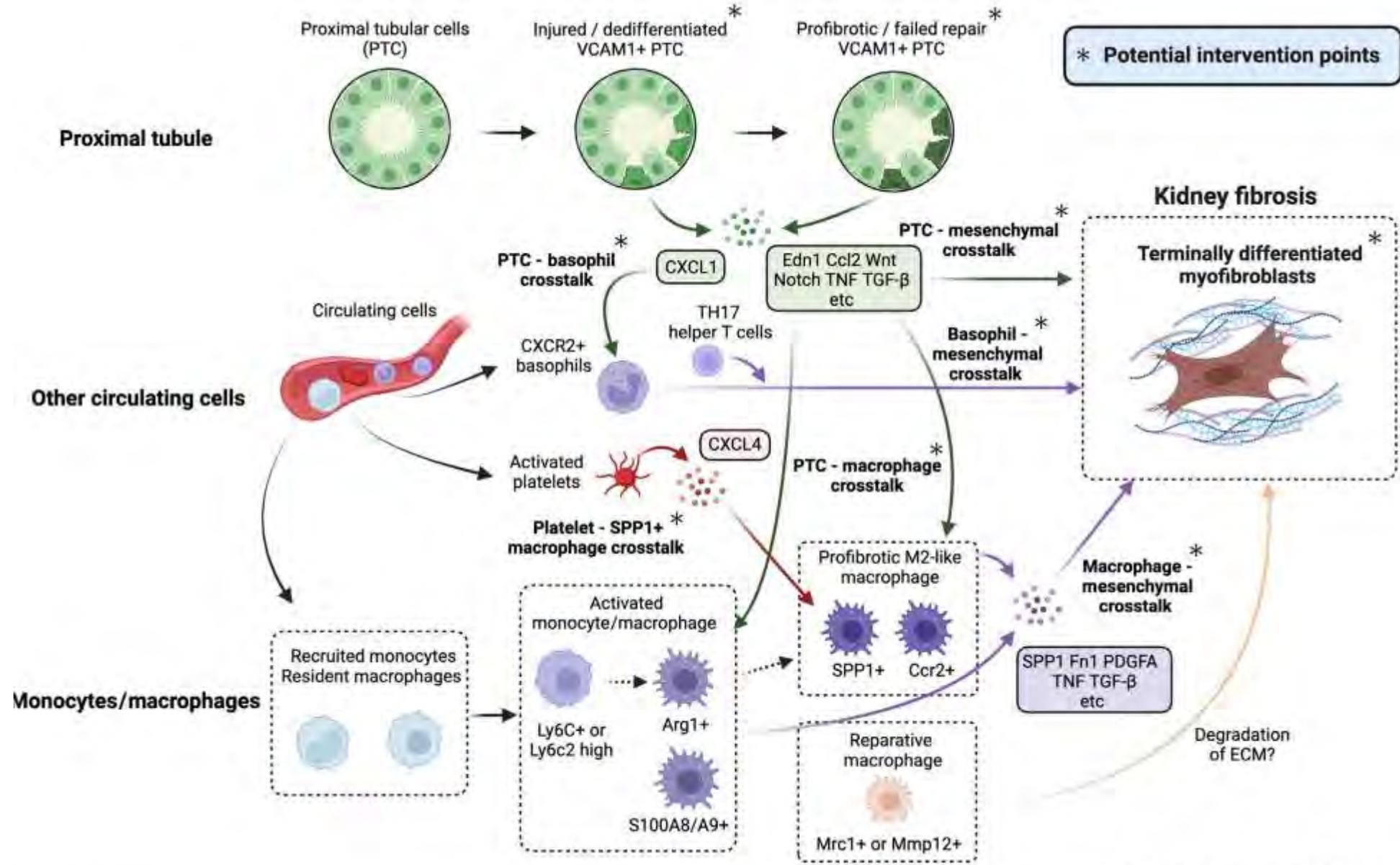
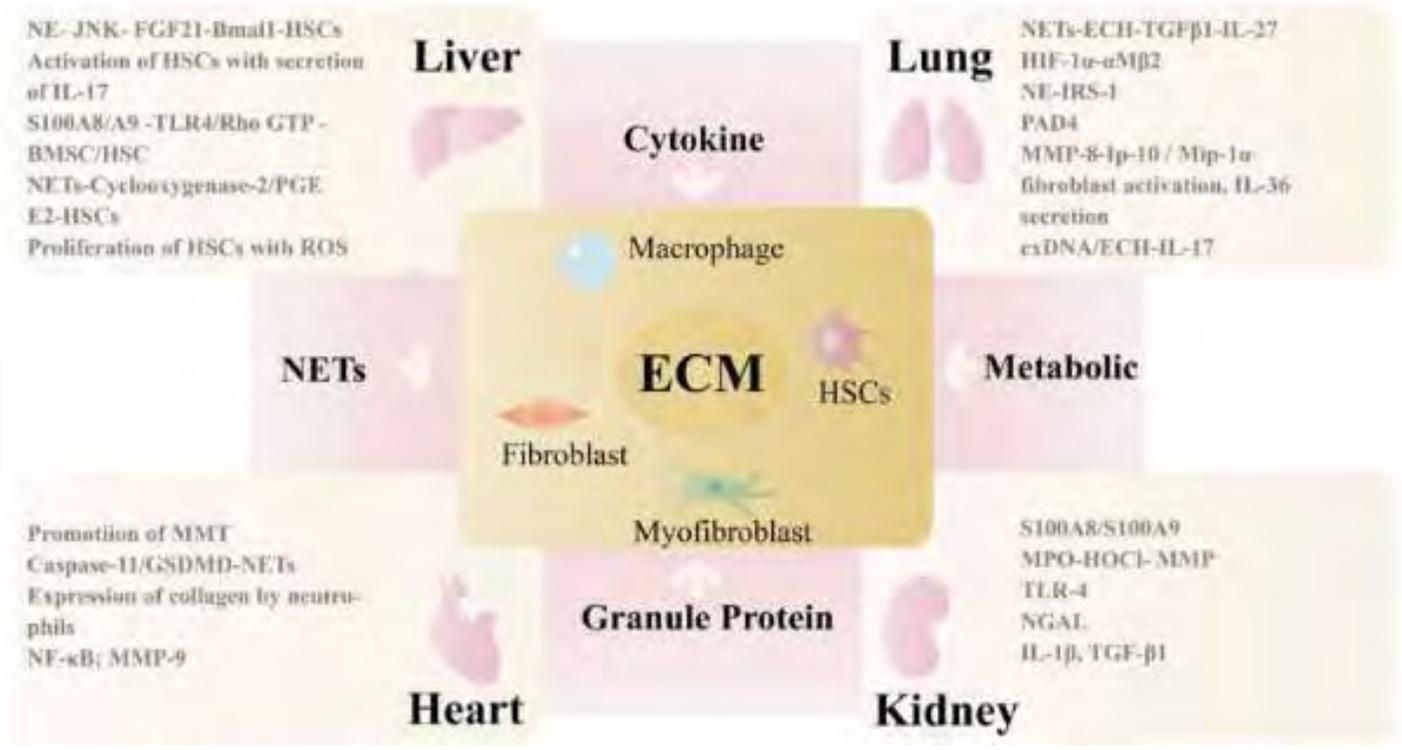
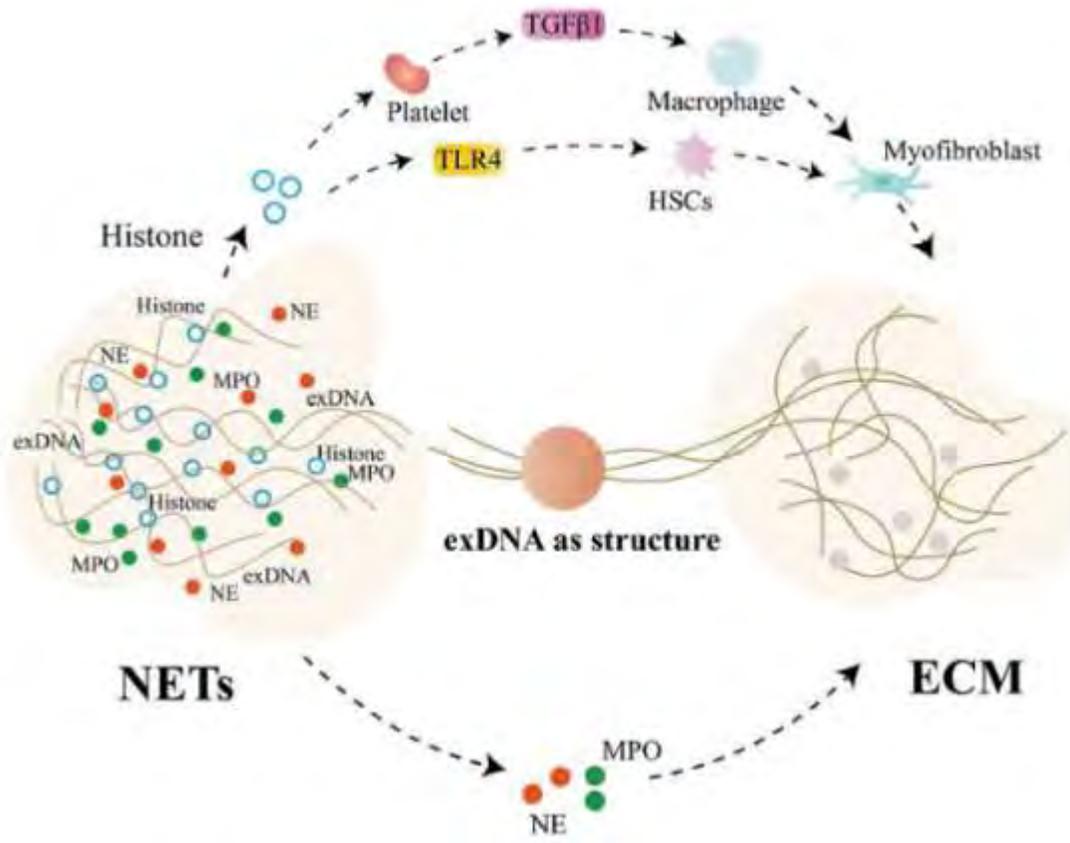


Figure 2. Cellular crosstalk driving kidney fibrosis, and potential intervention points. Proximal tubular epithelial cells (PTCs) are the major cellular component of the

Neutrofil sejtek és fibrosis



Szisztémás sclerosis

„scleroderma”: „sclero” (kemény) + „derma” (bőr)



Patogenezis

Fogékony szervezet

Exogén behatások

Immunrendszer aktivációja, fenotípusos változások

Immunsejtek

- B-sejtek
- $\Gamma\delta$ T-sejtek
- CD4+ T-sejtek
- CD8+ T-sejtek
- Macrophagok
- Hízósejtek
- pDC-k
- Dermális DC-k

Vascularis sérülés

Endothel aktiváció

- Strukturális károsodás
- Alvadási/ fibrinolitikus zavar
- Sejtadhéziós molekulák megváltozott expressziója
- Megváltozott citokin/kemokin expresszió

Hypoxia
Thrombosis

Infiltráció
Aktiváció

Fibroblast aktiváció

- Autokrin TGF- β aktiváció és visszacsatolás
- Megváltozott válaszreakció
- Th1/Th2/Th17 citokinek

- Fibrocyta
- Endotheliális-mesenchymális átalakulás
- Epitheliális-mesenchymális átalakulás
- Adipocyta-myofibroblast átalakulás
- Gyulladásos sejtek

Krónikus gyulladás

Szervek fibrosisa

Raynaud tünet

Vazokonstriktió ↑

A simaizomsejtek α -2
adrenoreceptorok reaktivitása ↑

Vazodilatáció ↓

A szenzoros afferens rostokból származó
vazodilatator neuropeptidek (pl. CGRP)
szintje ↓

Idegrostok
(szimpatikus
és szenzoros)

Simaizomsejtek

Endotheliális sejtek

Endothelin-1 ↑

NO ↓

PDGF receptor elleni antitestek
Oxidatív stressz
Endothel sejtek elleni antitestek

Thrombocytá
aktiváció/aggregáció ↑

Fibrinolysis ↓
Thrombin ↓
Vvt deformálódás ↓
Viszkozitás ↑

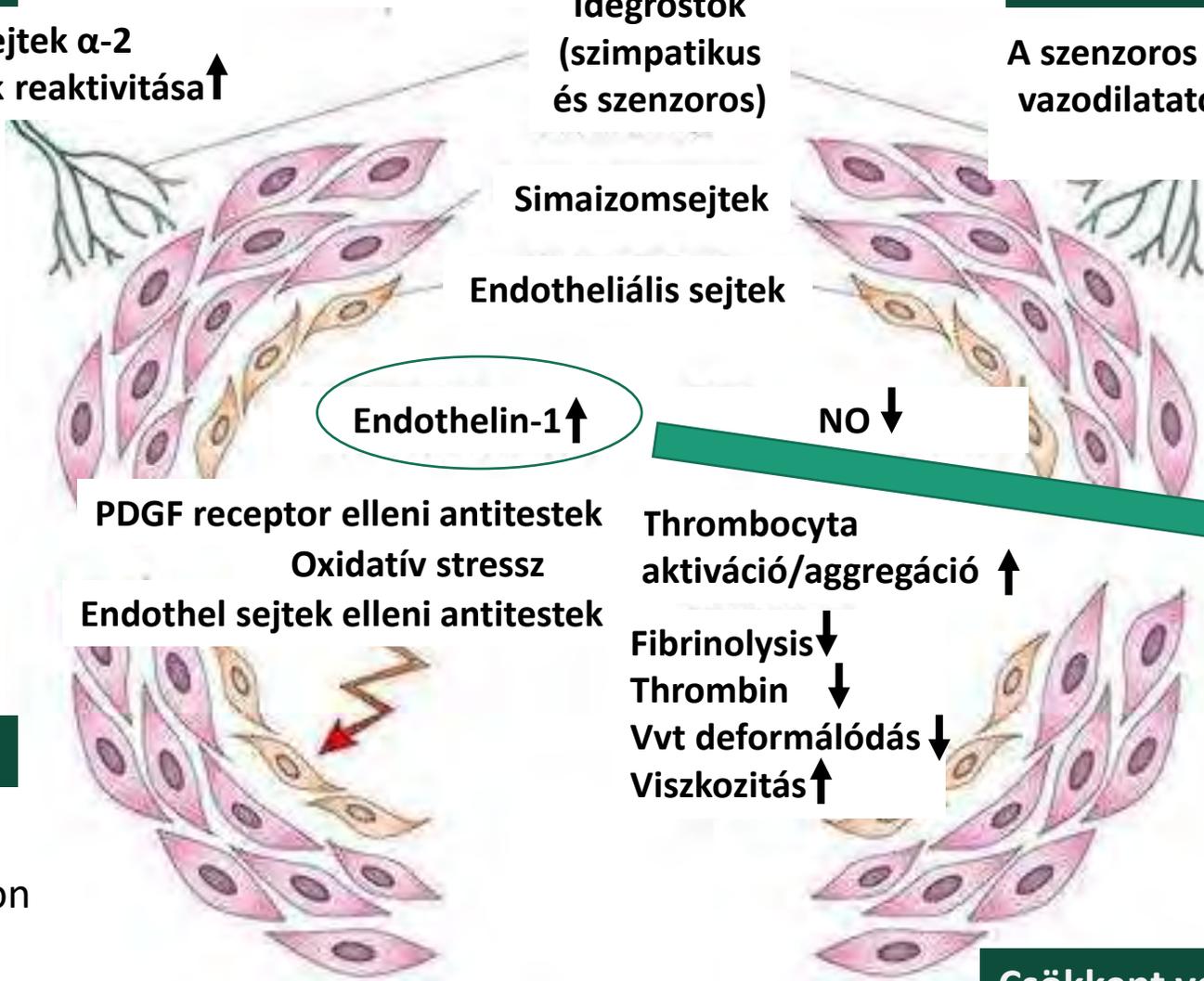
Fibrosis

Endothel sérülés

Csökkent véráramlás/
prokoaguláns állapot

Sejtek közötti adhézio, tight junction
fellazulása

A digitalis artériák hideghatásra,
vagy emocionális stresszre
bekövetkező kóros válaszreakciója,
fokozott vasokonstriktiója

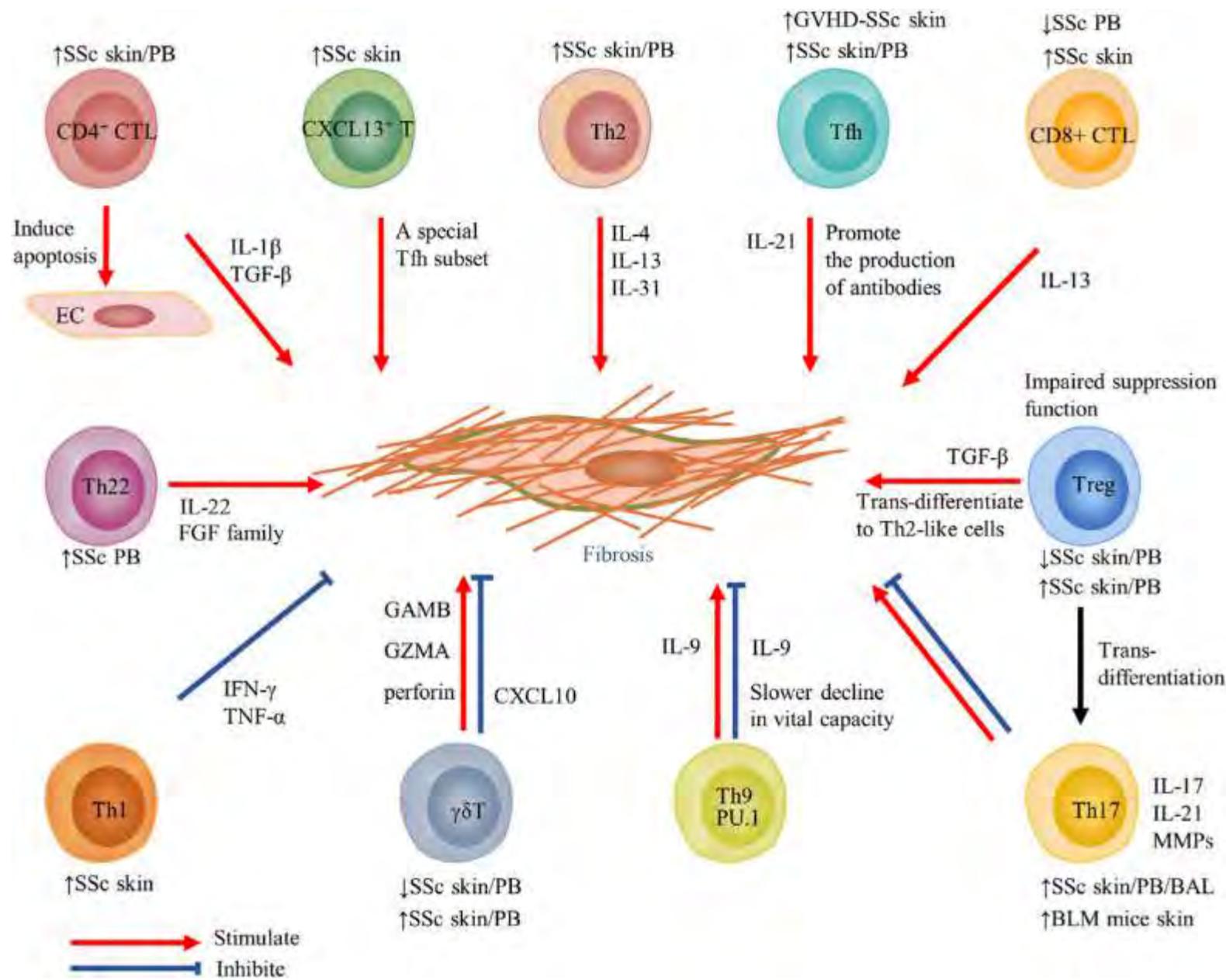


Contributions of Immune Cells and Stromal Cells to the Pathogenesis of Systemic Sclerosis: Recent Insights

Bingying Dai et al. 2022. Front. Pharmacol. 13:826839.

Adaptív immunitás

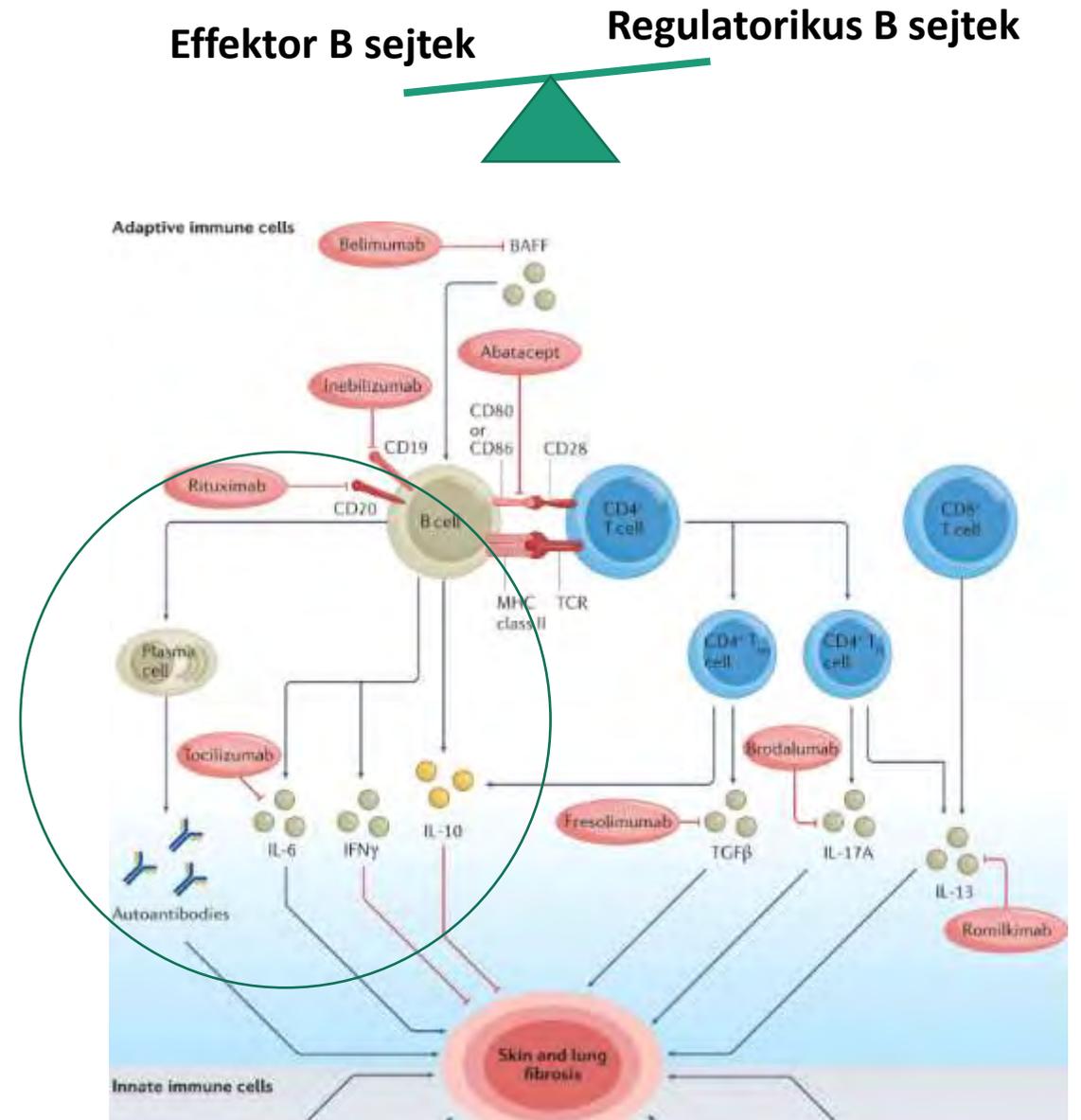
Contribution of T-cell subsets and their cytokines to fibrosis in SSc

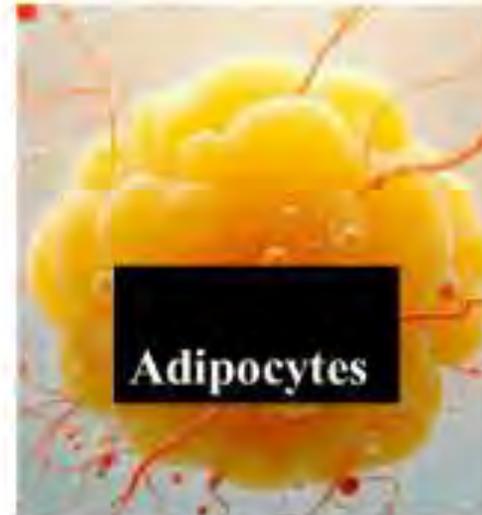
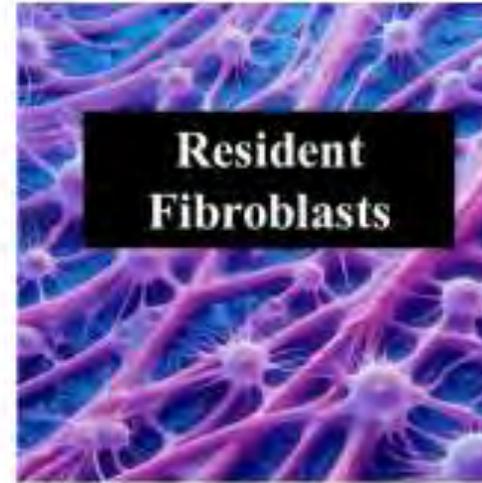
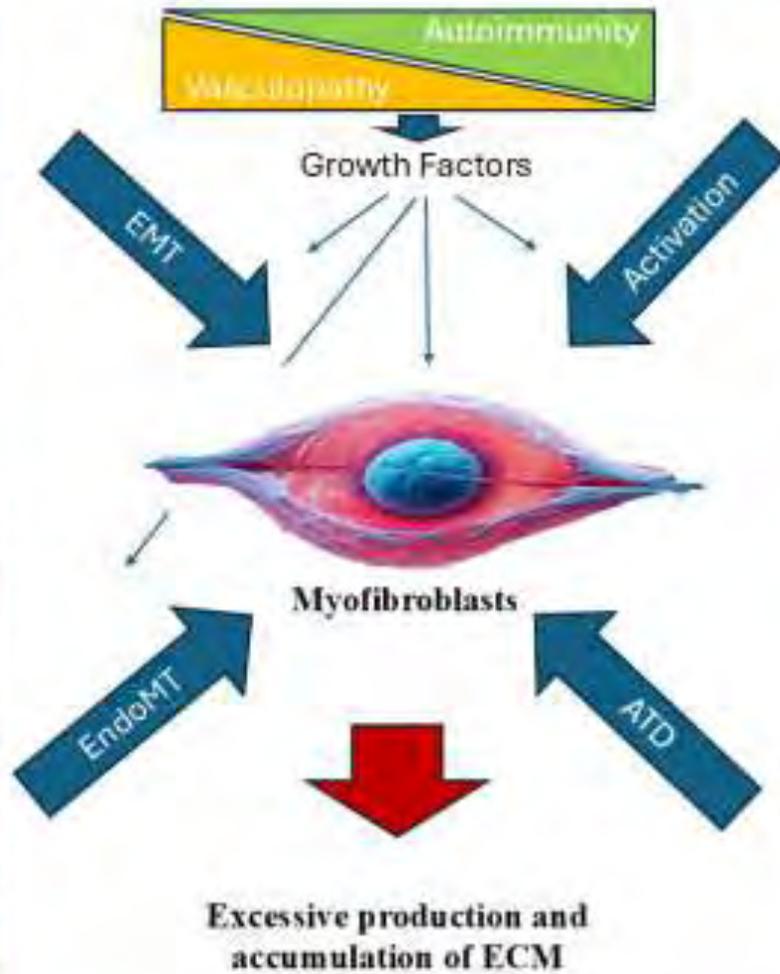
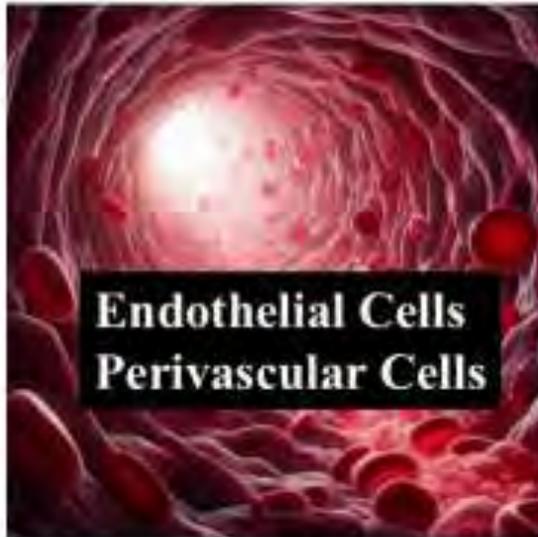
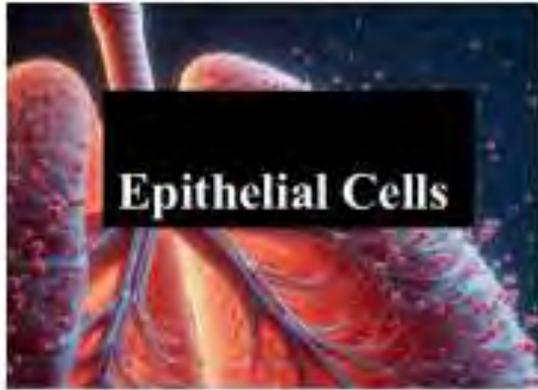


Adaptív immunitás

B-sejtek:

- Antitest termelés, citokin szekréció
- IL-6, IFN γ , GM-CSF
- Breg sejtek száma és funkciója is csökken: IL-10
- **BAFF: B-sejtek profibrotikus aktivitása nő, fokozódik a citokin szekréció**
- **Macrophagok M2 polarizációjában, T-sejtek, dendritikus sejtek aktivációjában is részt vesznek: innate-adaptív immunitás összeköttetés**





Fibrosis

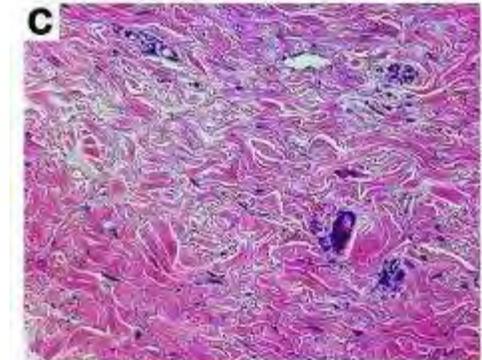
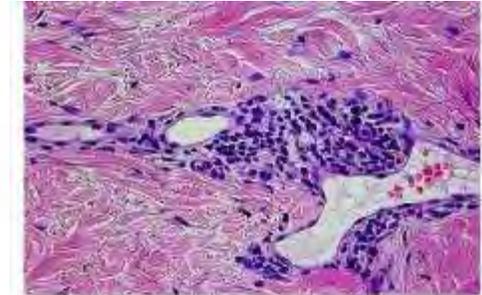
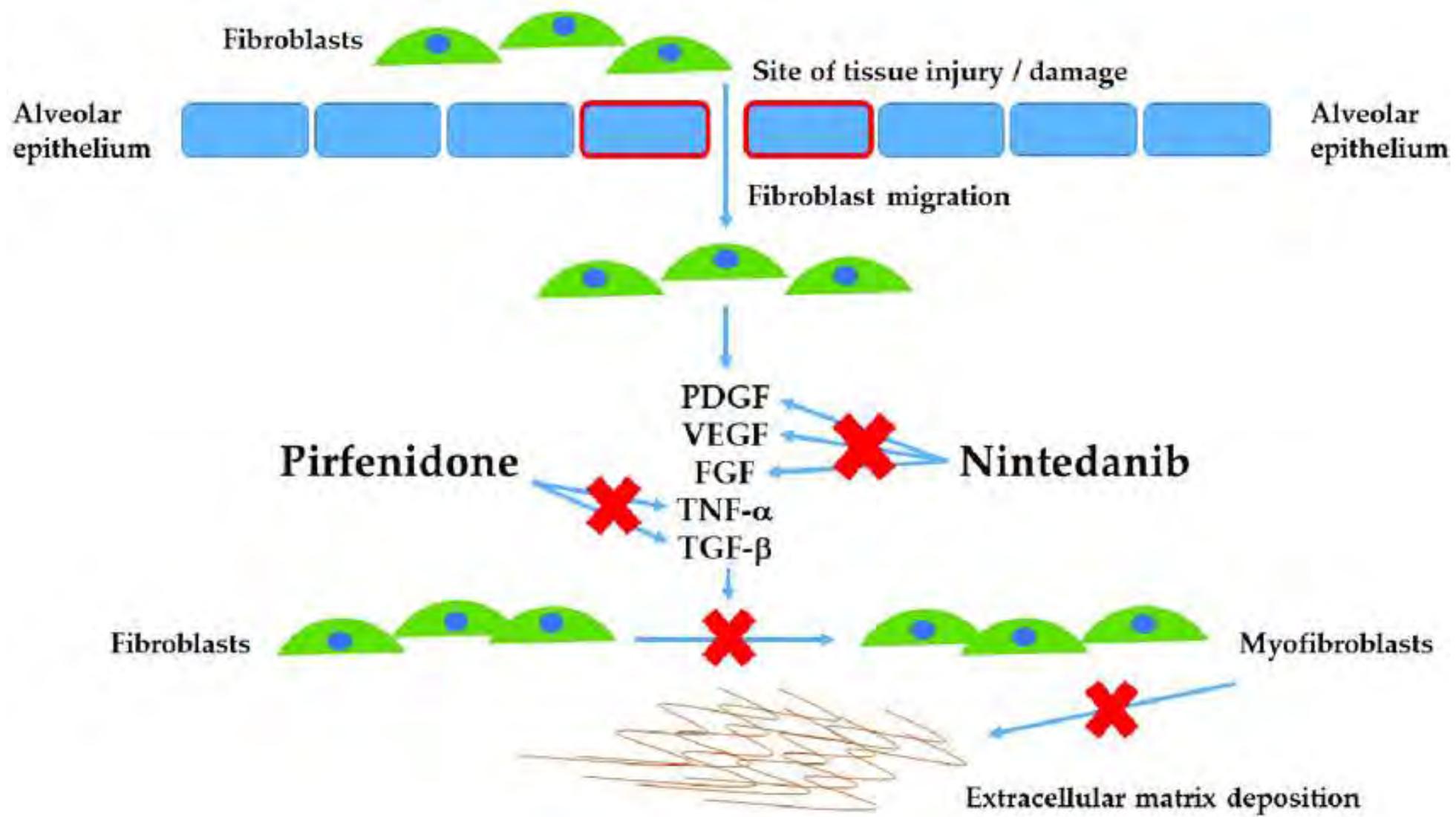


Figure 1. Pathophysiology of SSc. Early events, including endothelial cell dysfunction, vasculopathy,

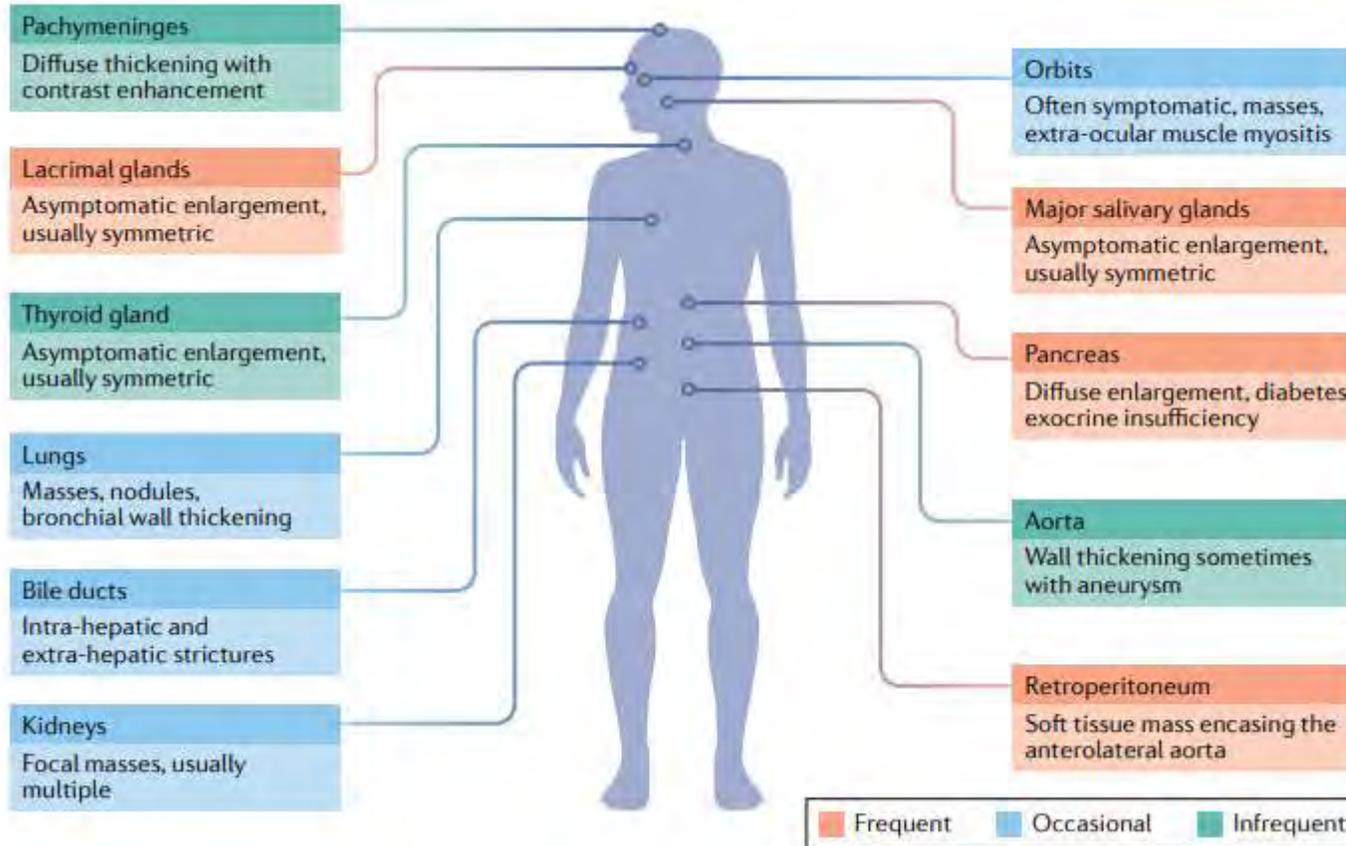
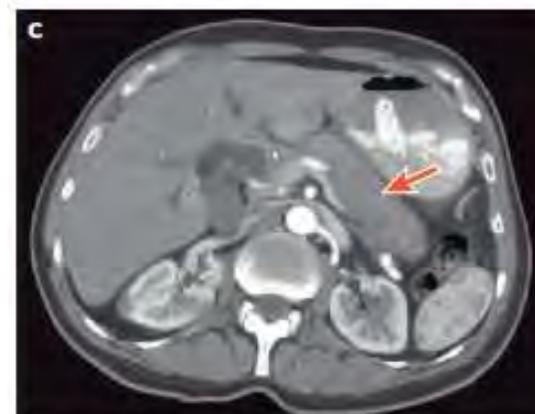
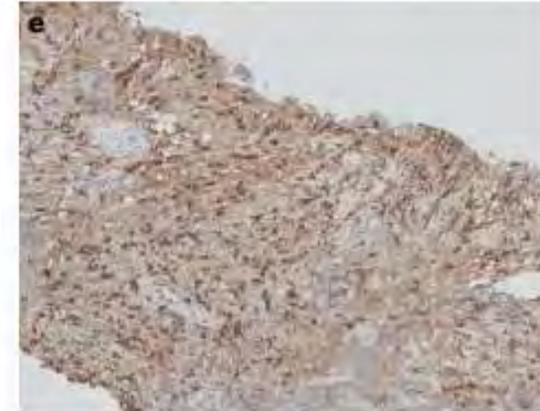
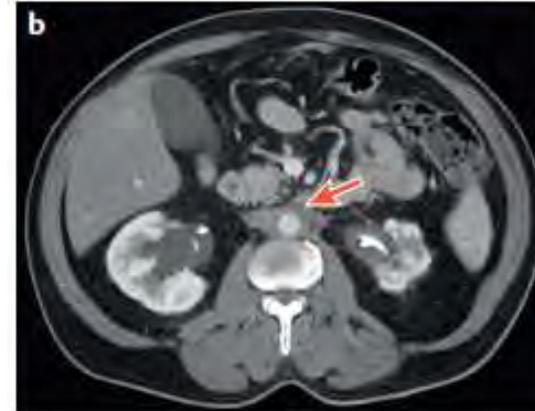
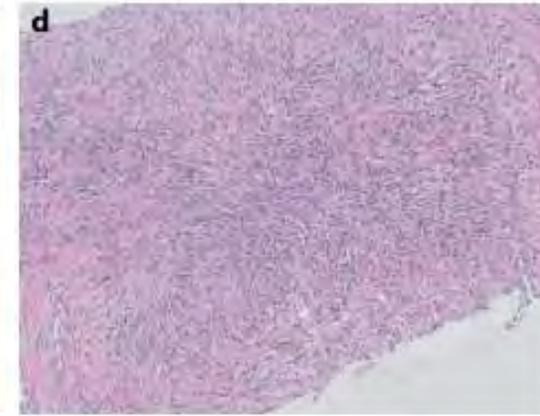


Szervi érintettségek pathogenezeise



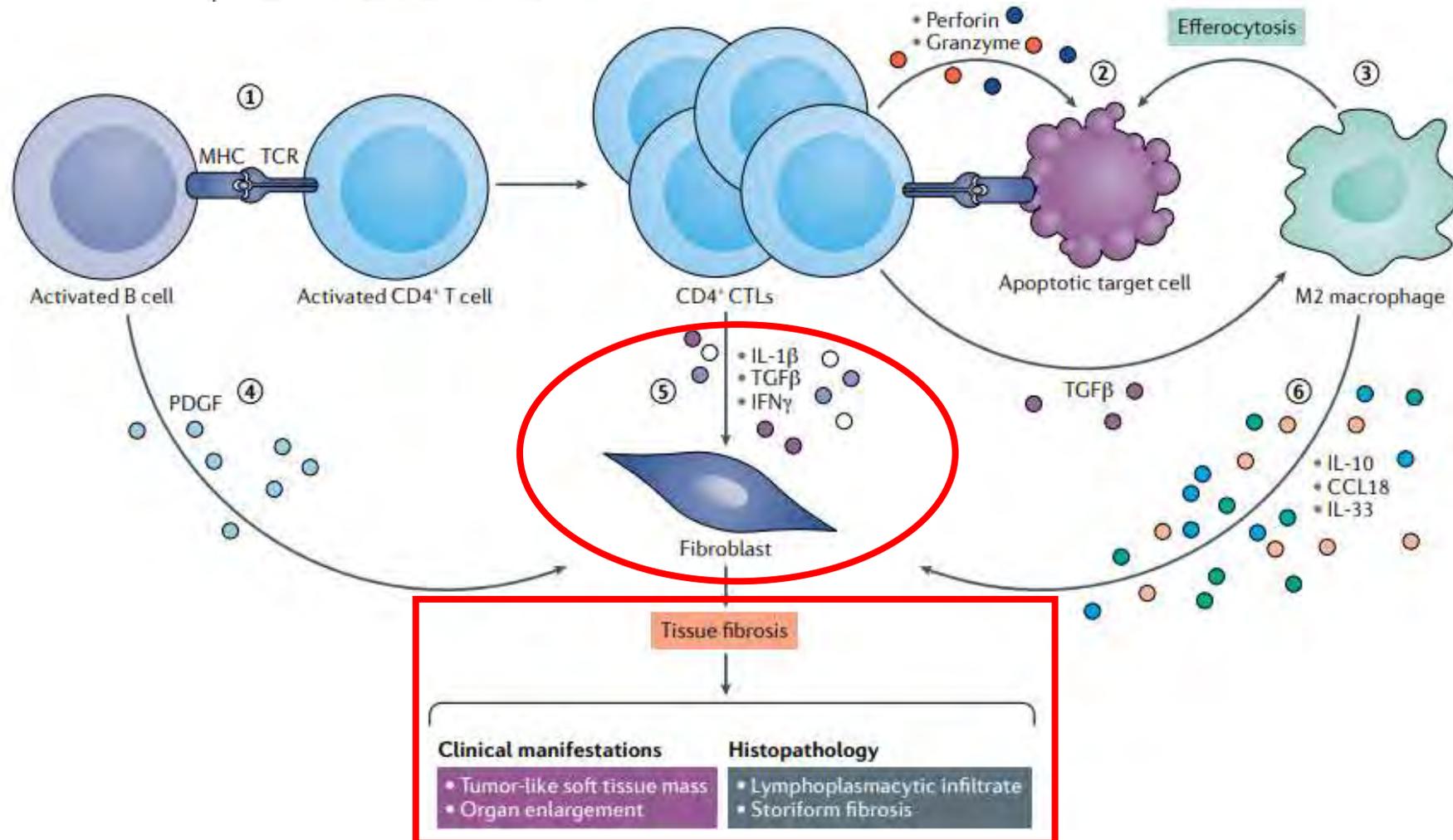
IgG4-related disease: an update on pathophysiology and implications for clinical care

Cory A. Perugino^{1,2} and John H. Stone¹ 



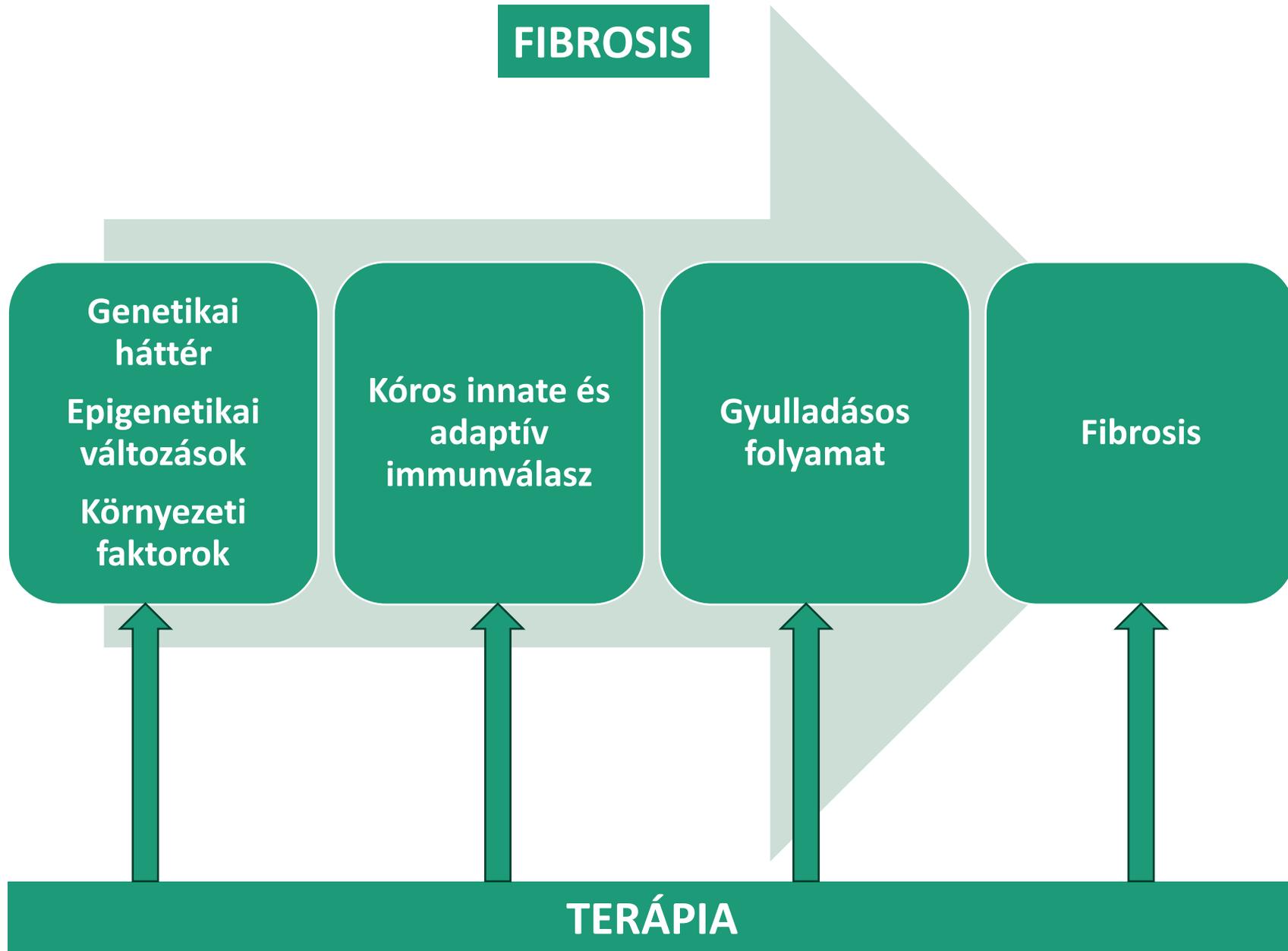
IgG4-related disease: an update on pathophysiology and implications for clinical care

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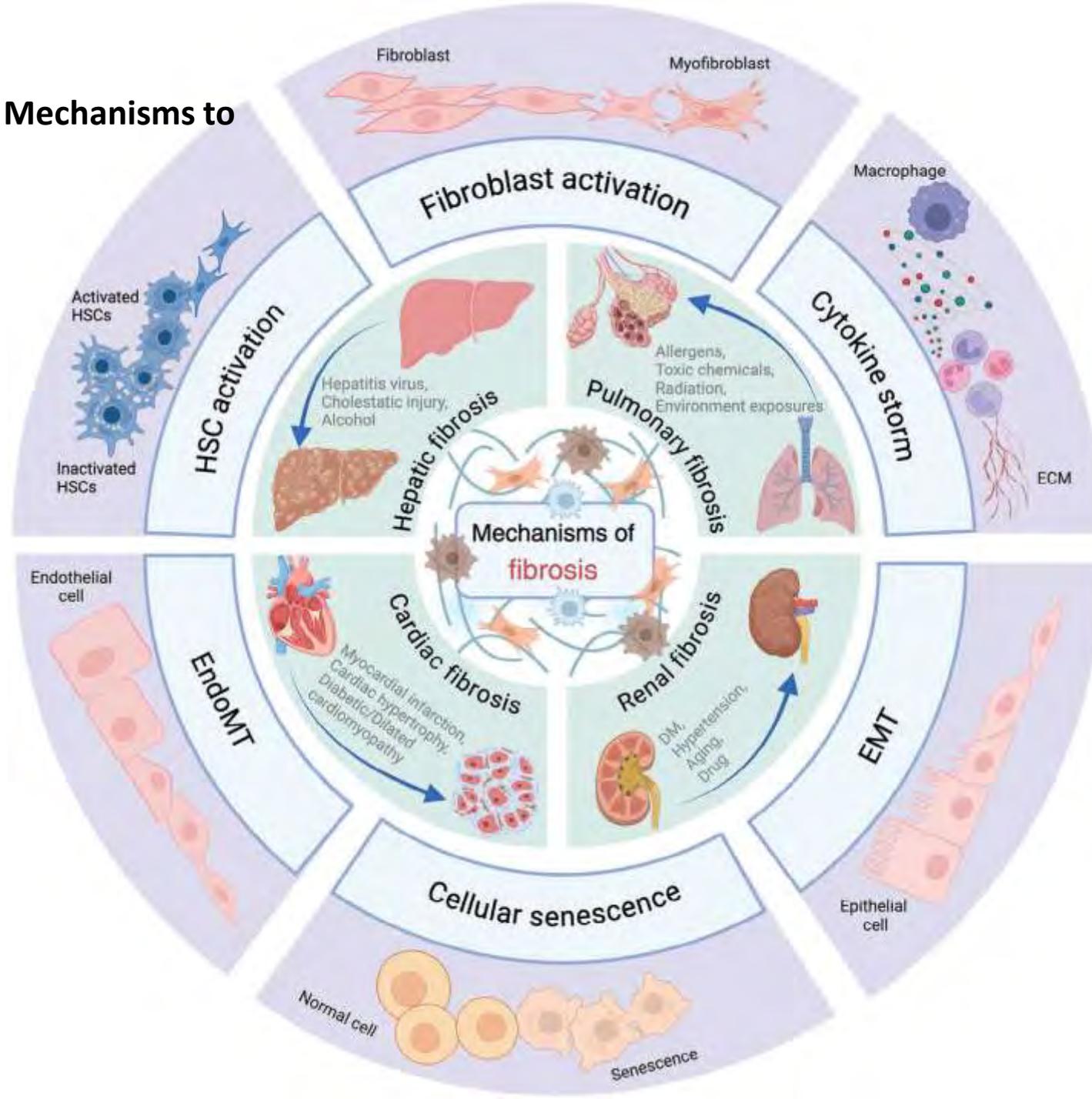


Fibrosissal járó kórképek kezelése

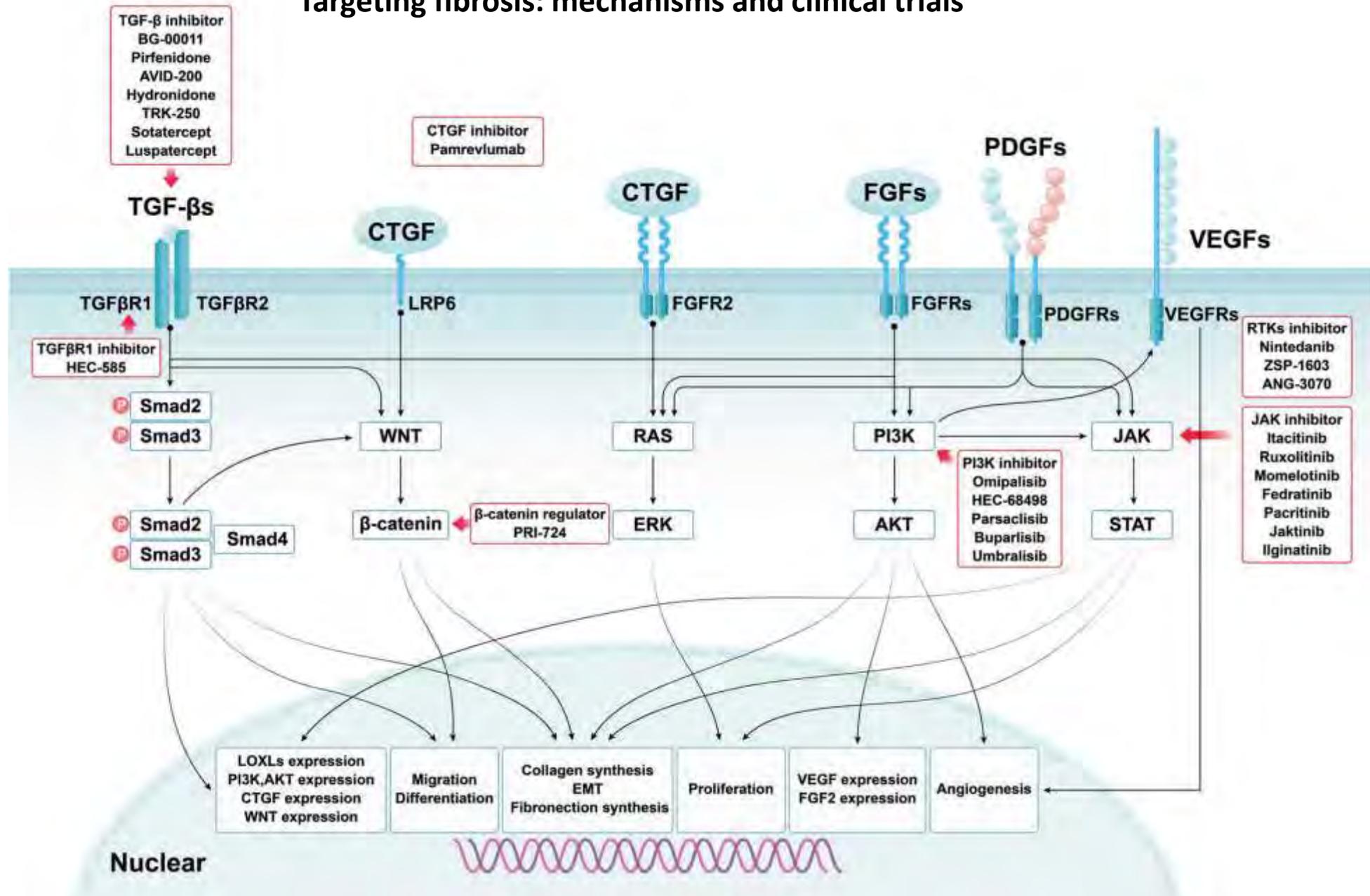
FIBROSIS



Targeting Fibrosis: From Molecular Mechanisms to Advanced Therapies



Targeting fibrosis: mechanisms and clinical trials



**Lactate and lactylation:
novel perspectives on
fibrosis pathogenesis and
therapeutic directions**

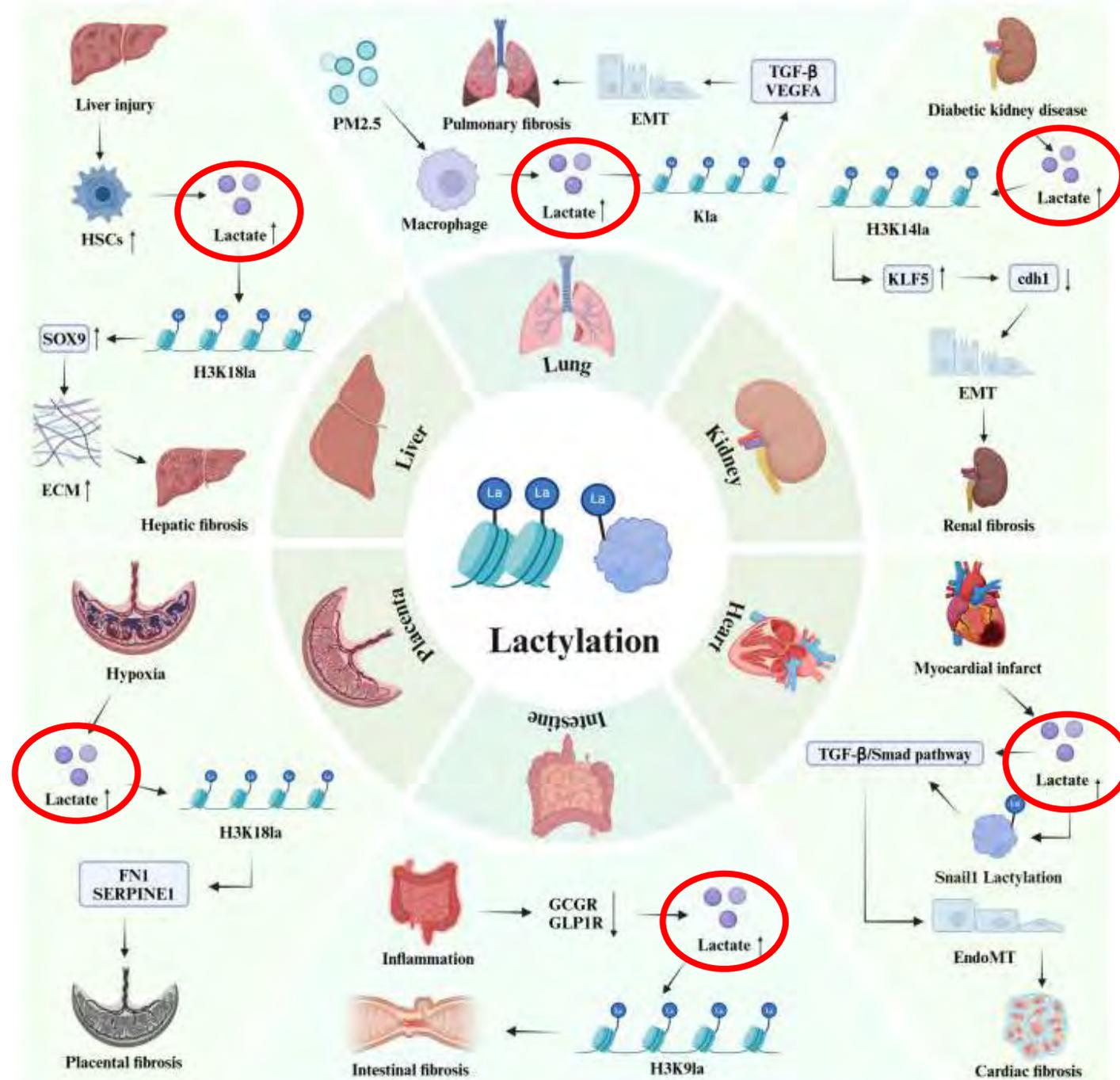


Fig. 3 Schematic diagram of the molecular mechanisms of lactylation modification in organ fibrosis. Emerging evidence highlights multiple Klf-related

Senescence and tissue fibrosis: opportunities for therapeutic targeting

Trends in Molecular Medicine, December 2024, Vol. 30, No. 12

Table 1. Senescence in fibrosis *in vivo*

Target organ	Disease model	Senotherapeutic agent(s)	Outcomes	Refs
Cardiac fibrosis	Aged INK-ATTAC and C57BL/6J mice	ABT-263 (navitoclax)	Pharmacological or genetic clearance of senescent cells in mice alleviated myocardial hypertrophy and fibrosis	[93]
	Ischemia reperfusion model in C57BL/6J mice	ABT-263 (navitoclax)	Navitoclax reduced senescence and improved cardiac function by attenuating the profibrotic SASP, reducing scar, and enabling increased angiogenesis	[94]
	Human cardiac fibrosis on a chip model	Quercetin, dasatinib	The senolytic drugs led to an improvement in contractile function, reduced passive tension, and downregulated senescence-related gene expression in the tissue	[95]
Renal fibrosis	Renal artery stenosis in INK-ATTAC mice	Quercetin, dasatinib	Both p16-specific and quercetin-dasatinib improved renal function and structure	[96]
	C57BL/6J mice on high fat diet	Quercetin	Improved renal function indices and alleviated fibrosis	[97]
	Aged and/or kidney injury models in C57BL/6J mice	ABT-263 (navitoclax)	ABT-263 treatment resulted in improved functional recovery and reduced fibrosis	[44]
	Lupus nephritis in MRL/lpr mice	Fisetin	Fisetin treatment attenuated kidney fibrosis, reduced SASP expression, and increased tubular epithelial cell proliferation	[98]
Lung fibrosis	Bleomycin lung fibrosis in INK-ATTAC mice	Quercetin, dasatinib	Both p16-specific and quercetin-dasatinib improved renal function and structure	[43]
	Ex vivo fibrotic 3D lung tissue	Quercetin, dasatinib	Pharmacological treatment significantly eliminated senescent markers and the SASP	[99]
	Bleomycin lung fibrosis in C57BL/6J mice	Nintedanib	Nintedanib suppressed senescent cell survival through the JAK2/STAT3 signaling pathway in the lung fibrosis model	[100]
	Intratracheal γ -irradiated IMR90 cells in mice	Digoxin	Digoxin effectively eliminated senescence-induced lung fibrosis	[101]
	Bleomycin and crystalline silica-induced lung fibrosis in mice	ABT-263 (navitoclax)	ABT-263 induced fibroblast apoptosis, decreased fibroblast numbers, and reduced fibrosis	[67,102]
	Bleomycin-induced lung fibrosis in mice	Rapamycin	Rapamycin inhibited pulmonary fibrosis and epithelial-mesenchymal transition in mice	[103]
	Radiation-induced lung fibrosis in C57BL/6 mice	FOXO4-DRI	FOXO4-DRI alleviated pulmonary fibrosis by targeting senescence-like fibroblasts <i>in vivo</i>	[104]
	Senescent IMR90 cells-induced lung fibrosis in mice	ABT-263 (navitoclax)	Navitoclax significantly reduced collagen content in fibrotic lungs, comparable with the effect of nintedanib and pirfenidone	[105]
Liver fibrosis	CCl ₄ - or NASH-induced liver fibrosis in C57BL/6N mice	α PAR-specific CAR T cells	CAR T cells efficiently eliminated senescent cells, reduced fibrosis, and improved liver function in mice	[98]

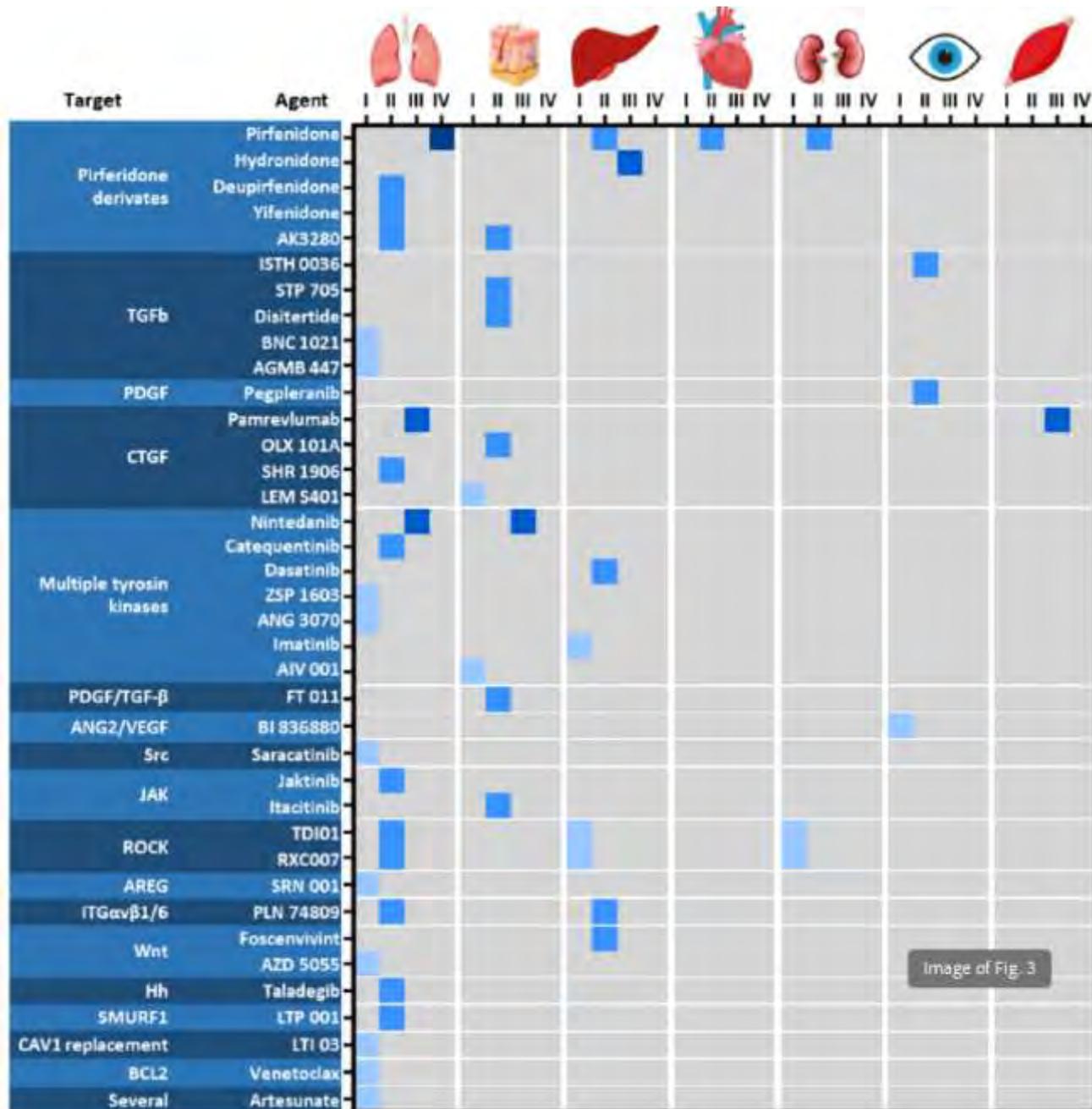
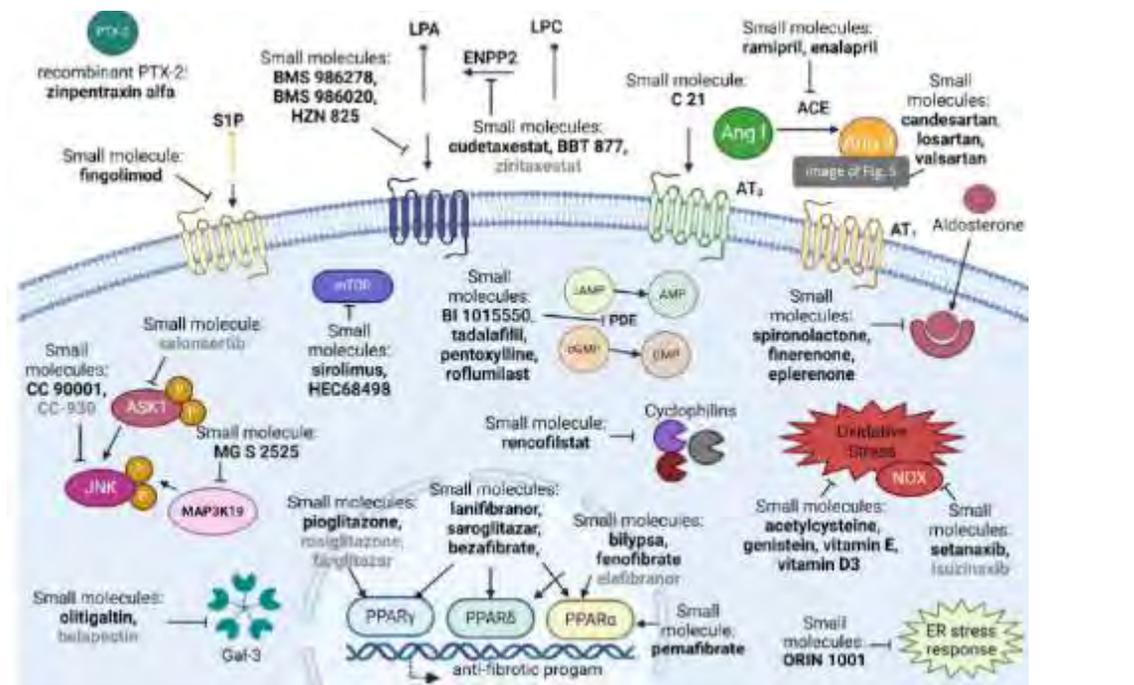
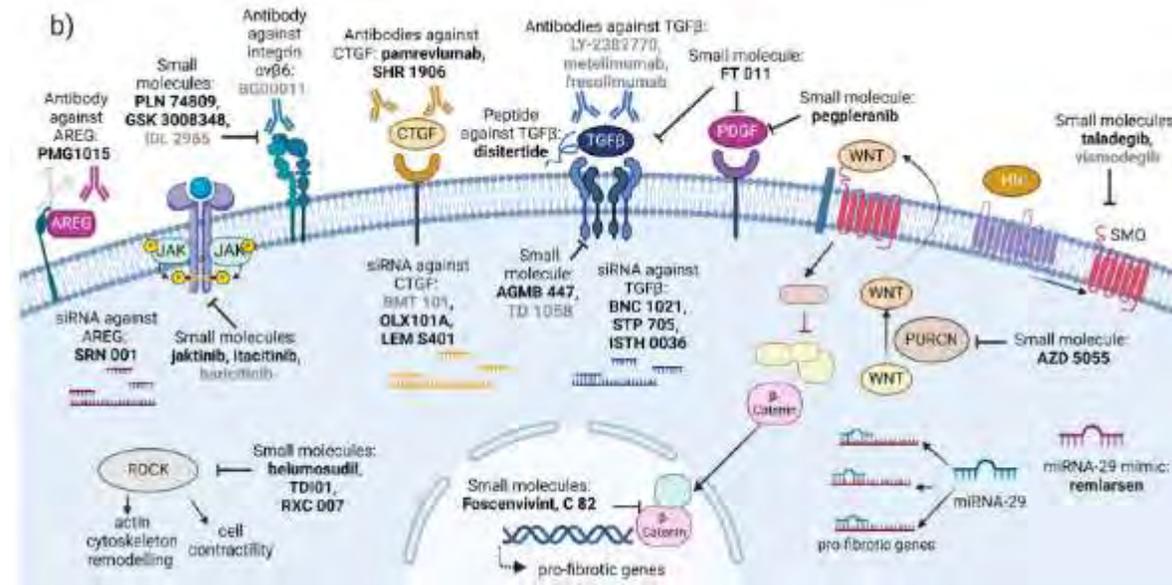


Image of Fig. 3

Új fibrosisgátló kezelési lehetőségek





Paracrine effects

Anti-inflammatory effects	Antifibrotic effect	Tissue regeneration
<ul style="list-style-type: none"> • Inhibit secretion of cytokines, chemokines and growth factors (IL-1β, IL-5, IL-6, IFNγ, TNFα, TGFβ) • Inhibit immunocyte infiltration • Promote polarization of M2 macrophage 	<ul style="list-style-type: none"> • Inhibit EMT • Inhibit ECM deposition • Inhibit activation of myofibroblasts • CAR-T against FAP⁺ cardiac myofibroblasts • Inhibit synthesis of TIMPs, increase synthesis of MMPs 	<ul style="list-style-type: none"> • Inhibit AEC2s senescence • Promote AEC2s proliferation • Replacement of damaged cells • Promote remuscularization of fibrotic tissue in the heart

Mechanisms of mesenchymal stem cell (MSC)-based therapy for fibrosis

ORIGINAL RESEARCH



CAR-Macrophage Therapy Alleviates Myocardial Ischemia-Reperfusion Injury

Jiawan Wang¹, Heng Du², Wanrun Xie³, Jinmiao Bi⁴, Hao Zhang⁵, Xu Liu⁶, Yuhan Wang, Shaolong Zhang, Anhua Lei, Chuting He, Hailong Yuan, Jiahe Zhang⁷, Yujing Li, Pengfei Xu, Siqi Liu⁸, Yanan Zhou, Jianghua Shen⁹, Jingdong Wu¹⁰, Yihong Cai¹¹, Chaofan Yang¹², Zeya Li, Yingxin Liang¹³, Yang Zhao¹⁴, Jin Zhang, Moshi Song¹⁵

Circulation Research. 2024;135:1161–1174

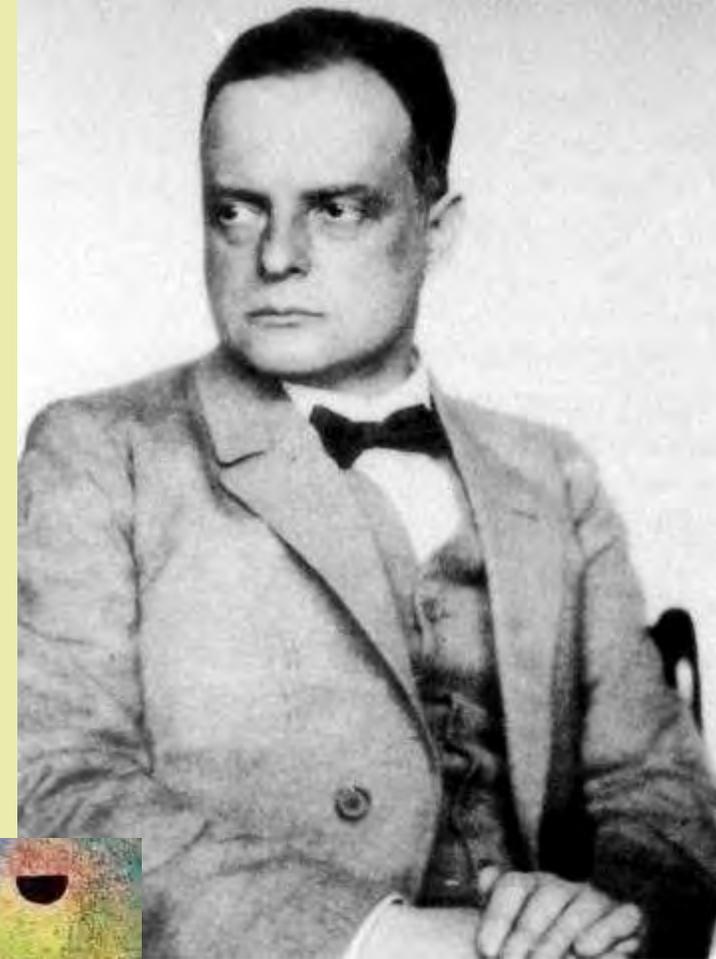
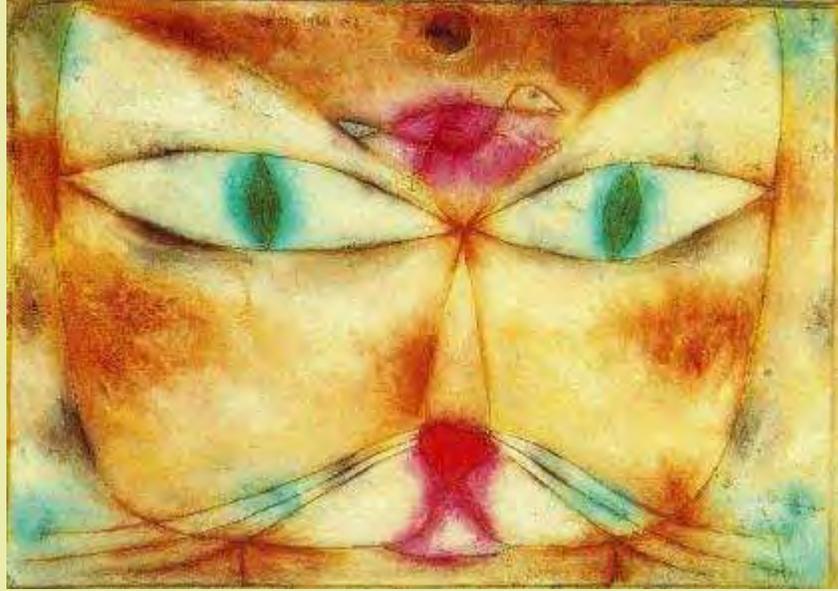
Cell

Article

Allogeneic CD19-targeted CAR-T therapy in patients with severe myositis and systemic sclerosis

Cell 187, 4890–4904, September 5, 2024

**KÖSZÖNÖM A
FIGYELMET!**



1879-1940

