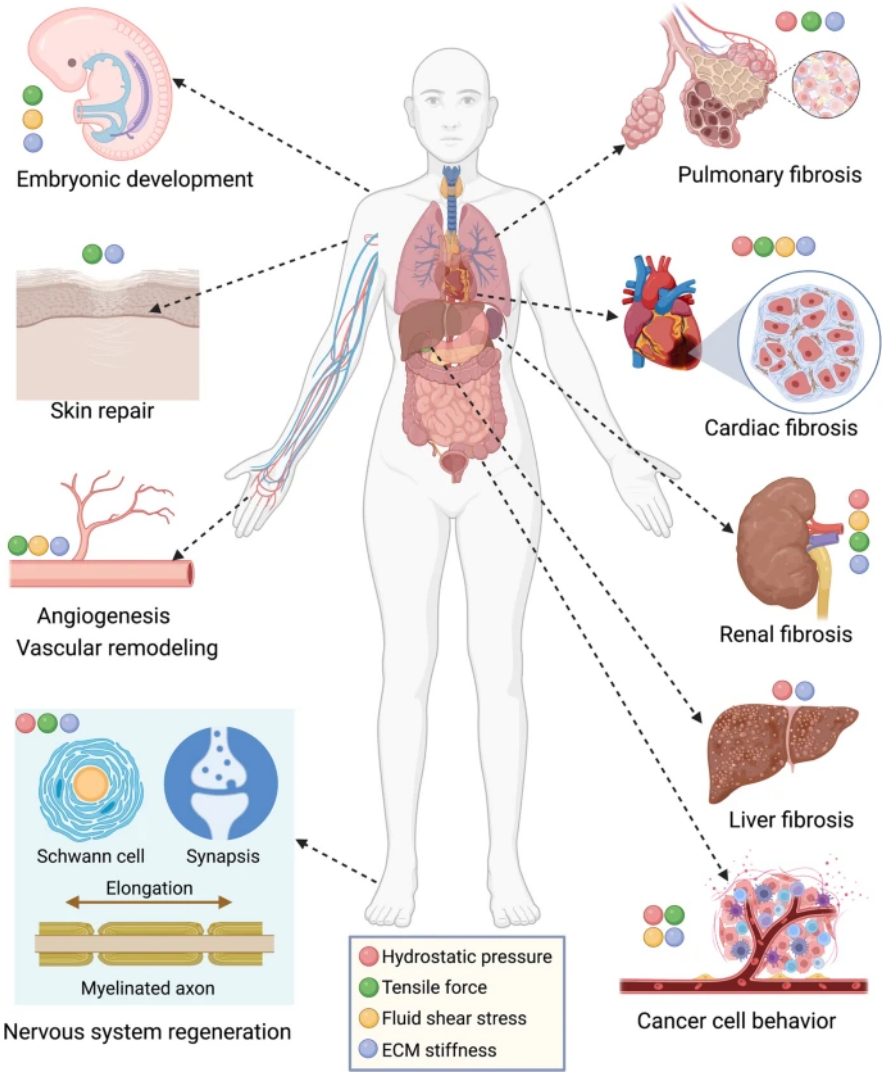
Mechanotranduction in health and disease



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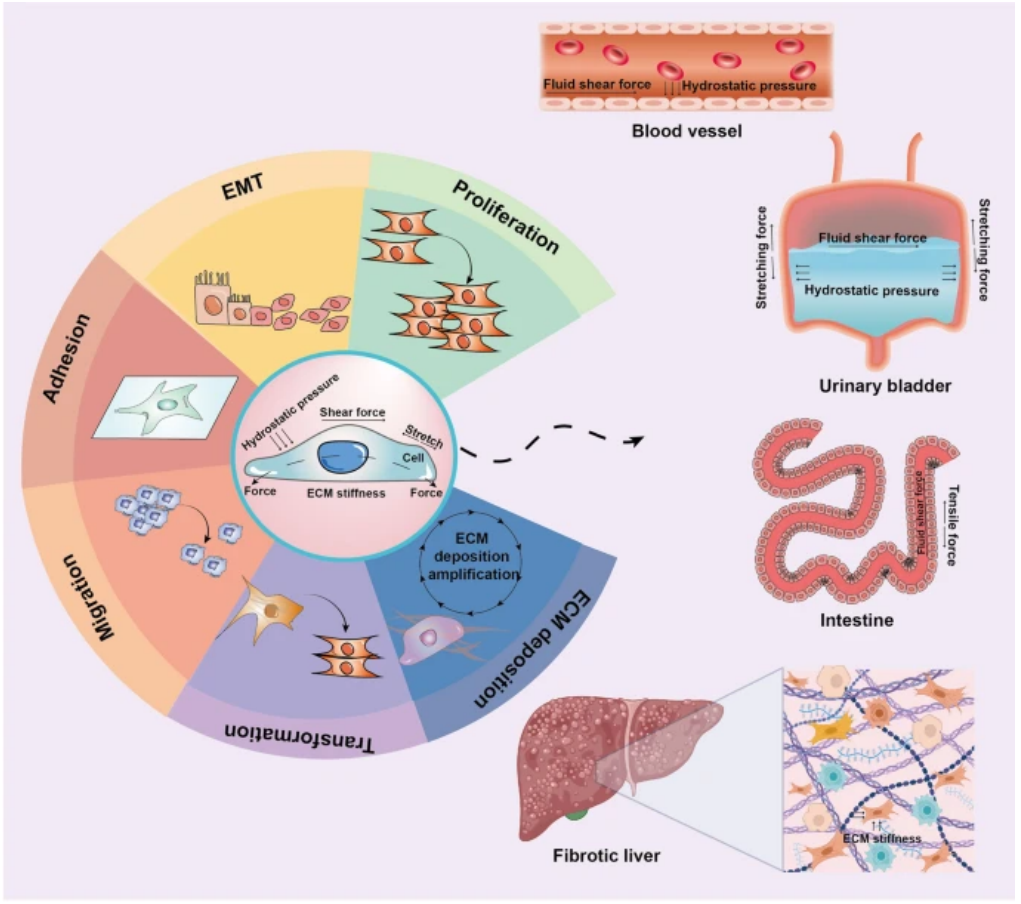

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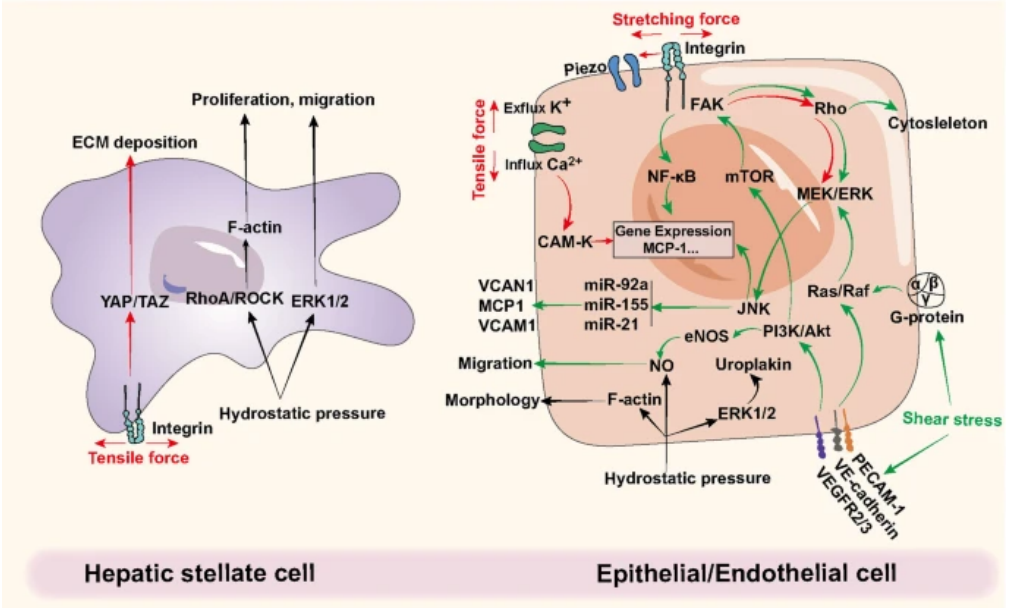
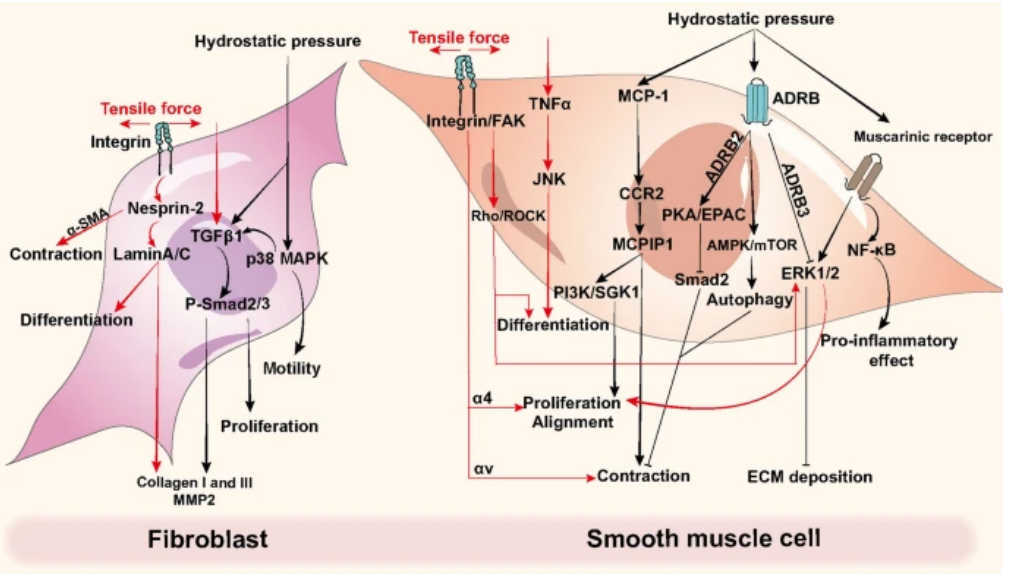
Hydrostatic pressure

- HP in the interstitial cavity is approximately −4 cmH_2O
- in solid tumors and edematous tissues, the pressure is 25–40 cmH_2O
- Studies have revealed that periodic HP promotes bone growth and organization. Osteogenesis and bone density can also be enhanced by HP
- HP -> Piezo1 (ion channel) -> mitogen- activated protein kinases (MAPK) and p38 signaling pathways -> bone morphogenetic protein 2 (BMP2) -> change phenotype of mesenchymal stem cells.
- The cytoskeleton-related signals (i.e., RhoA, ROCK, α-SMA) are enhanced by 50 mmHg of HP on hepatic stellate cells --> hepatic fibrosis
- Pathological high HP --> fibroblast motility --> high collagen deposition (via TGFβ1/Smad3 and p38 MAPK pathways)





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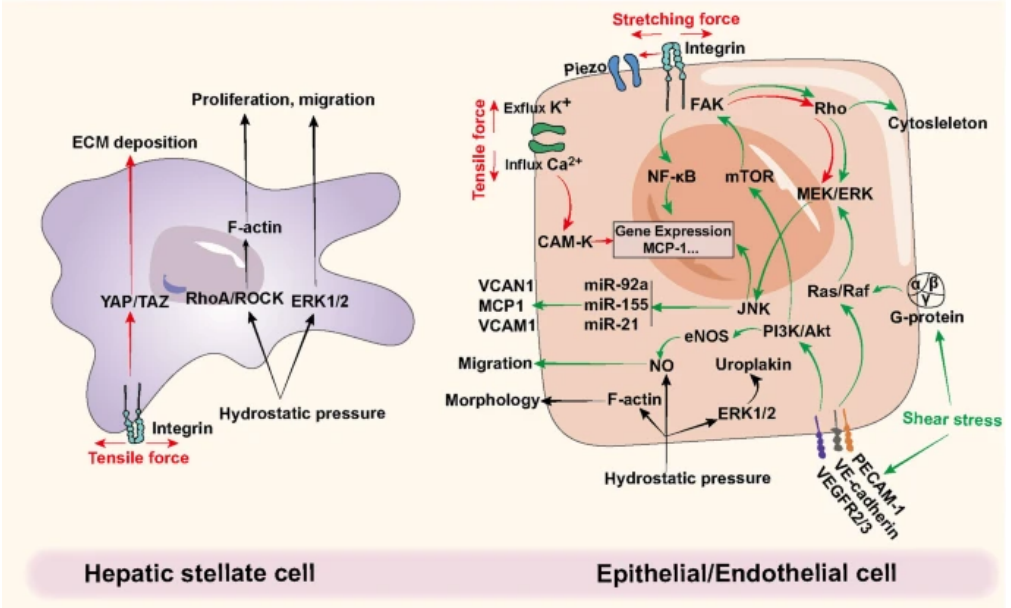
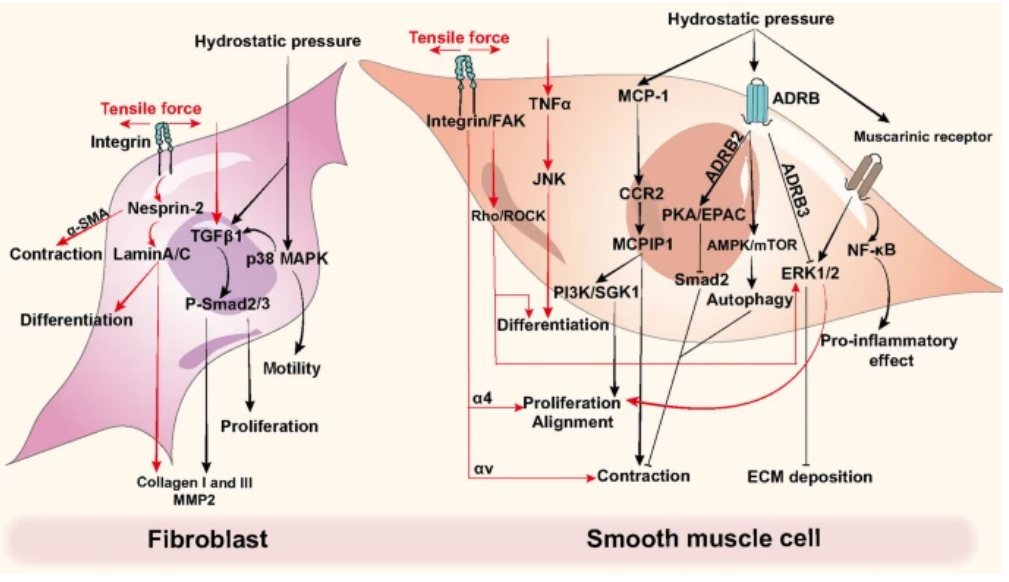
Fluid shear stress

- Typical FSS exists in human vasculature (i.e., vessel bifurcations, stenosis, aortic aneurysms, heart valves, and capillary networks), including shear and extensional flow.
- Stable flow or laminar flow functions in anti-inflammation, anti-adhesion, and anti-thrombosis in the vascular wall.
- However, persistent turbulent flow in the vascular wall can increase the endothelial permeability (i.e., junctional proteins alteration) and proinflammatory signaling (i.e., nuclear factor κB [NF-κB] signaling, adhesion molecules activation) to promote the formation of lesions.
- The blood flow-induced hemodynamic changes regulate multiple signaling pathways in various vascular wall cells.
- When the cells receive the FSS mechanical signals, several mechanosensors will be triggered, including integrins, the glycocalyx, primary cilia, G-protein-coupled receptors, and ion channels.
- A recent study concluded that β integrin, a specific sensor of unidirectional FSS but not bidirectional, drives the endothelial cell alignment and downstream cascade.





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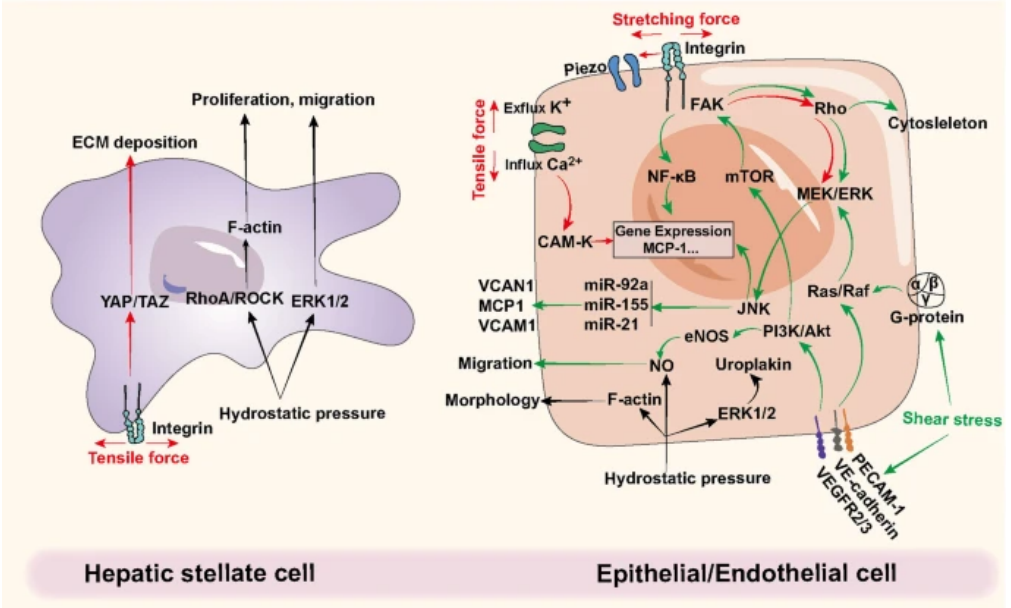
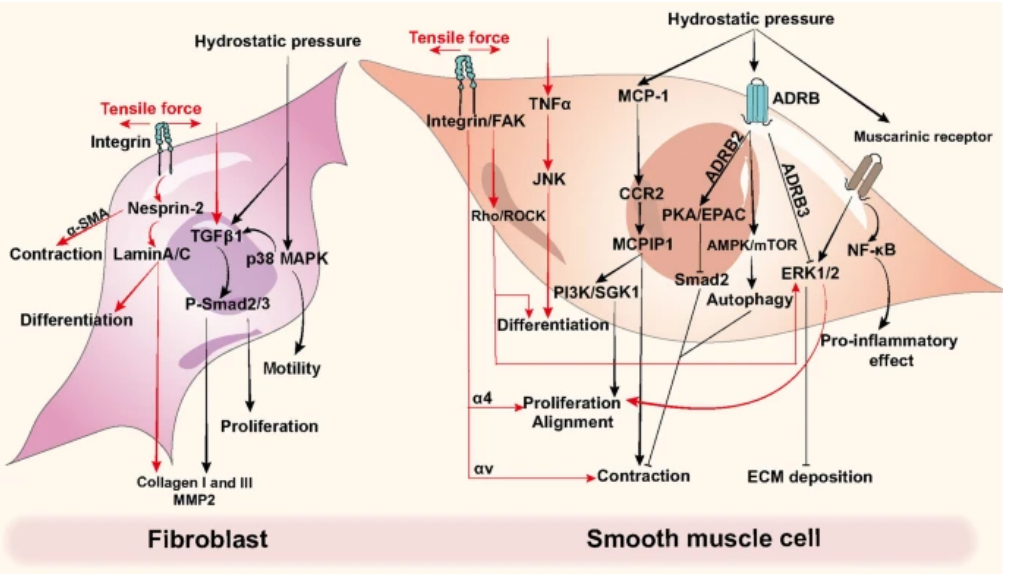
Tensile force

- important in muscle and joint movement, atherogenesis, cardiovascular remodeling
- In the vascular wall, TF promotes vascular remodeling and contraction
- TF can induce urothelium proliferation through α6-focal adhesion kinase (FAK) signaling.
- The magnitude, frequency, and duration of the TF can affect the alignment, differentiation, migration, proliferation, survival, apoptosis, and autocrine and paracrine functions of cells
- The nucleus membrane senses TF and reacts more rapidly than common biochemical transduction.
- During nuclear mechanosensing, the mechanosensitive pathways in mature tissues do not respond to intercellular tension. Thus, these signaling pathways do not influence fibroblast differentiation in subsequent fibrosis.
- It is worth noting that different TF intensities induce various effects on the chondrocyte mechanotransduction process --> role in arthritis





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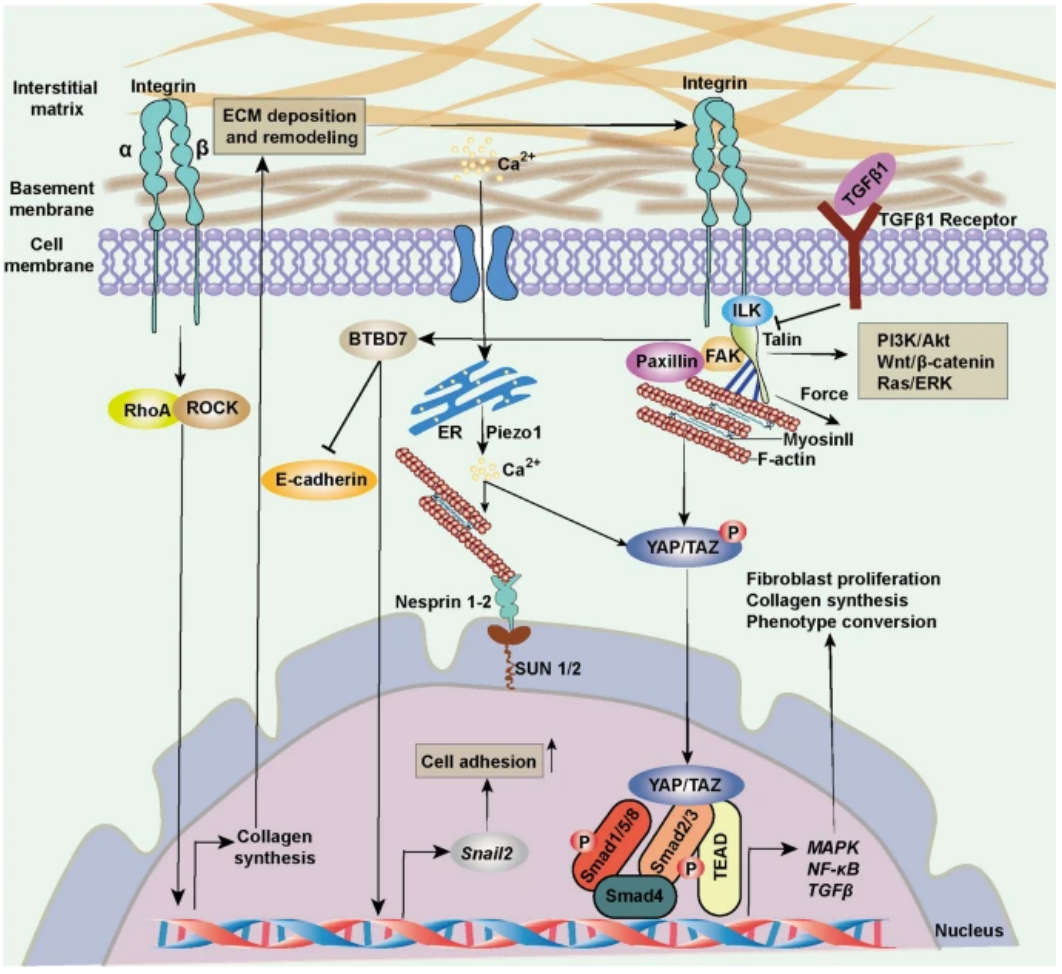
ECM stiffness

- In ECM, fibrillar proteins (collagen for example) have high tensile strength but low compliance. Elastic fibers (elastin) have high compliance and low strength.
- The cells communicate via the intracellular skeleton and cell surface adhesion molecules with the ECM and neighboring cells.
- ECM remodeling is associated with complicated physiological conditions. Pathological ECM has a prolonged impact on the morphology and functions of cells and forms an amplification effect to strengthen the ECM deposition process further, resulting in severe fibrosis.
- The available evidence demonstrated a predominant increase in type I and type III collagen fibers observed in hypertensive heart disease and aortic stenosis-associated heart failure.
- Liver fibrosis has been indicated to be triggered by myofibroblasts from chronic hepatotoxic injury (i.e.,hepatitis HBV or hepatitis HCV, alcohol abuse) or cholestatic injury (i.e., bile duct obstruction). HSCs-secreted ECM promotes transformation from fibroblasts to myofibroblasts.
- normal lung tissues have Young’s Modulus of approximately 1 kPa required for respiration. In IPF lung elasticity increases to 30–50 kPa



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ECF viscosity

- A recent study identified a novel mechanical cue, ECF viscosity, which could interact with ECM stiffness to induce cell migration and substrate mechanotransduction.
- cell migration and cancer dissemination are shown to be facilitated by increased ECF viscosity.
- The crosstalk between ECF and cells induces the actin-related protein-2/3 (ARP2/3)-complex-dependent actin network --> RhoA-dependent contractility is increased, thereby enhancing the motility of cells.
- ECF viscosity has also been confirmed to promote cell spreading dynamics based on integrin/YAP signaling.
- the mechanisms of the impact of ECF viscosity on cells are largely understudied.

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Table 1. Functions of Piezo channels in cellular mechanotransduction

Type	Target	Mechanical stimulation	Mechanism	Reference
Piezo1	Vascular endothelium development	Shear stress	Ca^{2+}influx→MTP-MMP signaling→focal adhesion and endothelial cell sprout formation;	232
	Vascular tone	Shear stress	Ca^{2+}influx→G-coupled endothelial adrenomedullin receptor→cAMP→eNOS→NO; Ca^{2+}influx→ATP→PI3K/AKT→eNOS→NO	198–200
	Vascular remodeling	Stretch	Ca^{2+}influx→transglutaminase →ECM remodeling	222
	Erythrocytes	Shear stress	Ca^{2+}influx→K^{+} efflux→red blood cells dehydration	201
	Erythrocytes	Shear stress	Ca^{2+}influx→pannexin-1→ATP release	202
	Nervous system	Traction force	Ca^{2+}influx→neural differentiation →neuron-astrocyte interaction	203,204
	Gastric mucosa	Antrum distension	Activated G cells→gastrin secretion	205
	Lung endothelium	Shear stress	Ca^{2+}influx→calpain→Src cleavage→stabilization of adherens junctions	206
	Lung endothelium	Hydrostatic pressure	Ca^{2+}influx→calpain→disruption of adherens junctions	207
	Aoveoli	Stretch	Ca^{2+}influx→Bcl-2 pathway→type II epithelial cells apoptosis	208
	Urinary bladder	Stretch	Ca^{2+}influx→ATP→attenuate storage disorders	209
	Tumor	ECM stiffness	YAP-Piezo1→proliferation; Ca^{2+}influx→AKT/mTOR phosphorylation→proliferation; Piezo1–mitochondrial calcium uniporter–HIF-1α–VEGF axis→metastasis	210,211,213
Piezo2	Gastrointestinal epithelium	Mucosal force	5-HT pathway→mucosal secretion	212
	Airway	Stretch	Ablation of *Piezo2*→Airway-innervating sensory neurons→ respiratory distress and death in newborn mice	214,215
	Urinary bladder	Stretch	Sensory neuron→bladder filling sensation	221
Piezo1/2	Baroreceptor reflex	Shear stress	Elevated blood pressure→Piezo1/2 →nodose-petrosal-jugular-ganglion complex→ decreased blood pressure and heart rate	216–218
	Chondrocyte anabolic and biosynthesis	Mechanical stress	GsMTx4→Piezo1/2 inhibition→ alleviate chondrocyte injury	219,220

ECM extracellular matrix, *MMP* matrix metalloprotease, *5-HT* 5-hydroxytryptamine

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Table 2. Typical clinical trials targeting integrins

Integrin subtype	Intervention/treatment	Disease type	Phase	Current status	ClinicalTrials.gov identifier
α5β1	Volociximab	Metastatic renal cell carcinoma	2	Terminated	NCT00100685
		Pancreatic cancer	2	Completed	NCT00401570
		Ovarian cancer, primary peritoneal cancer	1/2	Completed	NCT00635193
α4β7	Vedolizumab	Ulcerative colitis	4	Recruiting	NCT05481619
		Crohn's disease; ulcerative colitis	Not applicable	Completed	NCT02862132
		Inflammatory bowel disease	Not applicable	Completed	NCT02712866
		Type 1 diabetes	1	Recruiting	NCT05281614
αvβ1; αvβ3; αvβ6	IDL-2965 oral capsule	Idiopathic pulmonary fibrosis	1	Terminated	NCT03949530
αvβ6; αvβ1	PLN-74809	Idiopathic pulmonary fibrosis	2	Completed	NCT04072315
αLβ2; α4β1	7HP349	Solid tumor	1	Completed	NCT04508179

Table 3. Typical clinical trials targeting YAP/TAZ

Target	Intervention/treatment	Disease type	Phase	Current status	ClinicalTrials.gov identifier
YAP	Simvastatin	Prostate cancer	2	Recruiting	NCT05586360
	ION537	Advanced solid tumors	1	Completed	NCT04659096
YAP/TAZ	Zoledronate	Breast cancer	2	Terminated	NCT02347163
TEAD	IK-930	Solid tumors	1	Recruiting	NCT05228015

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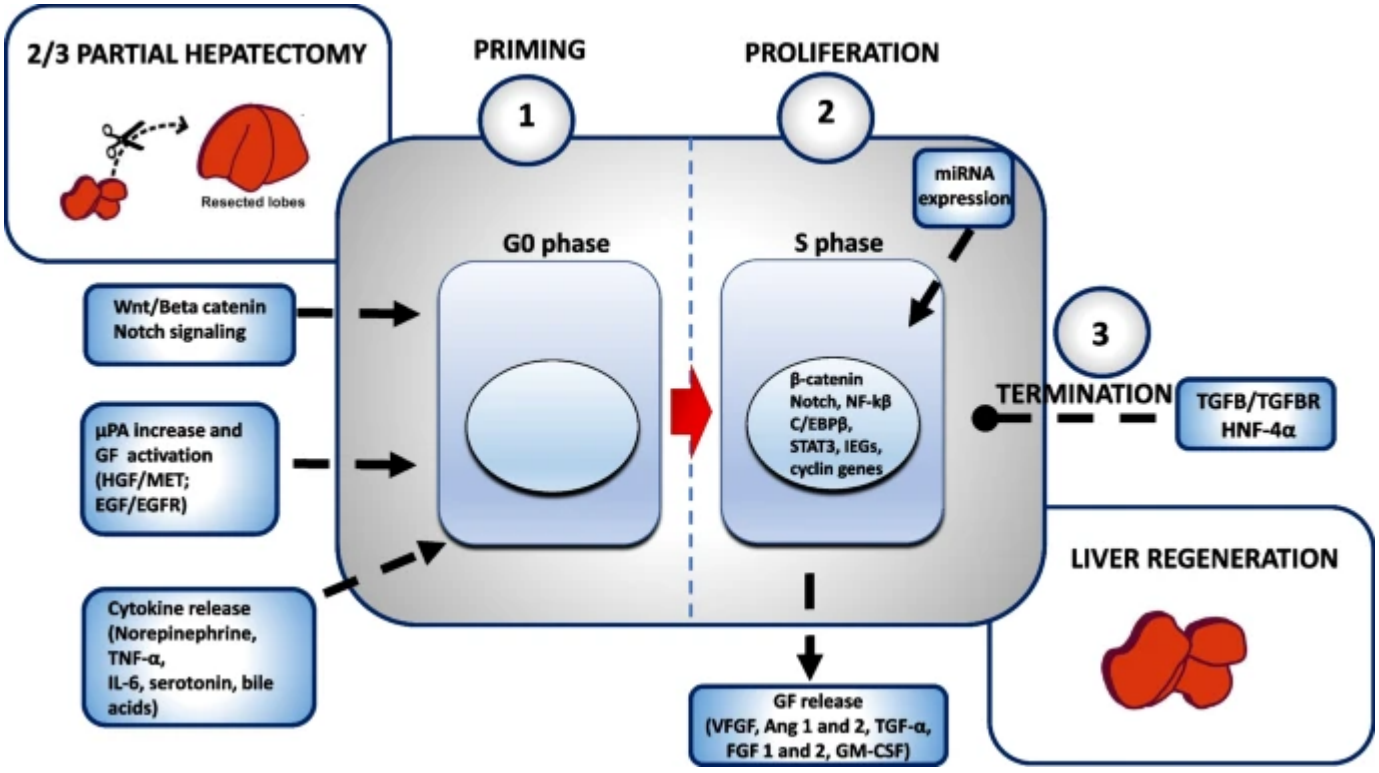
Hippo signaling in liver



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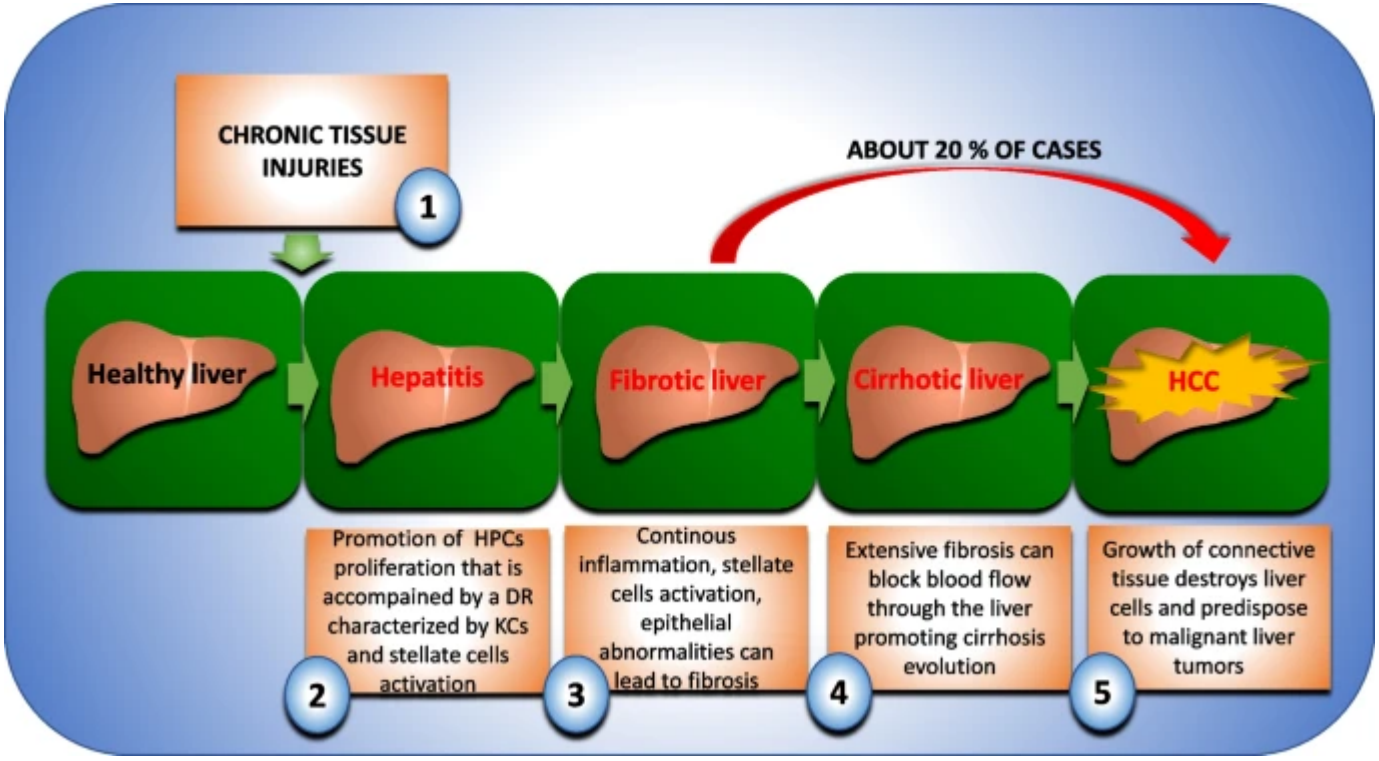
Hippo signaling in liver



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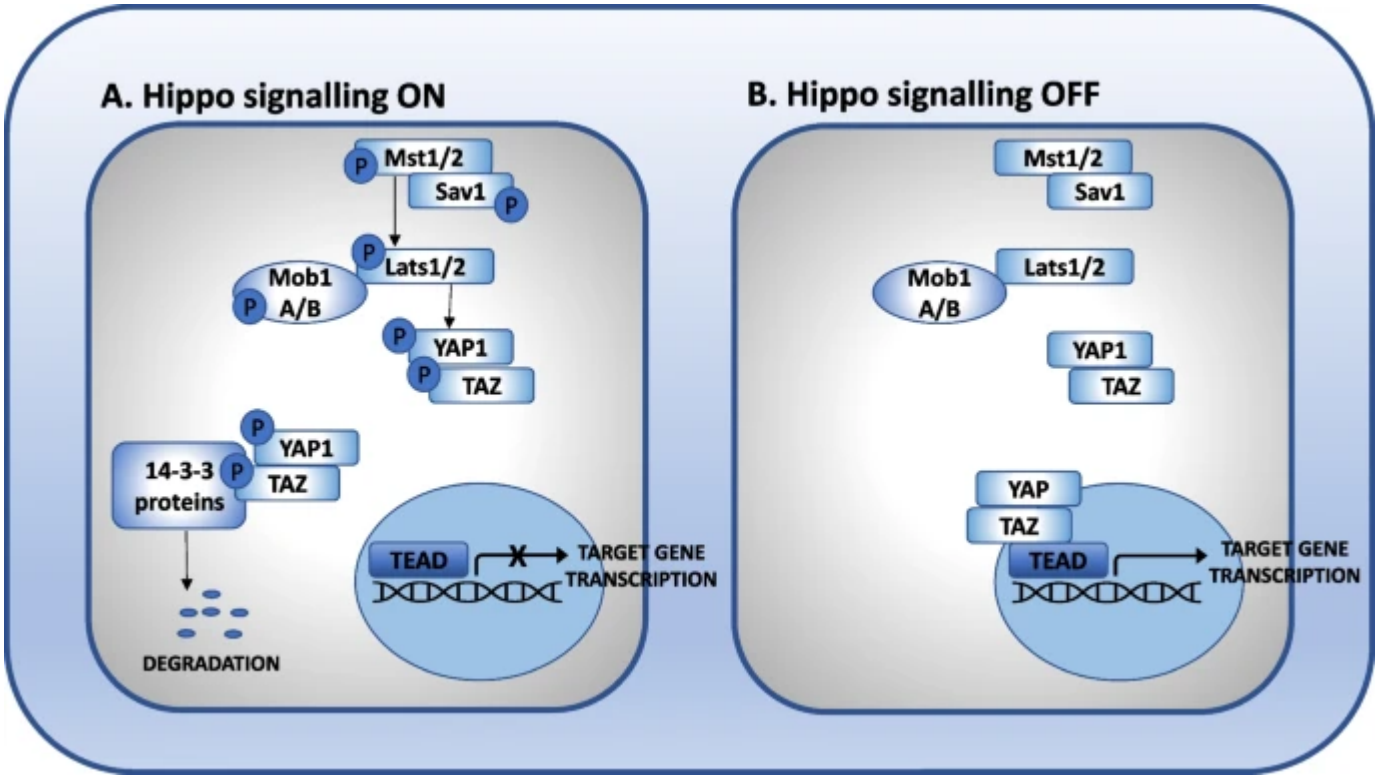
Hippo signaling in liver



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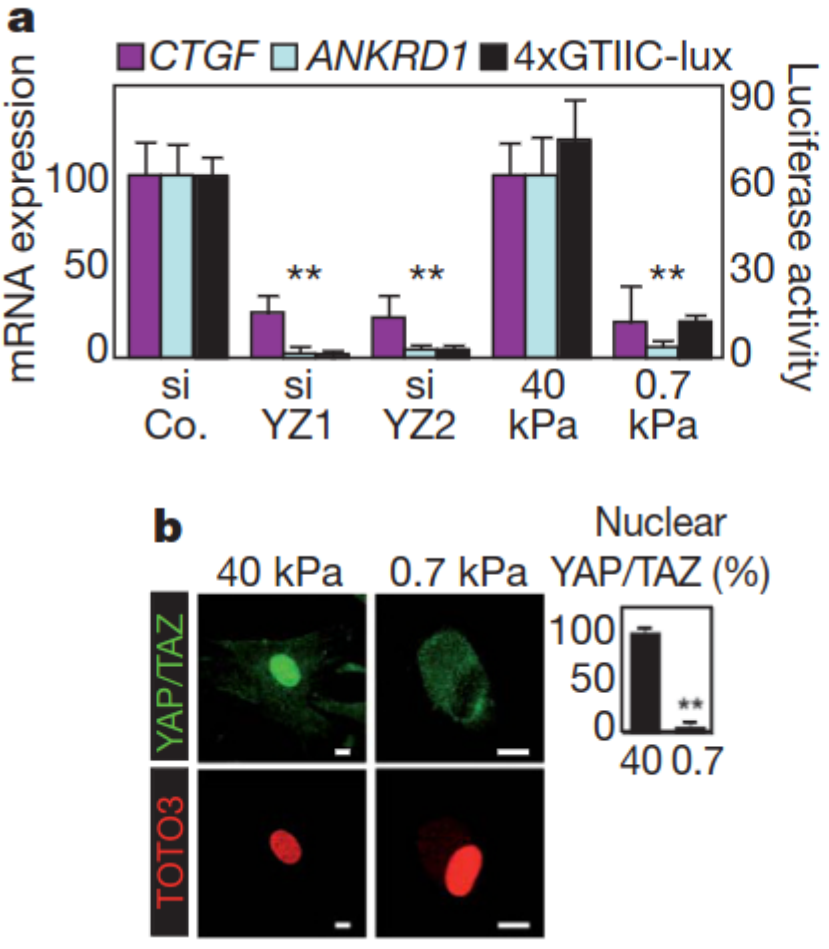
Role of YAP/TAZ in mechanotransduction

Sirio Dupont, Leonardo Morsut, Mariaceleste Aragona, Elena Enzo, Stefano Giulitti, Michelangelo Cordenonsi, Francesca Zanconato, Jimmy Le Digabel, Mattia Forcato, Silvio Bicciato, Nicola Elvassore & Stefano Piccolo

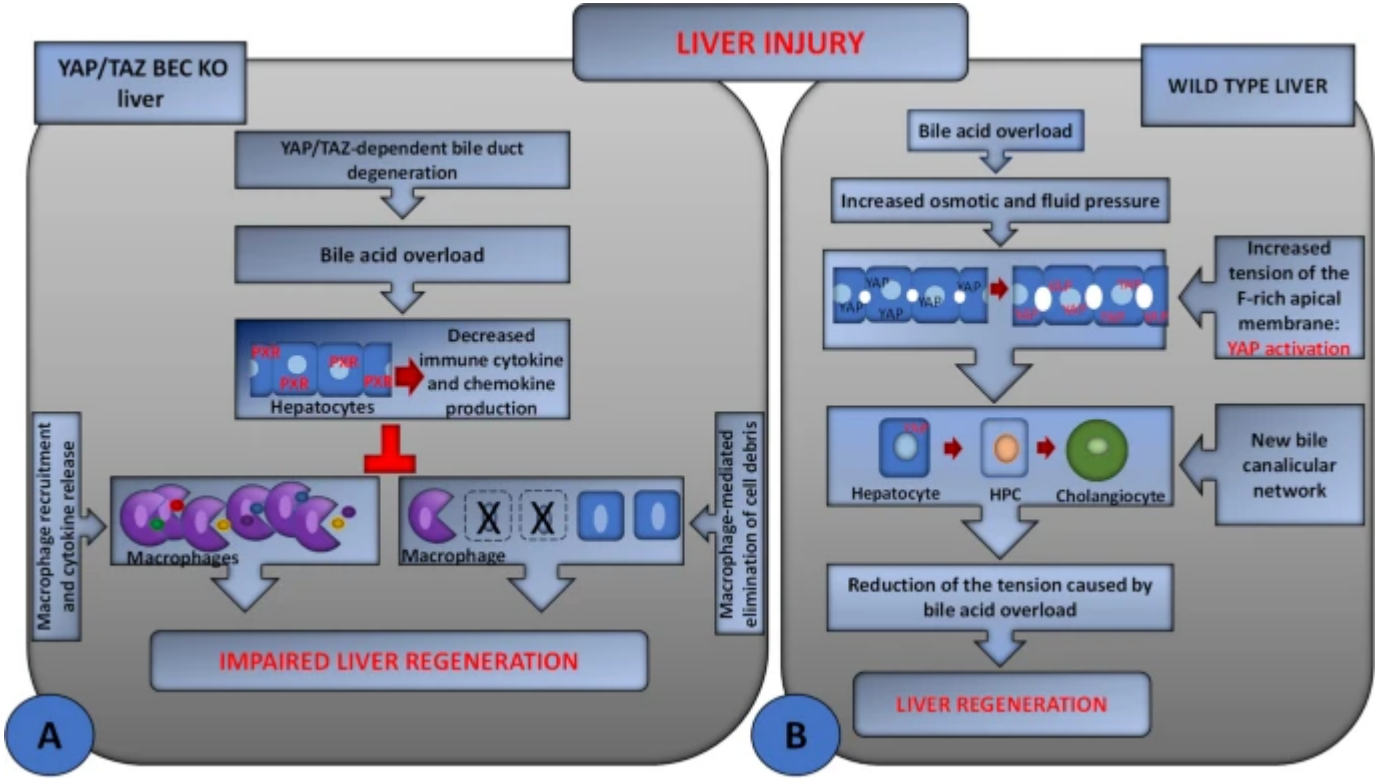
Nature **474**, 179–183 (2011) | Cite this article

Abstract

Cells perceive their microenvironment not only through soluble signals but also through physical and mechanical cues, such as extracellular matrix (ECM) stiffness or confined adhesiveness. By mechanotransduction systems, cells translate these stimuli into biochemical signals controlling multiple aspects of cell behaviour, including growth, differentiation and cancer malignant progression, but how rigidity mechanosensing is ultimately linked to activity of nuclear transcription factors remains poorly understood. Here we report the identification of the *Yorkie*-homologues YAP (Yes-associated protein) and TAZ (transcriptional coactivator with PDZ-binding motif, also known as WWTR1) as nuclear relays of mechanical signals exerted by ECM rigidity and cell shape. This regulation requires Rho GTPase activity and tension of the actomyosin cytoskeleton, but is independent of the Hippo/LATS cascade. Crucially, YAP/TAZ are functionally required for differentiation of mesenchymal stem cells induced by ECM stiffness and for survival of endothelial cells regulated by cell geometry; conversely, expression of activated YAP overrules physical constraints in dictating cell behaviour. These findings identify YAP/TAZ as sensors and mediators of mechanical cues instructed by the cellular microenvironment.



Hippo signaling in liver



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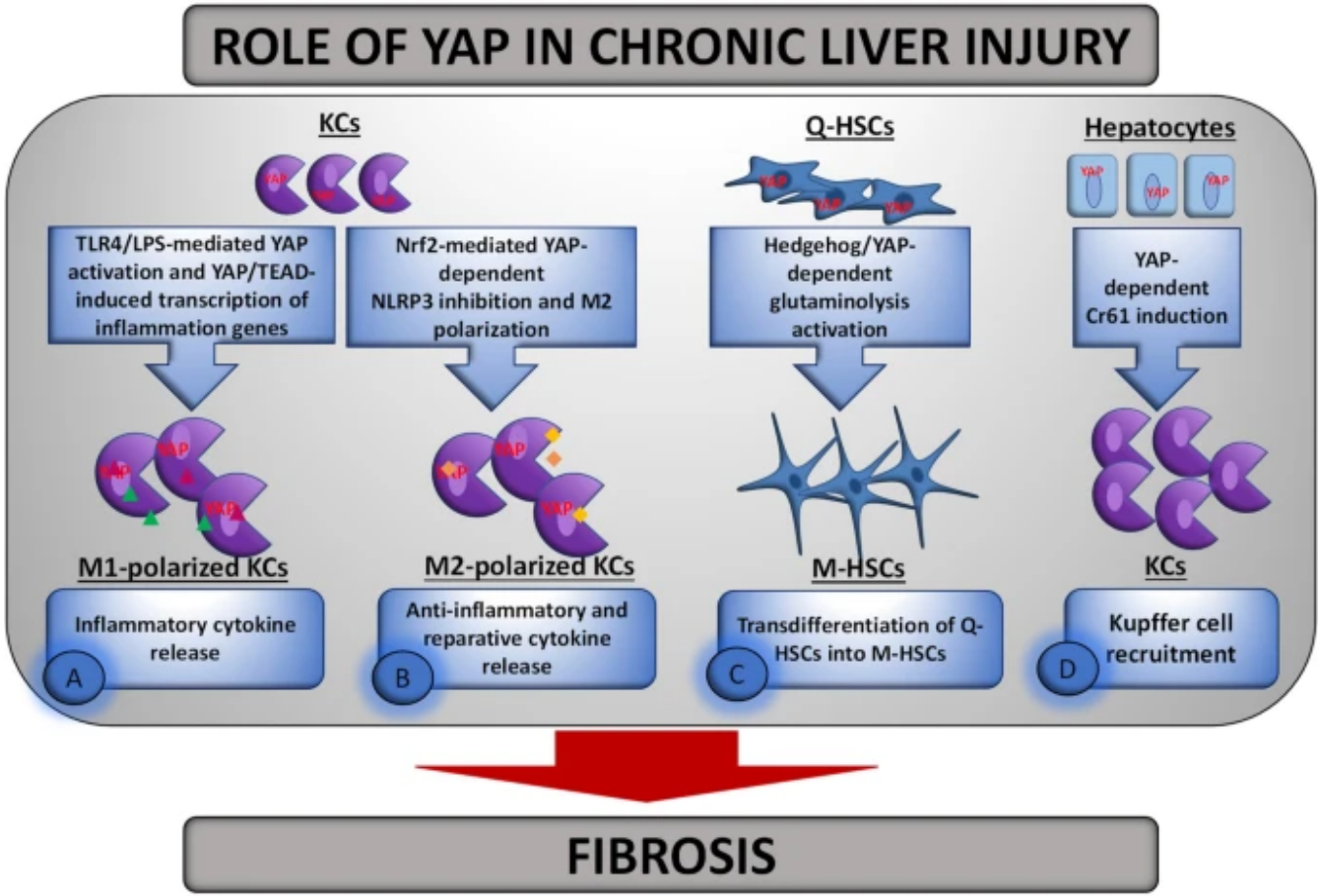
Hippo signaling in liver



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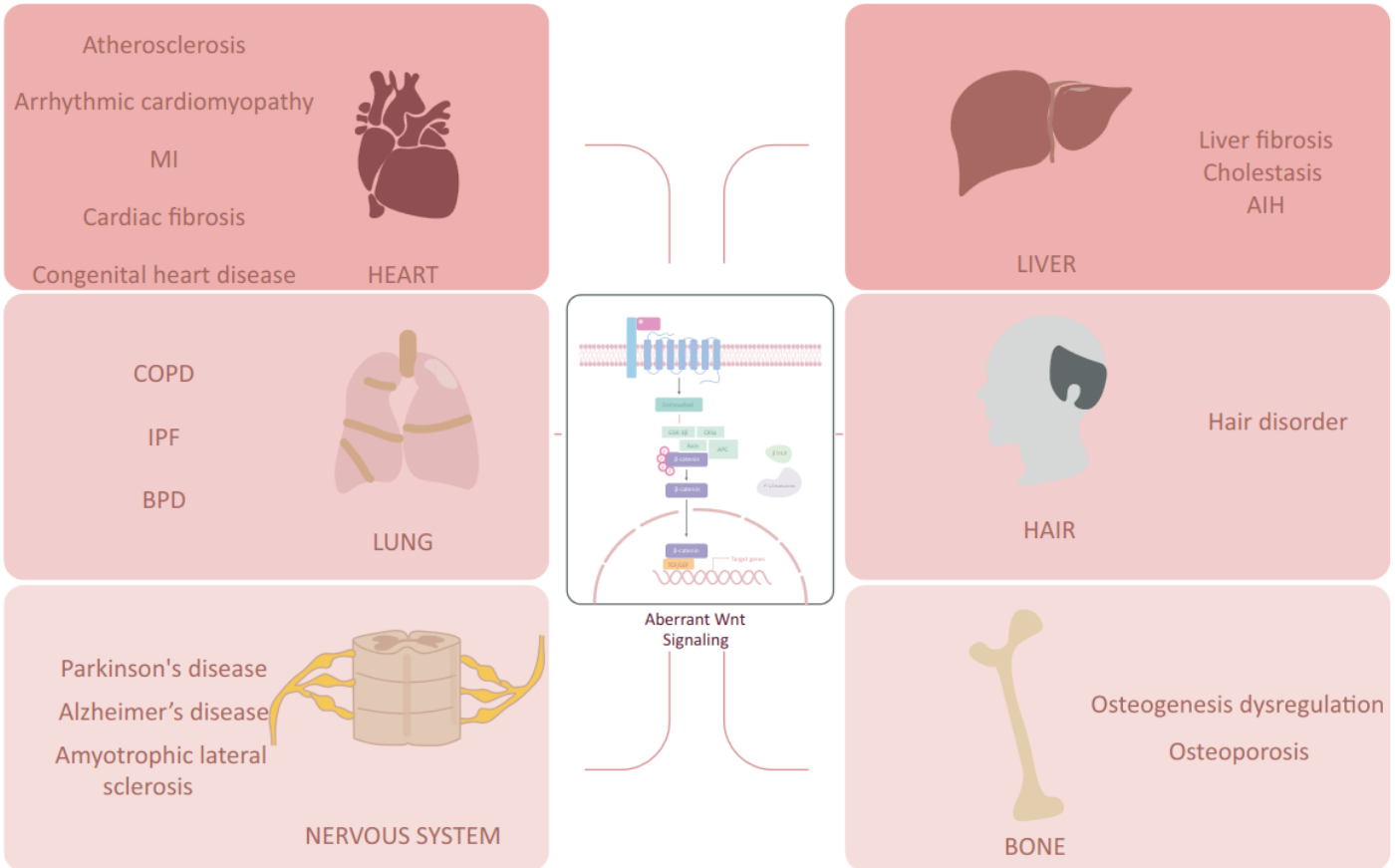
Wnt signaling



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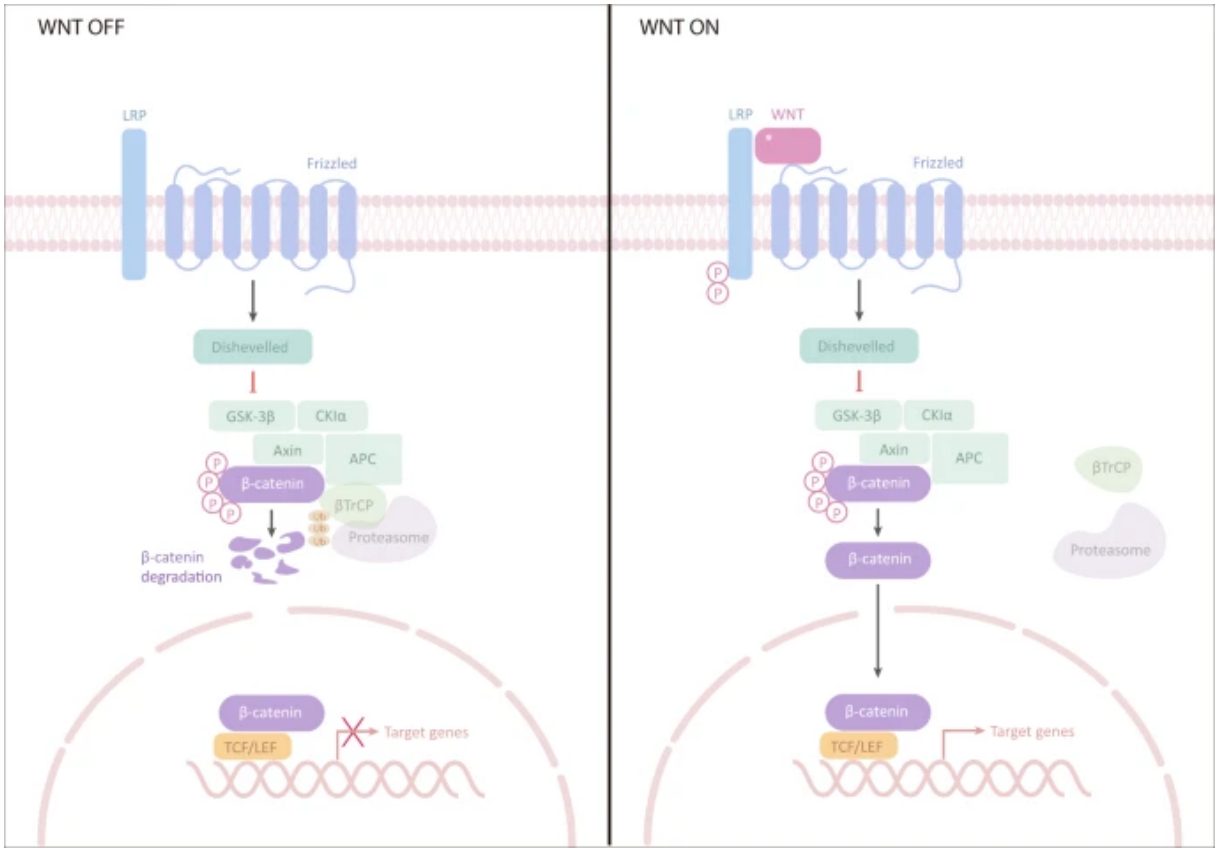
Wnt signaling



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Wnt signaling

Crosstalk between Wnt/β-catenin and other pathways

Pathway	Effector	Target	Effect on Wnt signalling	Reference
BMP	BMP2	SOST, DKK1	Inhibits	329,330
PI3K/AKt/mTOR	mTORC1	DVL	Inhibits	331
Hippo	TAZ	DVL	Inhibits	332
Hedgehog	/	β-catenin	Inhibits	333
p53	RARRES3, p53	Cyclin D, AXIN2, c-Myc, Wnt1/6/7a	Inhibits	334,335
TGF-β	TGF-β	Wnts, DKK1	Activates	113,336
Ras/Raf/Mek/Erk	Ras	β-catenin	Activates	337–339
Notch	Notch1/Notch2	PROX1, AXIN2, c-Myc, APCDD1, β-catenin/GSK3-β, C1q	Inhibits/activates	340–343

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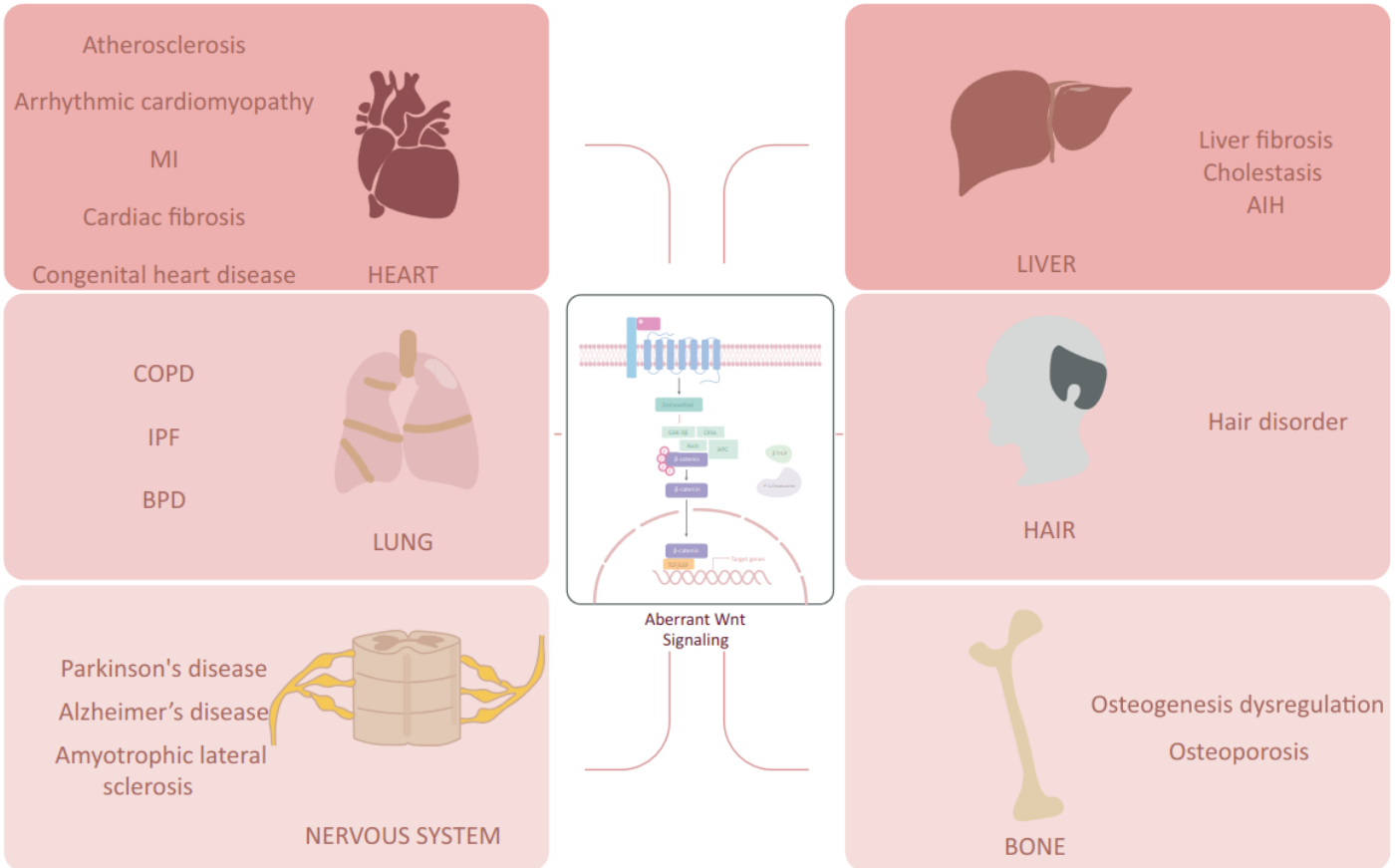
Wnt signaling and diseases



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In lungs

- Wnt/β-catenin signalling activity is reduced in the lung epithelial cells of COPD patients.
- The mechanisms responsible for its downregulation include cigarette smoke.
- Cigarette smoke can reduce the expression of Fz receptor in alveolar epithelial cells, inhibiting epithelial proliferation and alveolar repair mediated by the classic Wnt signalling pathway.

- In contrast to COPD, the Wnt/β-catenin pathway is activated in the lung epithelium of IPF.
- In IPF, abnormally activated Wnt signalling is detected. It promotes fibroblast proliferation and epithelial cell-mesenchymal transition, the pathological process of IPF.

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In cardiovascular system

- Atherosclerosis is characterized by the accumulation of lipid and fibre components on the arterial wall
- Activation of Akt/Wnt/β-catenin signal transduction by CXXL12/CXCR4 --> VE-cadherin --> maintain the integrity of endothelial cells and favours a contractile phenotype in arterial SMCs, thus inhibiting atherosclerosis.
- However, several studies have shown that activated Wnt/β-catenin signalling also play a vital role in causing the deterioration of atherosclerosis and coronary heart disease by promoting the calcification of vascular SMCs and valve sclerosis.

- Cardiac fibrosis, which is common in various heart injuries, can significantly reduce tissue compliance
- The absence of β-catenin in cardiac fibroblasts can reduce myocardial hypertrophy and post-TAC fibrosis and improve cardiac function.
- TGF-β stimulates Wnt secretion and activates the Wnt/β-catenin signalling pathway through the TAK1 pathway to promote myofibroblast differentia tion, which leads to myocardial fibrosis.

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