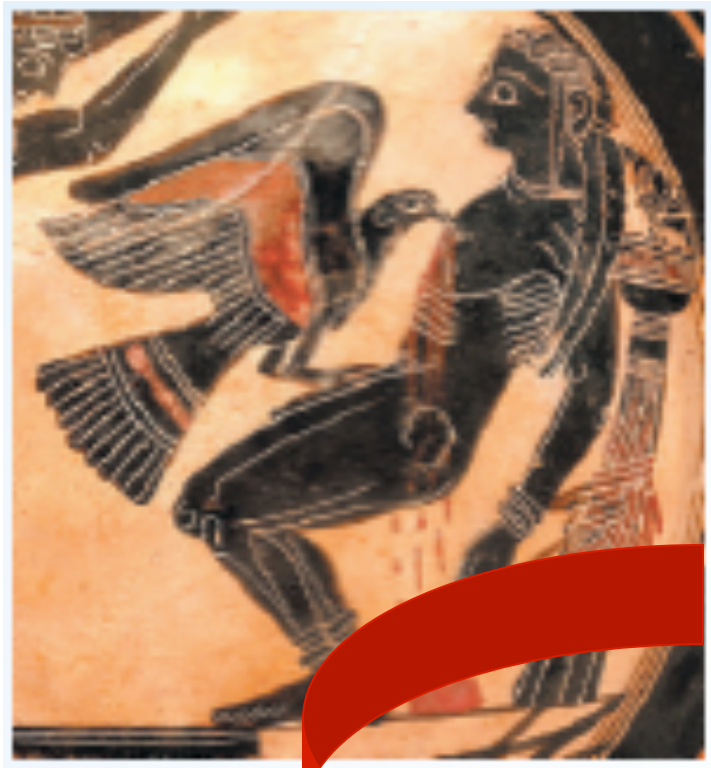
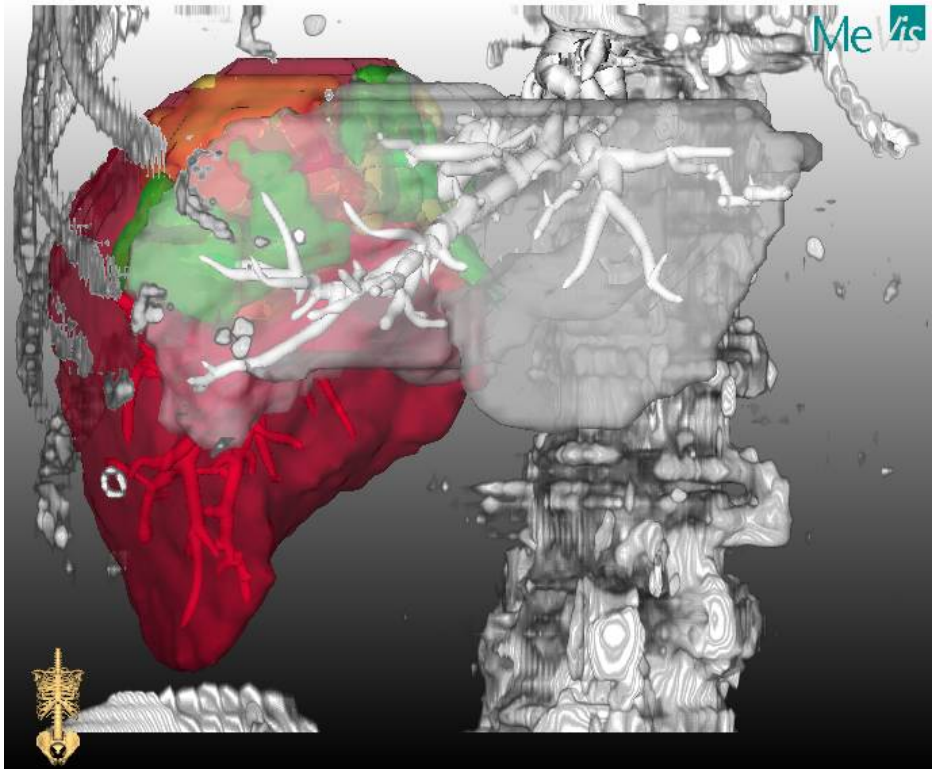
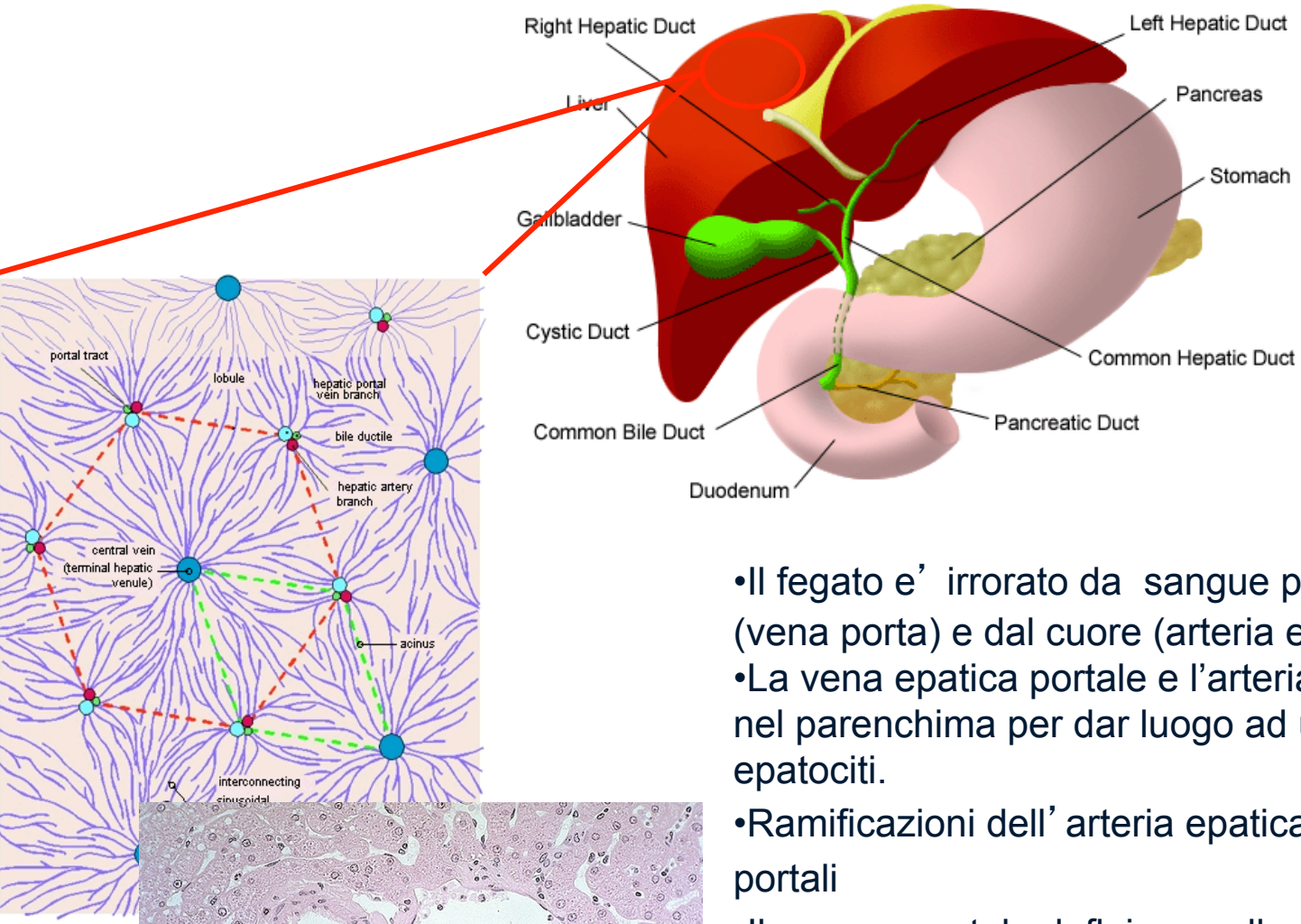
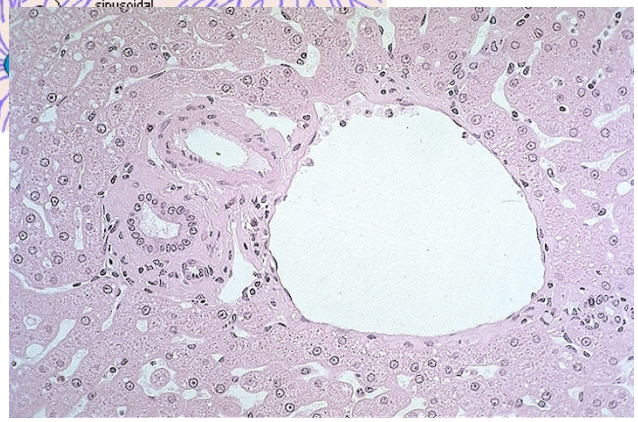
LIVER REGENERATION: FROM MYTH TO MECHANISM









- Il fegato e' irrorato da sangue proveniente dall'intestino (vena porta) e dal cuore (arteria epatica).
- La vena epatica portale e l'arteria epatica si ramificano nel parenchima per dar luogo ad un intimo contatto con gli epatociti.
- Ramificazioni dell' arteria epatica corrono negli spazi portali
- Il sangue portale defluisce nelle vene centrolobulari e di qui si riversa nelle vene intercalari, nella vena epatica che drena nella vena cava inferiore.
- La bile è secreta in *canalicoli biliari,* posti tra epatociti adiacenti, che drenano in dotti collettori negli spazi portali.

LIVER CELL TYPES AND FUNCTIONS

Hepatocytes: Parenchymal cells of the liver that comprise 70% of the liver cells and 90% of the liver volume; organized in single-cell plates; perform metabolic and detoxification function; maintain metabolic function while replicating during liver regeneration; can secrete HGF, IL-6, proteases and protease inhibitors.

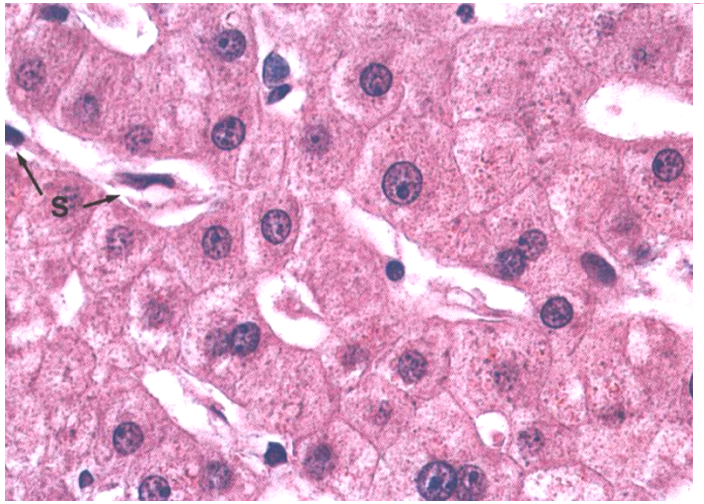
Sinusoidal endothelial cells: Line liver capillaries that separate hepatocytes from sinusoidal blood; pathogenic barrier and general selective barrier; involved in endocytosis and metabolism of molecules including glycoproteins, lipoproteins, ECM components; can produce TGFβ, HGF, IL-6 and nitric oxide.

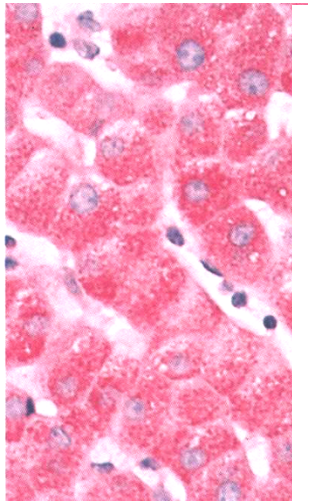
Biliary epithelial cells: Line bile ducts in hepatic portal triads; can secrete cytokines such as monocyte chemotactic protein-1 (MCP-1) and IL-6; promote fibrogenesis by attraction of hepatic stellate cells.

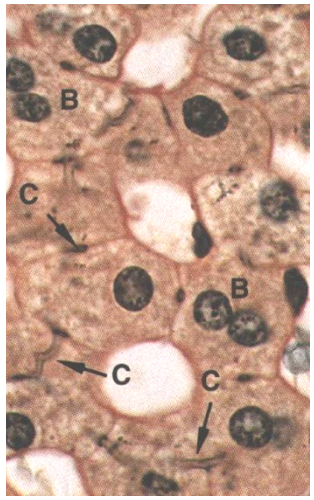
Hepatic stellate cells: Found within the peri-sinusoidal space; store vitamin A, secrete ECM proteins, including laminins, collagens and proteoglycans, growth factors such as HGF, FGF and TGFβ and cytokines such as IL-6; produce some MMPs and TIMPs.

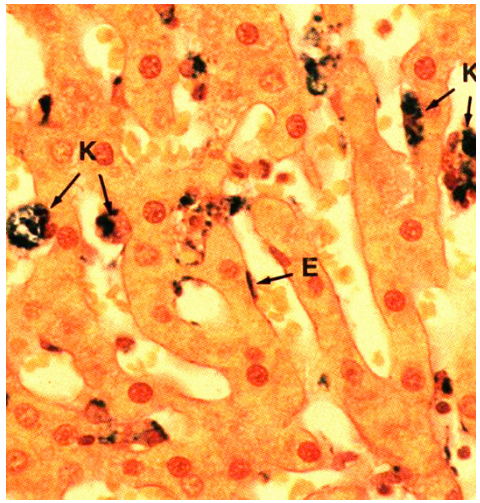
Kupffer cells: Resident liver macrophages found in sinusoids; phagocytosis of foreign particles and bacteria; major producers of cytokines including TNF and IL-6.

Oval cells: Hepatic progenitor cells; able to differentiate towards the biliary and the hepatocytic lineage through intermediate progeny; implicated in liver regeneration and hepatocarcinogenesis.









Higgins, G. M. & Anderson, R. M.

Experimental pathology of the liver. I. Restoration of the liver of the white rat following partial surgical removal.

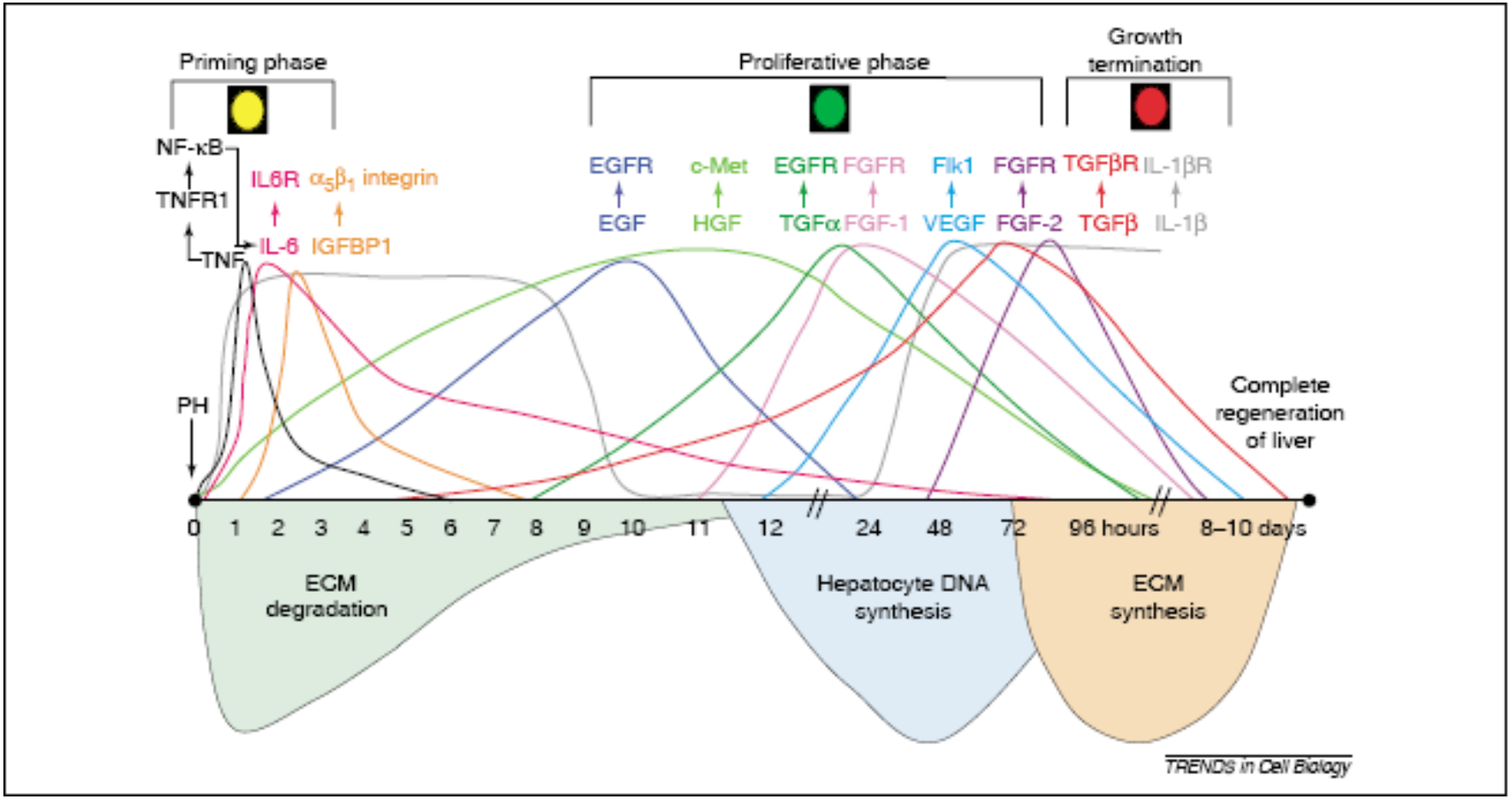
Arch. Pathol. **12**, 186–202 (1931).

In this experimental system there is a hyperplastic response:

liver regeneration does not require the recruitment of liver stem cells or progenitor cells, but involves replication of the mature functioning liver cells.

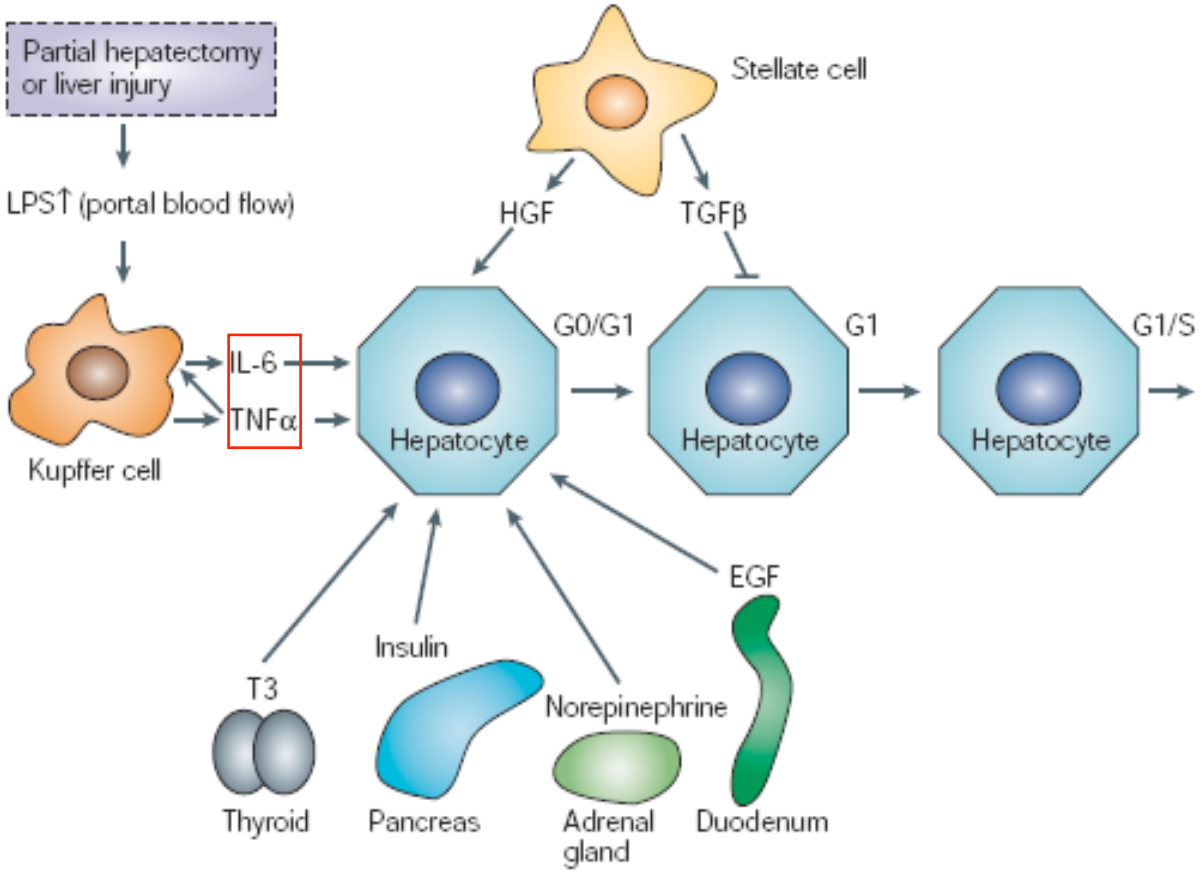
The regenerative process is compensatory: the size of the resultant liver is determined by the demands of the organism, and, once the original mass of the liver has been re-established, proliferation stops.

Liver regeneration: the timely sequence of morphological events



Liver regeneration proceeds along a sequence of distinctive phases:

1. An ***initiation*** or ***priming*** phase, rendering hepatocytes in a state of replicative competence
2. A ***proliferation*** phase, where expansion of the entire population takes place
3. A ***termination*** phase, where cell proliferation is switched off

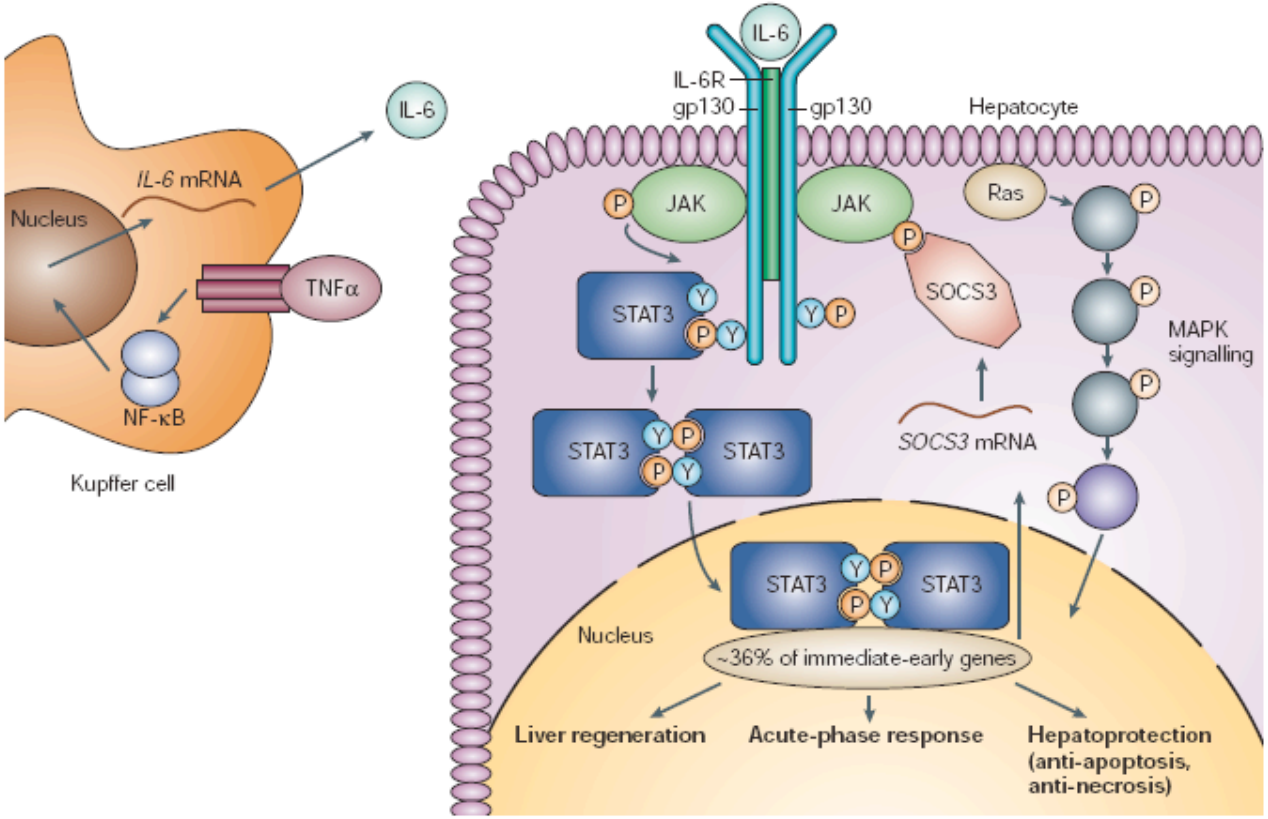


Gut-derived factors, such as lipopolysaccharide (LPS), are upregulated and reach the liver through the portal blood supply. They activate hepatic non-parenchymal cells (including Kupffer cells and stellate cells) and increase the production of tumour necrosis factor TNFα.

Other factors are released from the pancreas (insulin), duodenum (EGF), adrenal gland (norepinepherine), thyroid gland (triodothronine; T3) and stellate cells (HGF).

These cooperative signals allow hepatocytes to move from G0, through G1, to the S phase of the cell cycle. This leads to DNA synthesis and hepatocyte proliferation. TGFβ signalling, which inhibits hepatocyte DNA synthesis, is blocked during the proliferative phase but is restored at the end of the process of regeneration, helping hepatocytes to return to the quiescent state.

1- Initiation phase

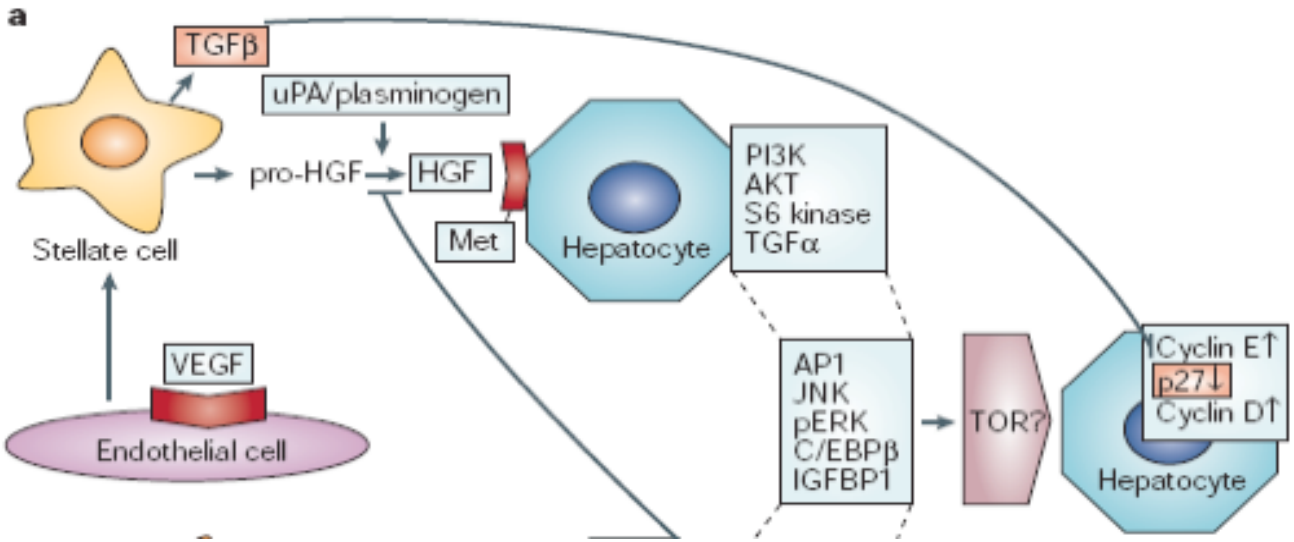


Tumour necrosis factor α binds to its receptor on Kupffer cells, which results in the upregulation of interleukin-6 (*IL-6*) transcription by the nuclear factor (NF)-κB pathway. IL-6 binds to its receptor on hepatocytes and activates Janus kinase (JAK). Activated JAK triggers two pathways:

1) The MAPK pathway, activated by SHP2–GRB2-SOS–Ras signal transduction;

2) The STAT3 pathway, activated through JAK-mediated tyrosine phosphorylation. STAT3 transcription factor activates transcription of ~36% of immediate-early target genes.

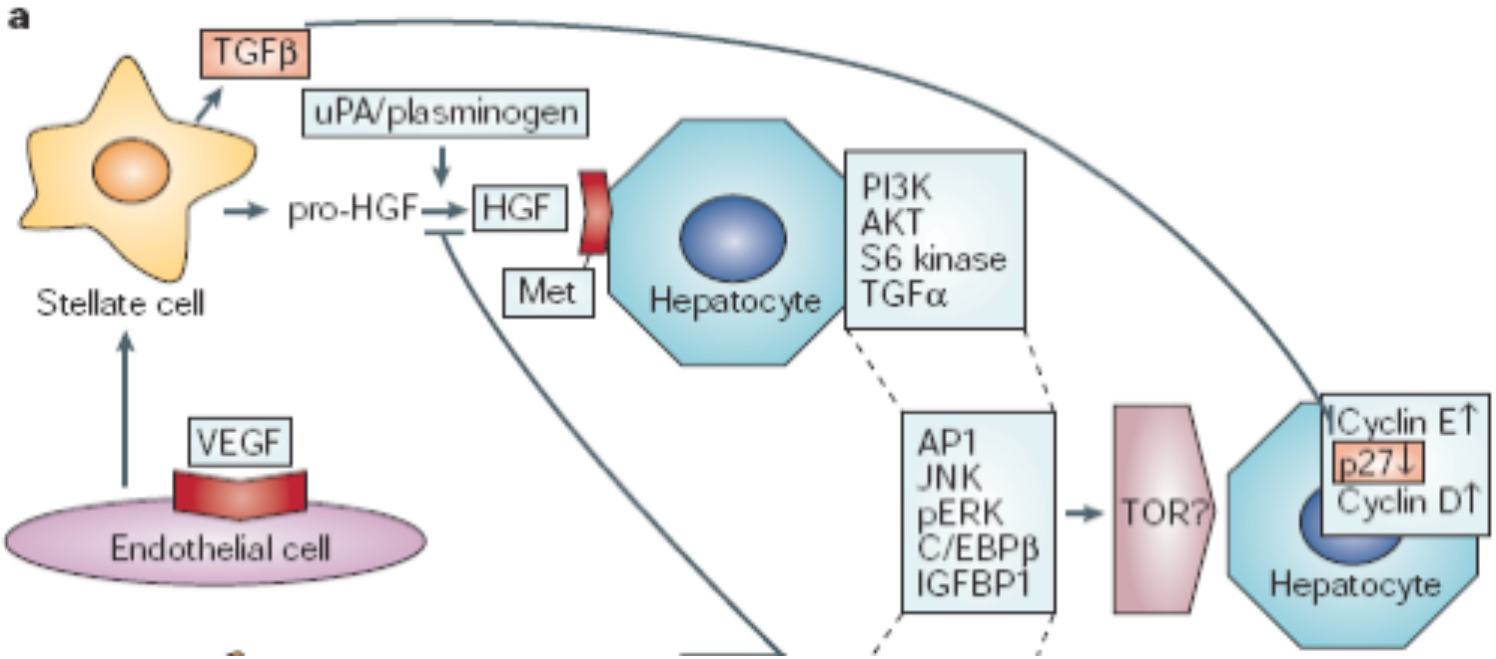
2- Proliferation phase



Progression of primed/competent hepatocytes throught G1 and subsequent replicative cycling is dependent on hepatocyte growth factor (HGF) and Transforming growth factor-α signalling; afterwards the proliferation process proceeds autonomously under the control of cyclins and cyclin-dependent kinases

Vascular endothelial growth factor (VEGF) binds to endothelial cells, triggering the release of the HGF precursor, pro-HGF, from stellate cells. The urokinase-type plasminogen activator (uPA) and plasminogen proteases cleave pro-HGF to HGF. HGF binds to the Met receptor on hepatocytes to activate the phosphatidylinositol 3-kinase (PI3K), AKT and S6 kinase signal-transduction pathways. HGF signalling releases transforming growth factor (TGF)α and triggers other downstream signals such as AP1, Jun amino-terminal kinase (JNK), phosphorylated extracellular signal-regulated kinases (pERKs), CCAAT-enhancer-binding protein (C/EBP)β and insulin-like-growth-factorbinding protein (IGFBP)1. These factors lead to cell-cycle transition by increasing the expression of cyclins D and E and reducing p27 levels.

3- Termination phase



Subsequent to the expansion phase, the growth response must be terminated: major factors involved in this step are members of the TGFβ superfamily, which includes TGFβ1, 2 and 3, activins and inhibins, all signaling through TGFβ receptors. They regulate hepatic mass, inhibit DNA synthesis in hepatocytes and induce apoptosis via a c-Jun dependent mechanism.

WHAT ABOUT THE OTHER CELL TYPES??

…in liver regeneration and repair

Hepatocytes are themselves the **functional stem cells** of the liver.

More severe liver injury can activate a potential stem cell compartment located within the intrahepatic biliary tree, giving rise to cords of **bipotential transit amplifying cells** (**oval cells**), that can ultimately differentiate into hepatocytes and biliary epithelial cells.

Table 1. Origin of Hepatocytes in Liver Regeneration and Repair

Growth processes that depend of the replication of differentiated hepatocytes
Liver regeneration after partial hepatectomy[2]
Hepatocyte regeneration after carbon tetrachloride and acetaminophen (centrolobular) injury[131]
Conditions in which oval cells proliferate and generate hepatocytes
Experimental
Injury caused by galactosamine[132]
Choline-deficient diet combined with ethionine or AAF[133,134]
Partial hepatectomy combined with AAF or Dipin[135,136]
Carbon tetrachloride combined with AAF[137]
3,5-dietoxycarbonyl-1-1, 4-dihydrocollidine (DCC)[138]
Allyl alcohol[9]
Human disease
Atypical ductular reactions in advanced stages of cirrhosis of various etiologies
Fatty liver disease
Small cell dysplasias
Massive hepatocyte necrosis[17,52,68,139]
Conditions in which small hepatocyte precursor cells (SHPC) represent a large fraction of the proliferating cells
Injury caused by retrorsine[61,62] and galactosamine[63]

Abbreviation: AAF, N-2-acetylaminofluorene.

NOTE. Only representative publications are listed.

What then is the evidence that the adult liver has any stem cells at all?

The only general principle underlying oval cell activation is liver injury combined with an inability of hepatocytes to divide in response to the damage.

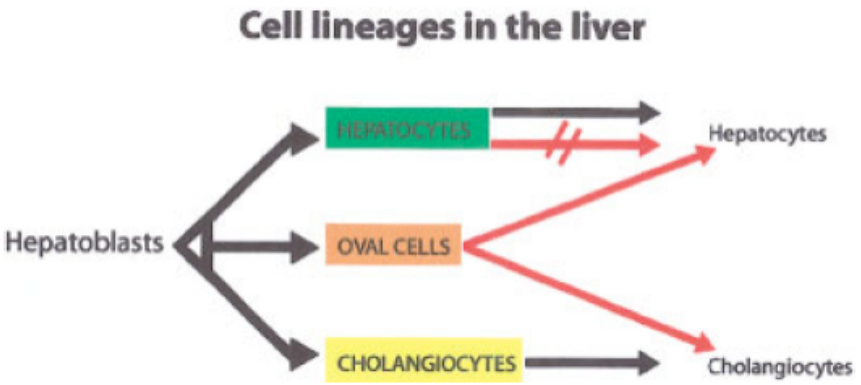
OVAL CELLS

Analysis of expression markers suggests that proliferating oval cells constitute a heterogeneous cell compartment containing cells that may differ in their differentiation capacity and stage of differentiation. Some of these cells may function as hepatocyte progenitors (expressing AFP and albumin), whereas others may be indistinguishable from cholangiocytes (expressing cytokeratins 7 and 19). Oval cells also express markers of ematopoietic stem cells. Among these are Thy-1, CD34, CD45, Sca-1, c-Kit, and flt-3.

Table 1. Marker genes commonly used to identify oval cells in adult liver

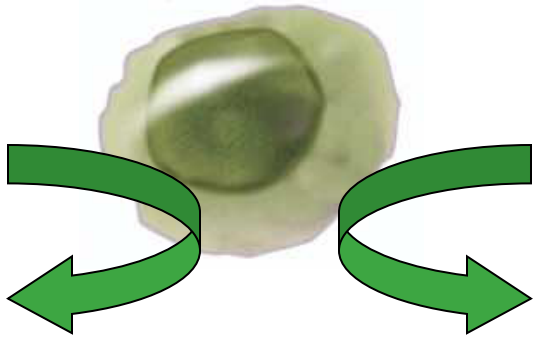
Marker	Oval cells	Hepatocytes	Bile duct cells	Refs.
Albumin	+	+	–	86,87
AFP	+	Fetal	+	86–88
π-GST	+	Fetal	–	89
M2-PK	+	Fetal	+	90
CK7	+	–	+	91
CK8	+	+	+	91,92
CK14	+/–	–	–	93
CK18	+	+	–	91
CK19	+	–	+	91,92
OV-6	+	–	+	94
A6	+	–	+	95
Thy-1	+	–	–	82
c-kit	+	–	–	96
SCF	+	–	–	96
Sca-1	+	–	–	97
Dlk	+	–	–	98

AFP, alpha-fetoprotein; GST, glutathione s transferase; PK, pyruvate kinase; CK, cytokeratin; SCF, stem cell factor.



1. They are scarce in healthy liver, appearing near the portal triad, adjacent to the terminal ducts of the biliary tree, during chronic liver injury,
2. They express markers in common with bile duct cells, fetal and adult hepatocytes
3. They are basophilic, possess ovoid nuclei and scant cytoplasm, and are substantially smaller than adult hepatocytes (approximately 10μm in diameter, versus 50 for hepatocytes),
4. They are immature, and possess a high turnover rate and proliferative capacity
5. They are involved in the regeneration of liver following injury, but are also a cellular precursor to hepatocellular carcinoma (HCC).

OVAL CELLS



Dr Jekyll

Mr Hyde

During liver regeneration, oval cells give rise to both hepatocytes and bile duct cells. This pathway can be viewed as a 'second line of defence' following liver injury, when hepatocyte-mediated repair cannot be accomplished.

Years of experimental evidences have shown a second role for these cells during liver injury: carcinogenesis. The flip-side of regenerative oval cell proliferation is the increased probability of liver tumour formation.

Unanswered questions:

- how does the regenerating liver stop proliferating when appropriate mass is restored?

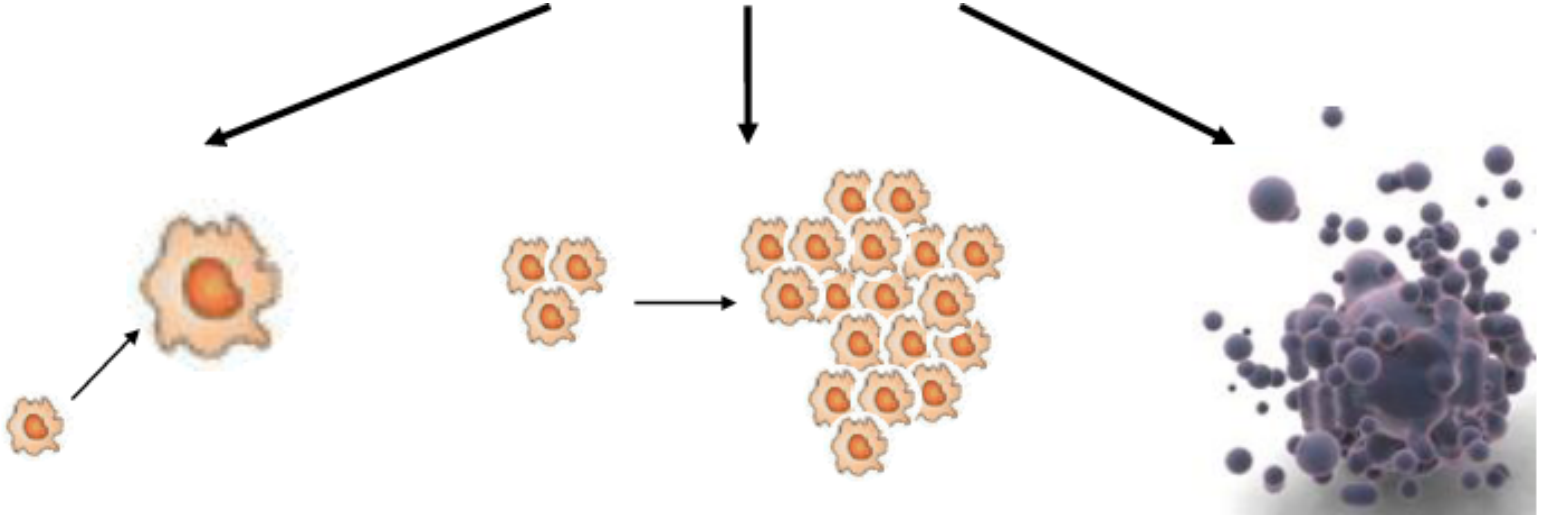
- how do these mechanisms relate to normal regulation of organ size during development?

Organ size control

Most organs have an intrinsic genetic program regulating the final size to be achieved during the embryonic development

In case of damage, the size genetic program is reactivated, therefore the regenerated organ maintains its original size

How is the organ size regulated?



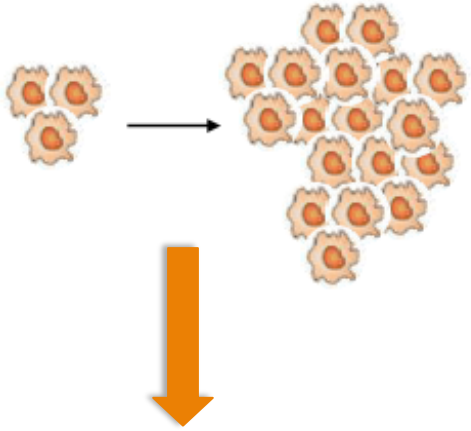
Hypertrophic growth

Proliferation

Apoptosis

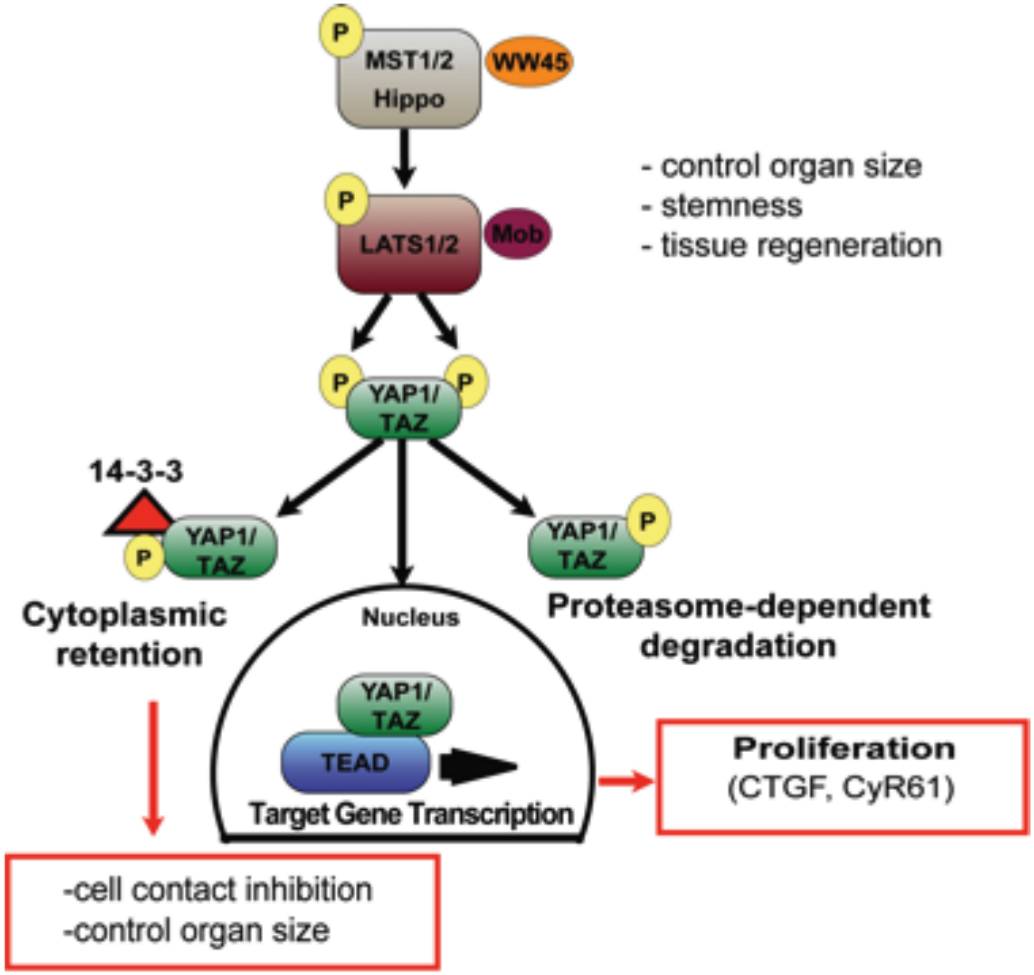
Proliferation

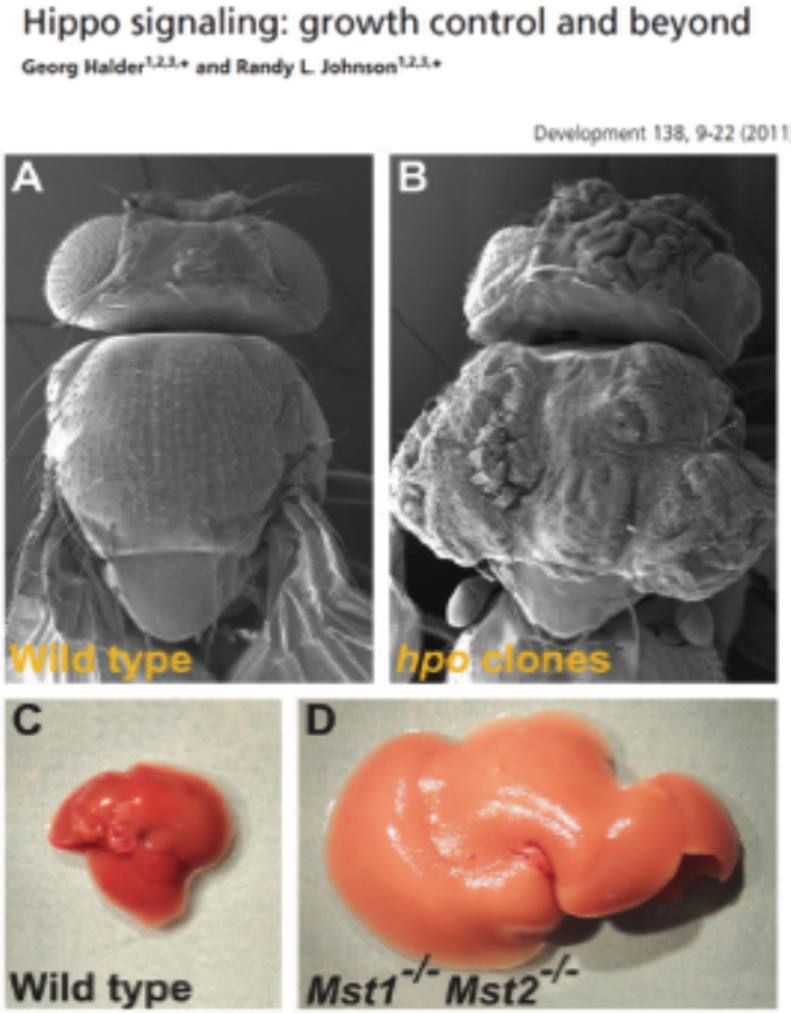
(Hyperplastic growth)



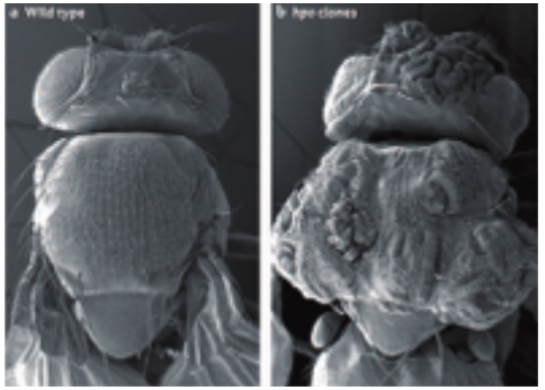
Hippo Pathway

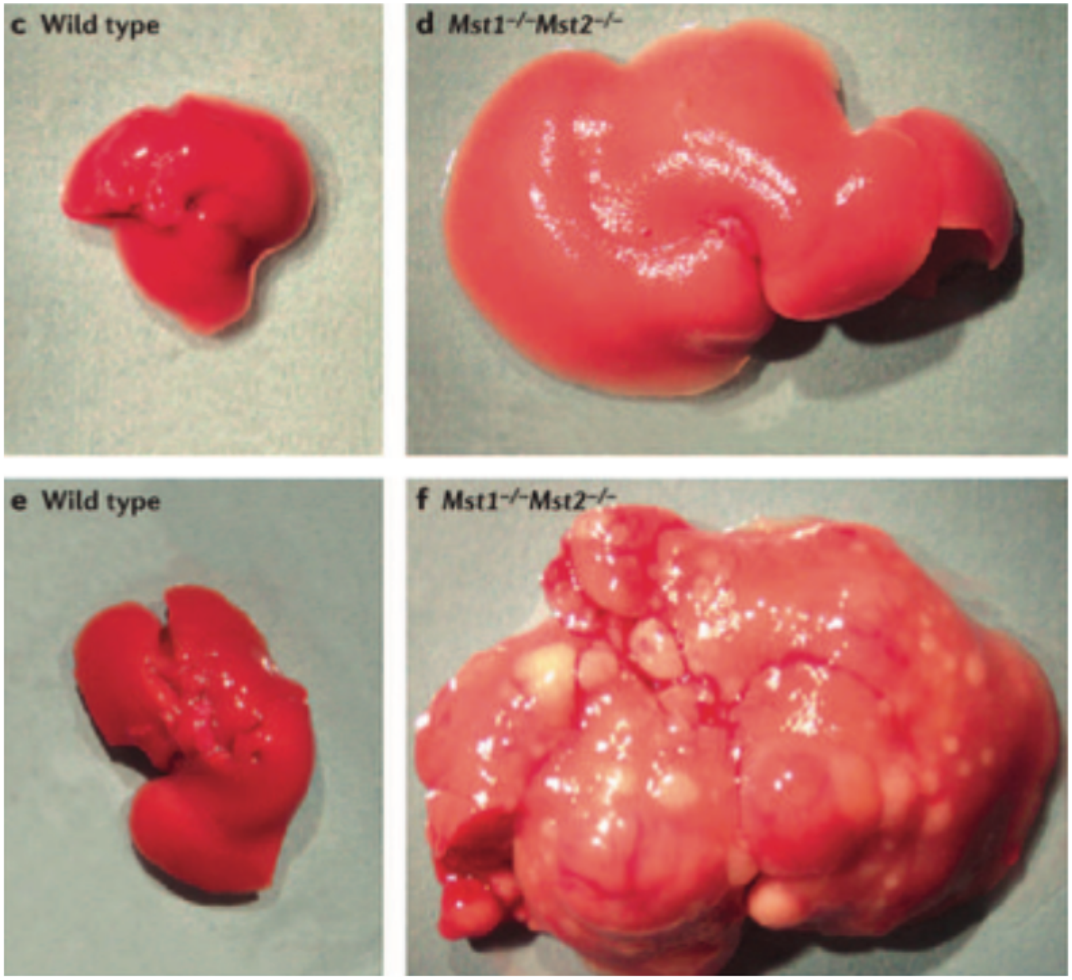
Hippo/YAP Signaling Pathway





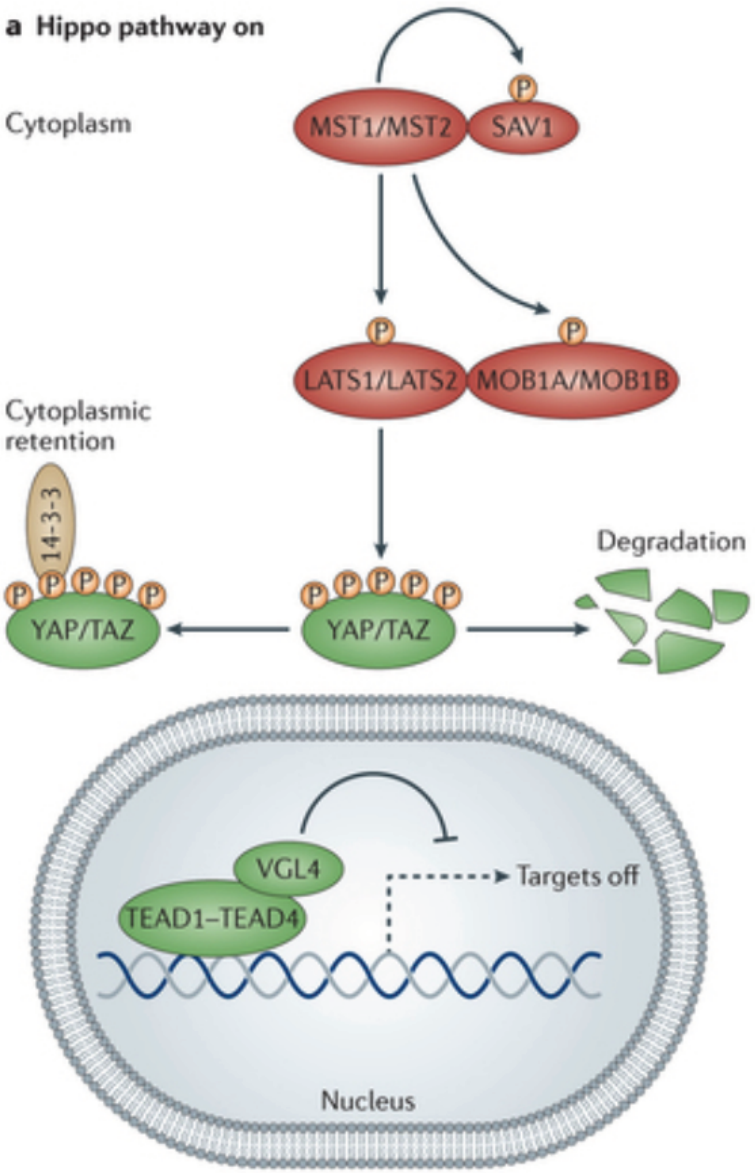
Hippo signaling pathway





- Wts, Hpo, Mats and Sav KO mice show an identical phenotype, characterized by a massive tissue hyperproliferation, due to an increase of cellular proliferation and diminished apoptosis

- All these genes are connected in a signaling cascade, whose main target is the transcription factor Yorkie (Yki)



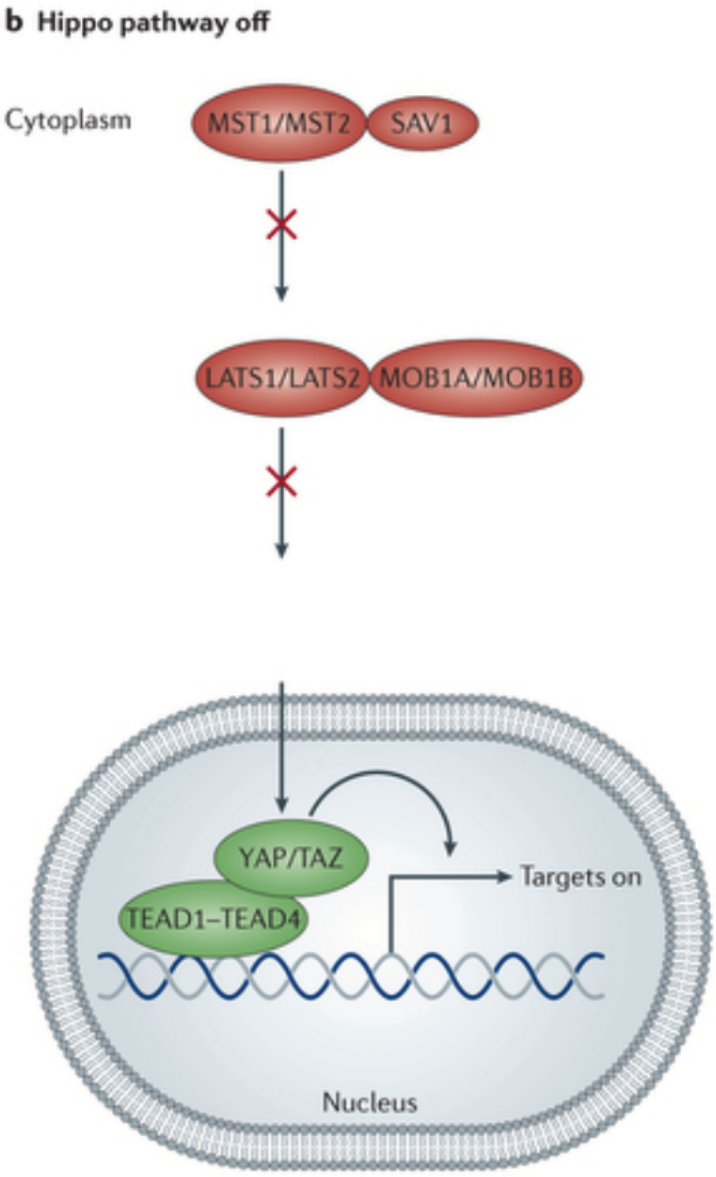
Johnson et al., 2013.

Hippo signaling pathway

When the Hippo pathway is **ON**, the mammalian STE20-like protein kinase1 (MST1) or MST2 phosphorylate Salvador homolog 1 (SAV1) and together they phosphorylate and activate MOB kinase activator 1A, MOB1B, the large tumor suppressor homolog 1 (LATS1) and LATS2 kinases, which then phosphorylate the Yes-associated protein (YAP) and the transcriptional coativator with PDZ-binding motif (TAZ).

Phosporylated YAP and TAZ are sequestered in the cytoplasm by the 14-3-3 protein and shunted for proteasomal degradation.

As a results, the TEA domain containing sequence-specific transcription factors (TEADs) associate with the transcription cofactor vestigial-like protein4 (VGL4) and suppress target gene expression (pro-proliferative and anti-apoptotic genes).



Hippo signaling pathway

When the Hippo pathway is **OFF**, the kinases MST1, MST2, LATS1 and LATS2 are inactive, so YAP and TAZ are not phosphorylated and accumulate in the nucleus where they displace VGL4 and form a complex with TEADs, which promote the expression of target genes.

YAP and TAZ

Regulatory domains of the Hippo pathway effectors TAZ/YAP.

Important domains and regulatory modifications within YAP and TAZ.

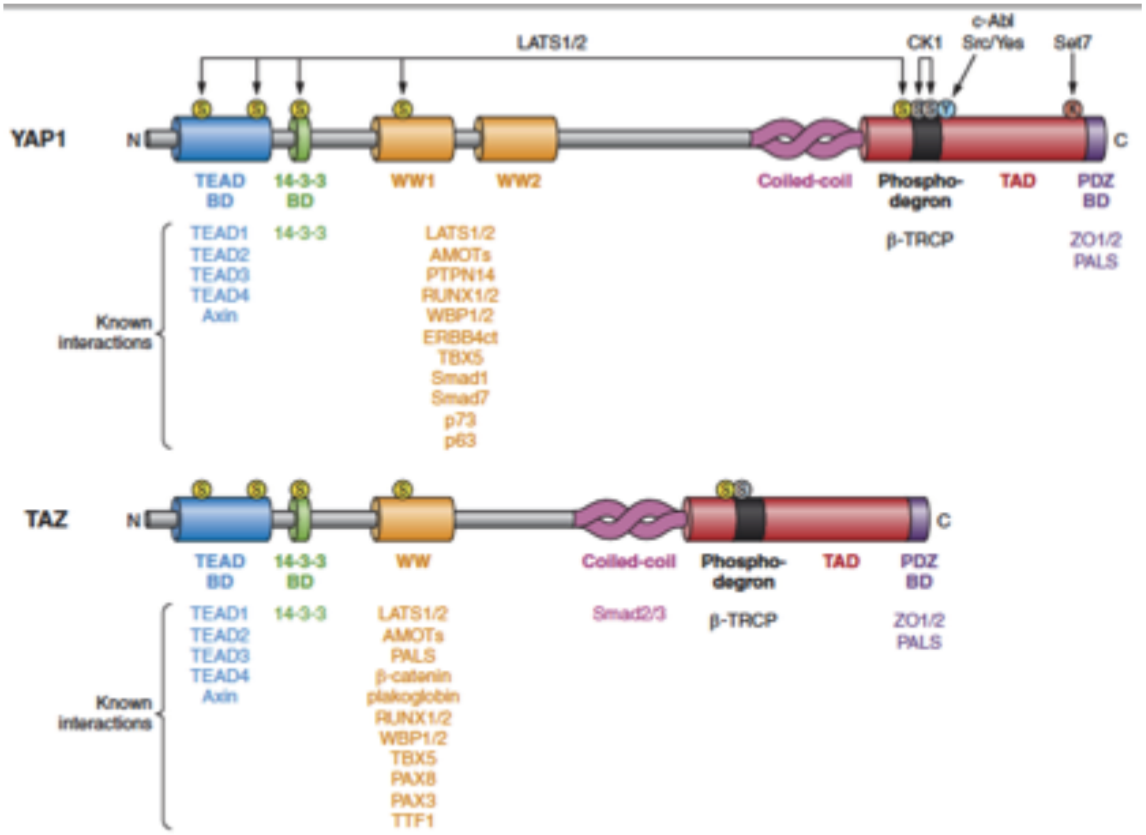


Table 2. Post-translational modifications controlling TAZ/YAP activity

Modification	Regulatory enzyme	Functional consequence
YAP		
S61-p	LATS1/2	Cytoplasmic retention?
S109-p	LATS1/2	Cytoplasmic retention?
T119-p	CDK1	Cell cycle regulation
S127-p	LATS1/2	14-3-3 binding/cytoplasmic retention
S164-p	LATS1/2	Cytoplasmic retention?
S289-p	CDK1	Cell cycle regulation
S367-p	CDK1	Cell cycle regulation
S397-p	LATS1/2	Primer for S400/403-p
S400-p	CK1ε/δ	Degradation/β-TrCP recruitment
S403-p	CK1ε/δ	Degradation/β-TrCP recruitment
Y407-p	ABL/SRC/YES	Altered nuclear activity
K494-meth	SET-7	Cytoplasmic retention
TAZ		
S58-p	GSK3β	Degradation
S62-p	GSK3β	Degradation
S66-p	LATS1/2	Cytoplasmic retention?
S89-p	LATS1/2	14-3-3 binding/cytoplasmic retention
S117-p	LATS1/2	Cytoplasmic retention?
S311-p	LATS1/2	Primer for S314-p
S314-p	NEK1/CK1ε/δ	Degradation/β-TrCP recruitment
Y321-p	ABL	Altered nuclear activity

Prominent regions include the WW domain(s), the coiled-coil (CC) domain, the SH3-binding domain, the TEAD transcription factor-binding domain, the transcriptional activation domain (TAD) and the PDZ-binding motif

YAP conservation through evolution

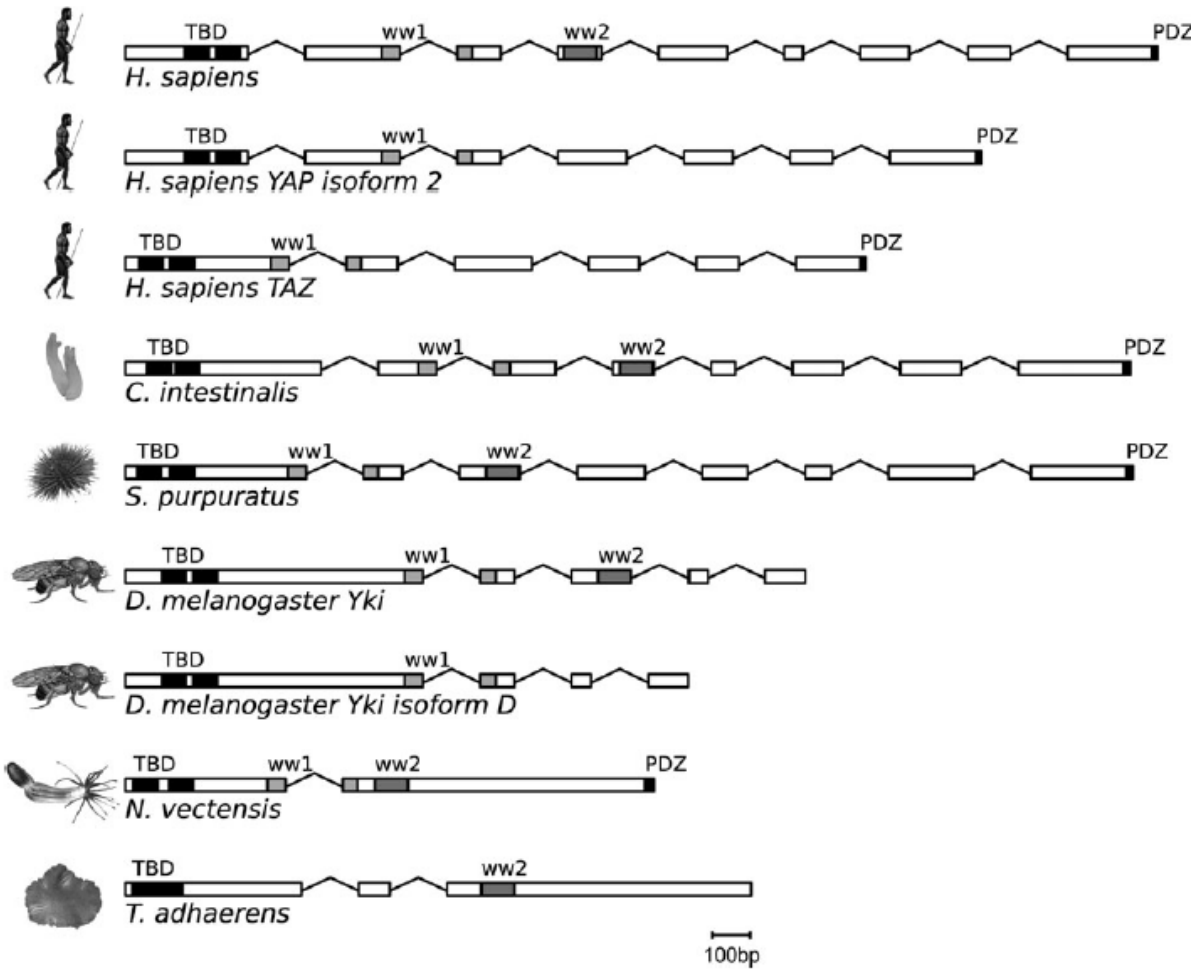
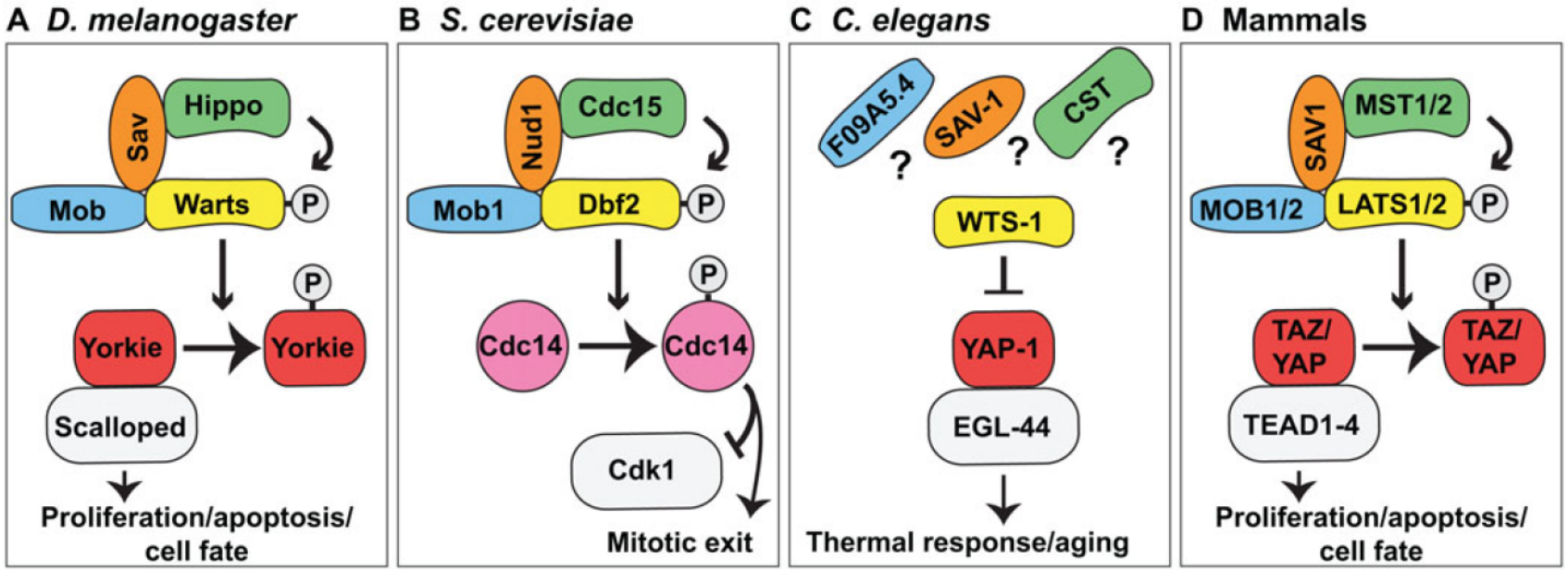


FIG. 4. Genomic structure of YAP in representative metazoans. Major domains are marked with rectangles. The transcript coding region is drawn to scale and introns positions are illustrated but their size is not drawn to scale.

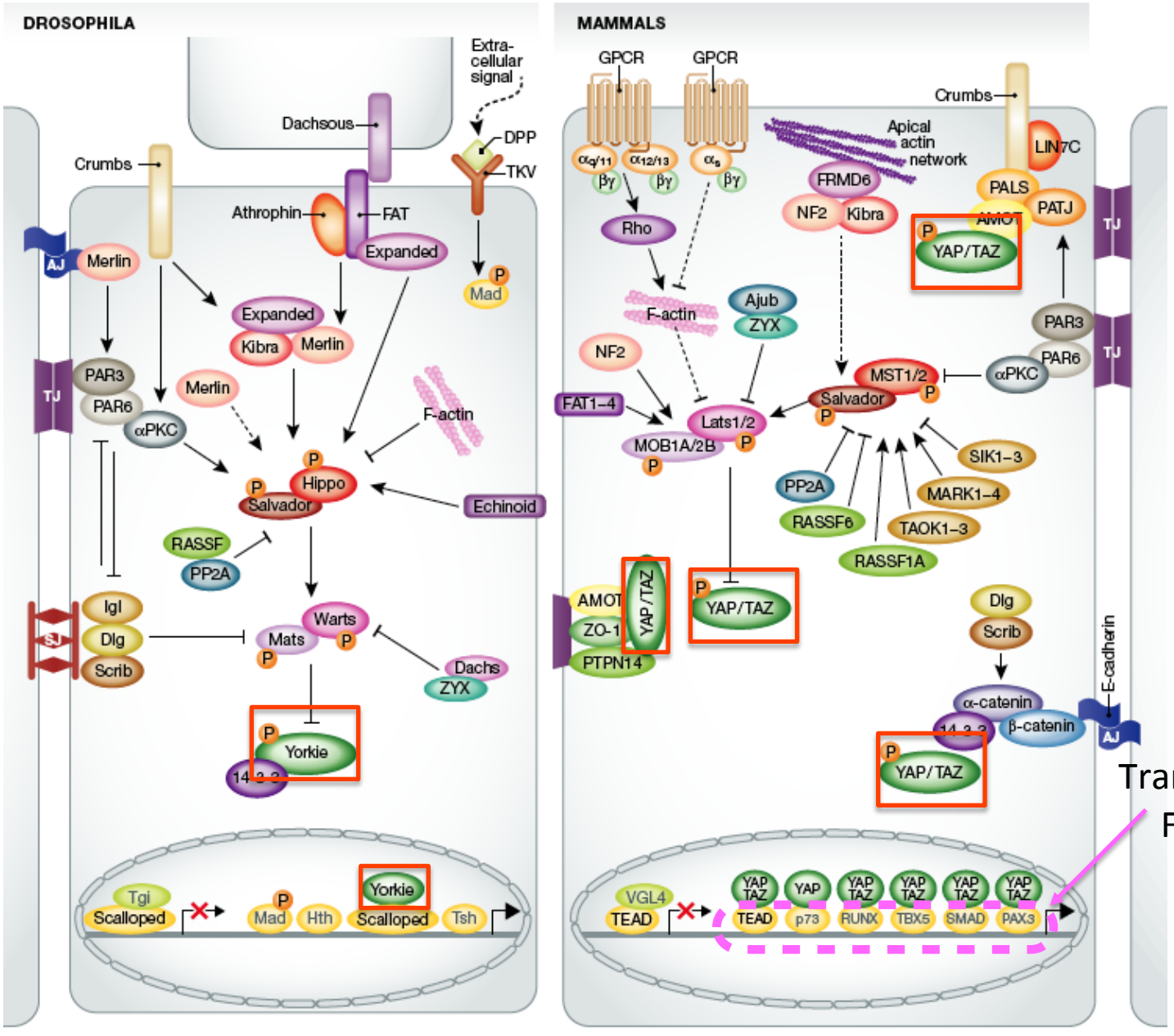
The Hippo pathway is quite conserved throughout evolution



The core components of the Hippo signaling pathway: the functionally conserved factors are matched by color.

In S. cerevisiae these signals are known as the mitotic exit network, which controls mitotic exit and cytokinesis.

In C. elegans these signals control transcriptional events important for thermal response and aging, whereas in D. melanogaster and mammals this network controls transcriptional events that direct proliferation, apoptosis and cell fate.



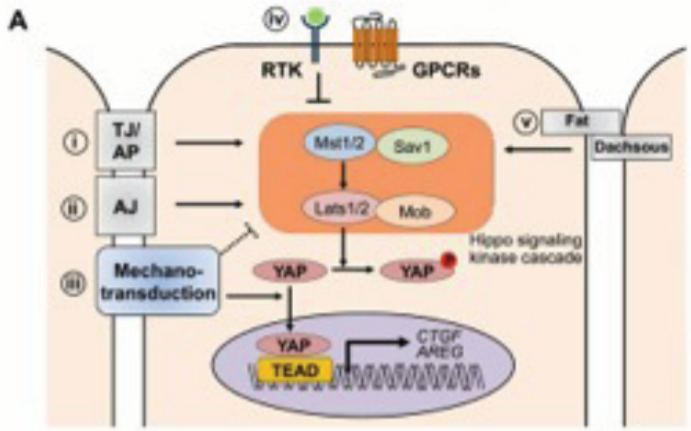
Lots of Transcriptional Factors!!!

Figure 1. Schematic models of the Hippo pathway in *Drosophila* and mammals.
Cells are shown with respective cellular junctions; adherens junction (AJ), tight junction (TJ), septate junction (SJ). Hippo pathway components in *Drosophila* and mammals are shown in various colors, with arrows and blunt lines indicating activation and inhibition, respectively. The yellow spheres indicate phosphorylation of target proteins by kinase. Continuous lines indicate known interactions, whereas dashed lines indicate unknown mechanisms. See introduction for further details.

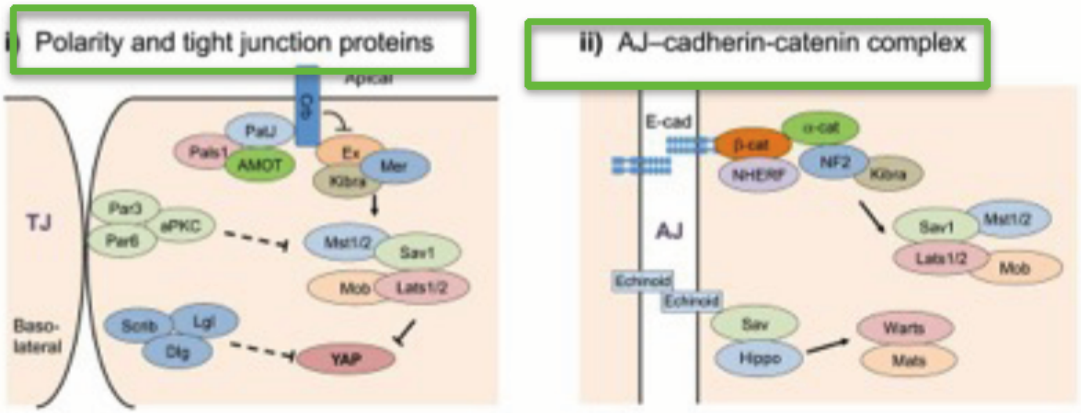
Hippo Pathway plays a key role in lots of different cellular processes

GPCR mediated signaling

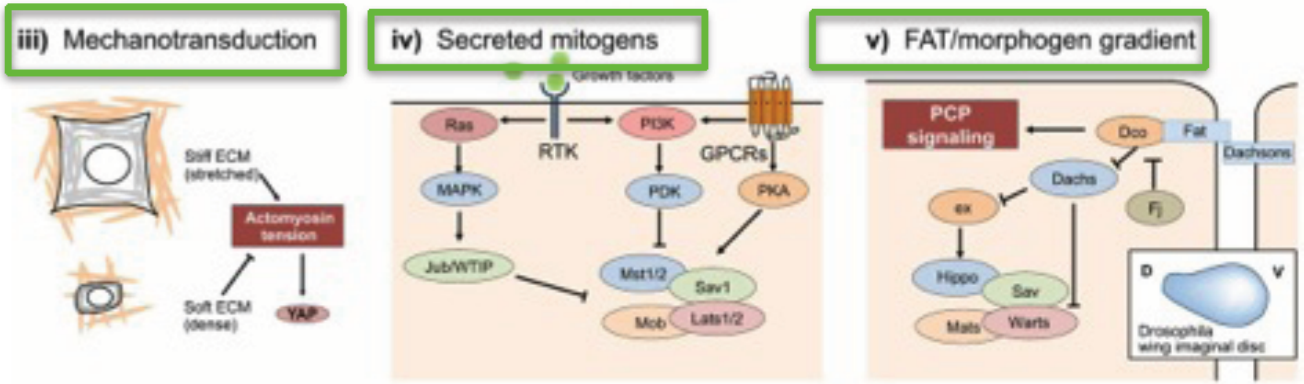
external signals: hormones and growth factors

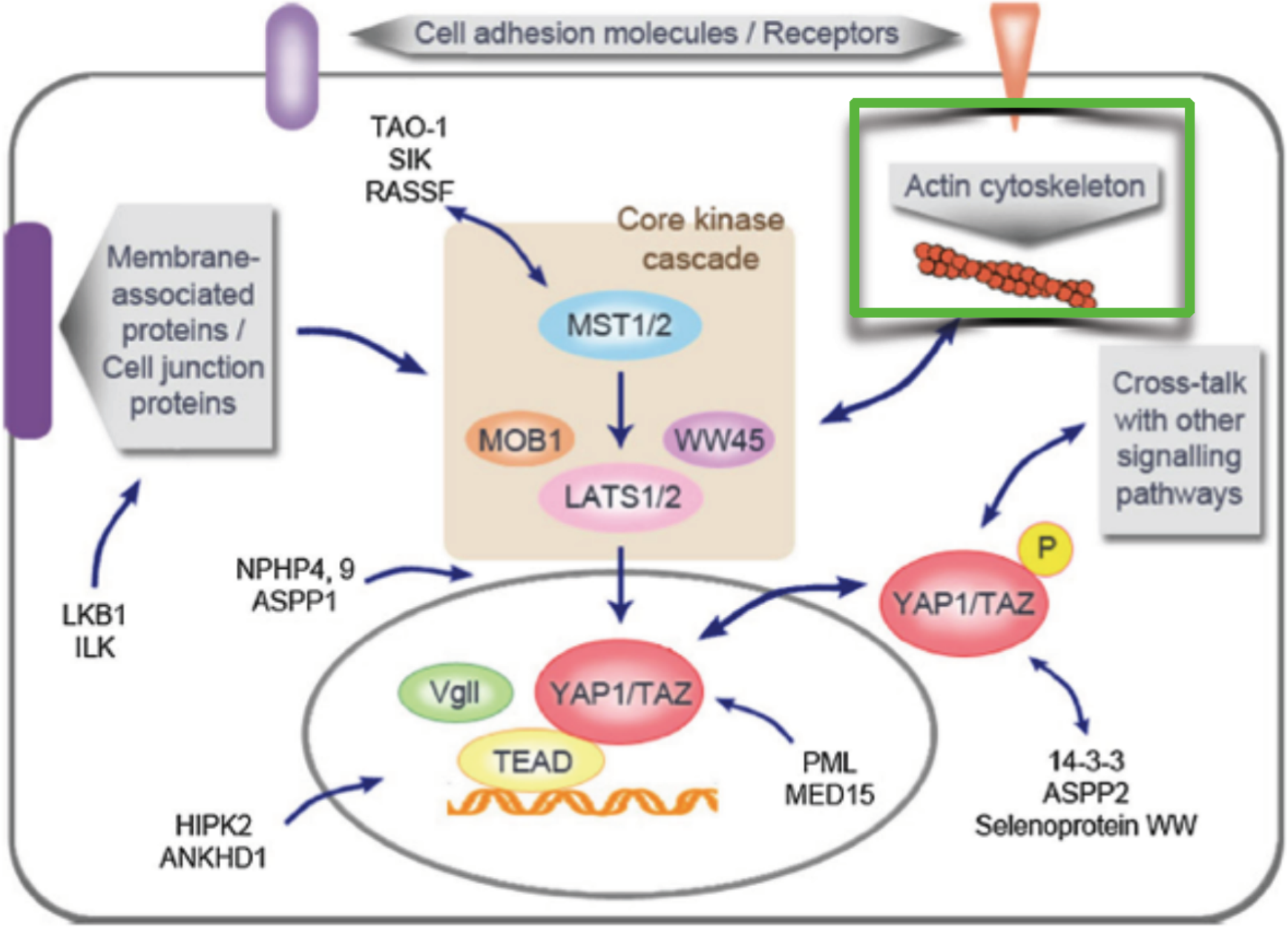


cell-cell contact
cell polarity

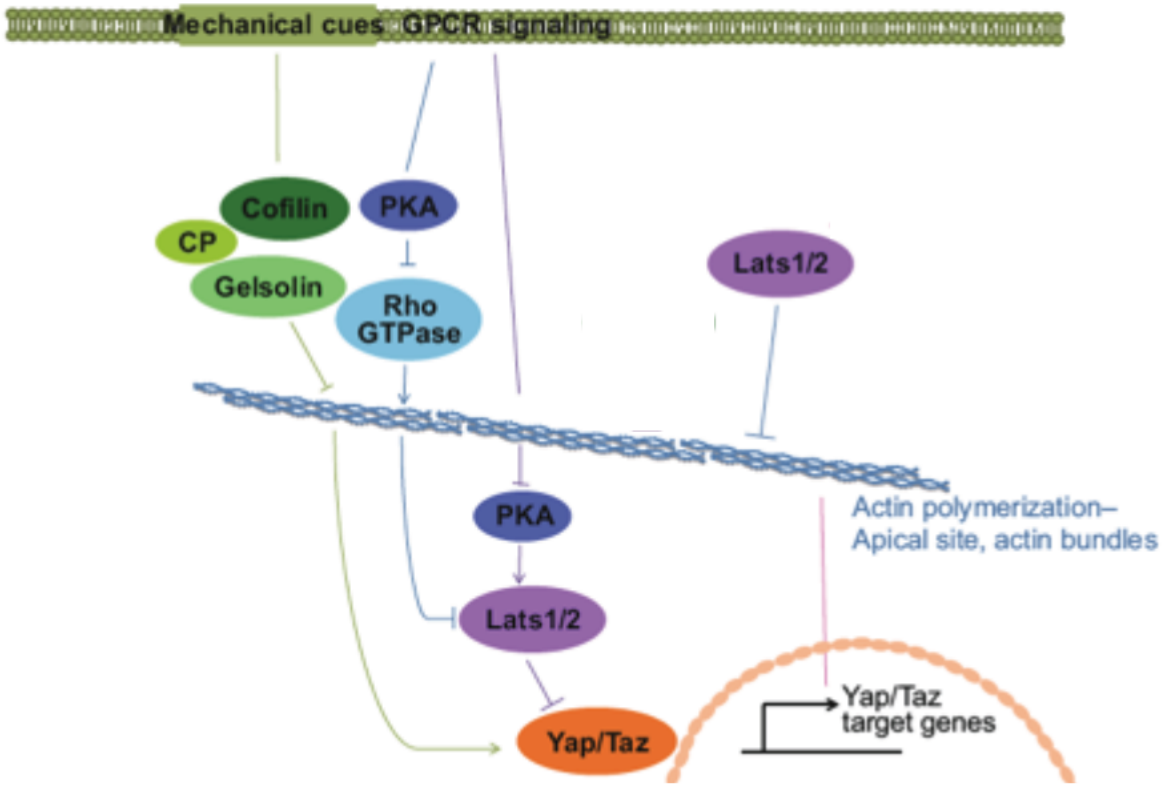


external signals: ECM, secreted factors




Cell adhesion molecules / Receptors
TAO-1
SIK
RASSF
Core kinase cascade
MST1/2
MOB1
WW45
LATS1/2
Actin cytoskeleton
Membrane-associated proteins / Cell junction proteins
Cross-talk with other signalling pathways
LKB1
ILK
NPHP4, 9
ASPP1
P
YAP1/TAZ
Vgll
YAP1/TAZ
TEAD
PML
MED15
HIPK2
ANKHD1
14-3-3
ASPP2
Selenoprotein WW

Mutual regulation between actin cytoskeleton and the Hippo pathway in mammalian cells



In mammalian cells, mechanical cues control actin cytoskeleton and Yap/Taz activity **independently from the Hippo pathway.**

- Negative regulators of F-actin, such as CapZ, Cofilin, and Gelsolin, are required in this regulation.
- GPCR signaling also influences actin cytoskeleton and the activity of Yap/Taz, but in a Lats1/2-dependent manner. Involvement of Rho GTPase and PKA is reported in this regulation. Lats1/2 proteins can directly bind to β-actin, suppressing F-actin polymerization.

Yurika Matsui[1], Zhi-Chun Lai[1,2,3]

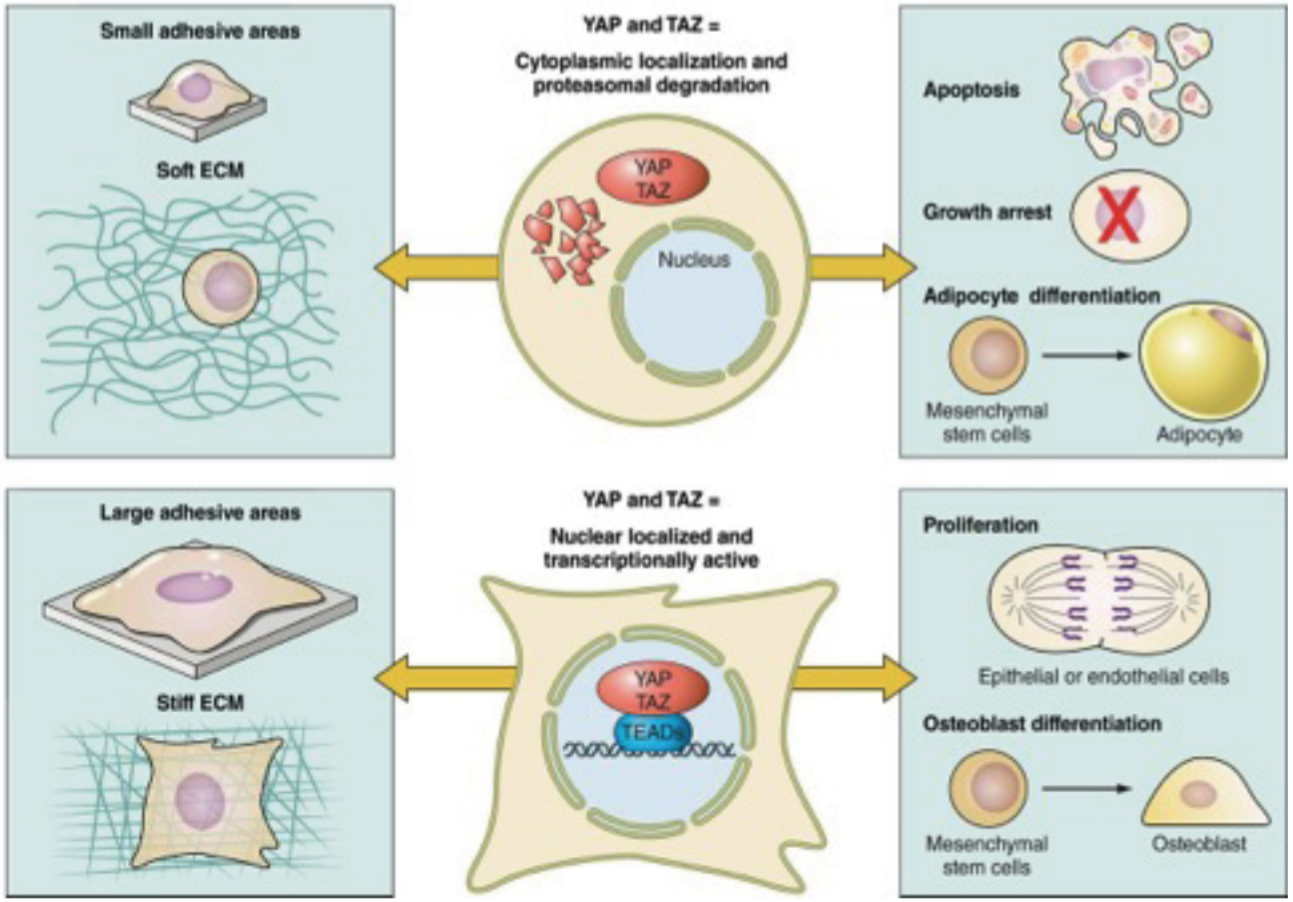
REVIEW

Mutual regulation between Hippo signaling and actin cytoskeleton

ABSTRACT

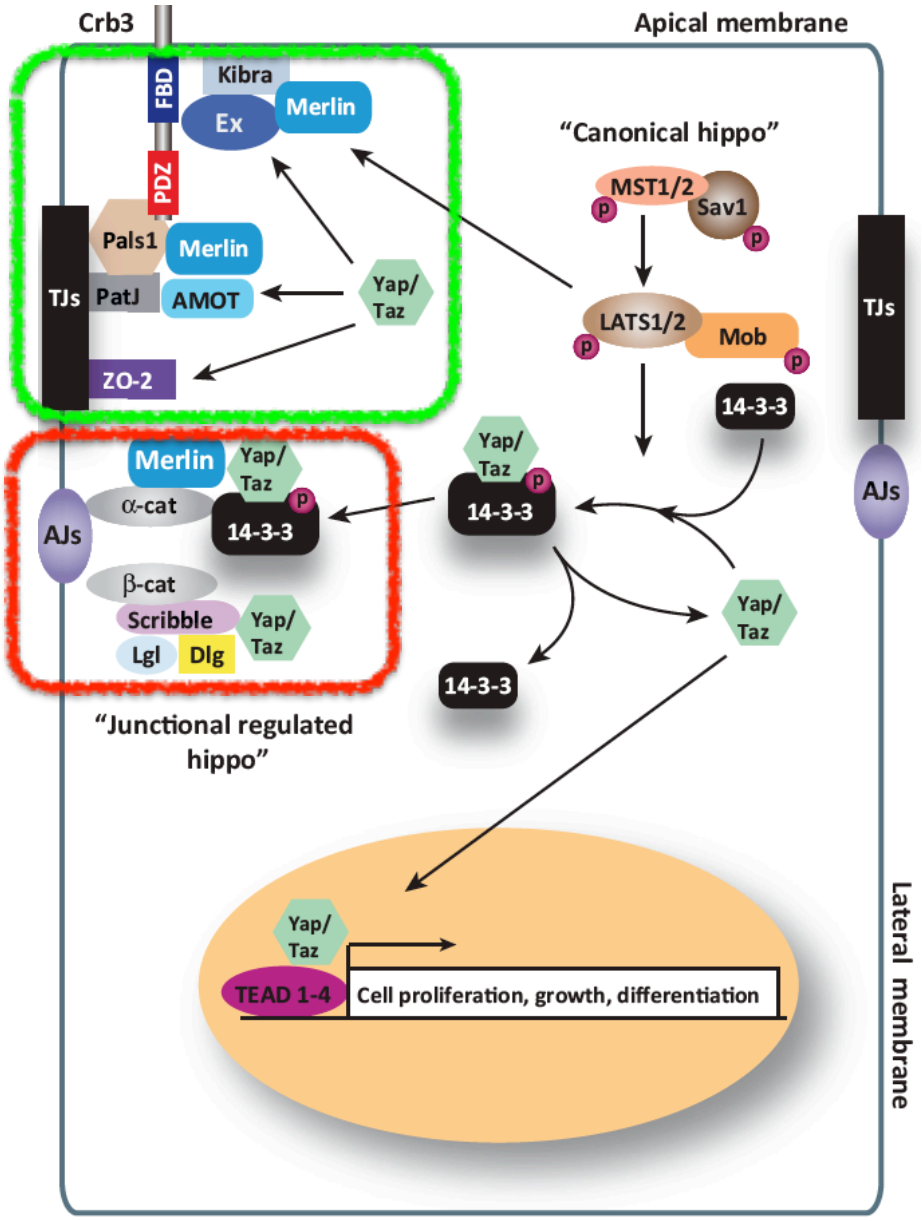
Hippo signaling plays a crucial role in growth control and tumor suppression by regulating cell proliferation, apoptosis, and differentiation. How Hippo signaling is regulated has been under extensive investigation. Over the past three years, an increasing amount of data have supported a model of actin cytoskeleton blocking Hippo signaling activity to allow nuclear accumulation of a downstream effector, Yki/Yap/Taz. On the other hand, Hippo signaling negatively regulates actin cytoskeleton organization. This review provides insight on the mutual regulatory mechanisms between Hippo signaling and actin cytoskeleton for a tight control of cell behaviors during animal development, and points out outstanding questions for further investigations.

YAP/TAZ in mechanotransduction



Dupont et al 2014

Regulation of Yap/Taz by the canonical Hyppo pathway and cellular junction sequestration



In the skin, **adherens junctions** (AJs) control the Hippo pathway through the interaction of phospho-Yap1/14-3-3 with **merlin and a-catenin**. When the Hippo pathway is inactivated, Yap/Taz is dephosphorylated and transported to the nucleus, leading to the upregulation of genes that promote cell proliferation, growth, and differentiation.

At the level of **tight junctions** (TJs),Yap/Taz interacts with different members of the Crumbs complex. Merlin is an upstream regulator of Hippo that binds to kibra and LATs, which has recently been described as binding to AMOT and forms a complex with PatJ and PalS1 at TJs. Crb directly binds to Expanded/FMRD6 (Ex), an upstream regulator of the Hippo pathway, through its juxtamembrane FERM-binding motif (FBM). The PDZ-binding domain of Yap/Taz mediates interactions with ZO-2, which has an important role in Yap/Taz localization under certain conditions. In mammalian embryonic lung and breast epithelia, Yap/Taz forms a complex with Scribble at the plasma membrane, probably through interaction with b-catenin.

The two faces of the Hippo signaling pathway:

1.Regeneration

2. Cancer

Am J Physiol Gastrointest Liver Physiol 307: G196–G204, 2014.
First published May 29, 2014; doi:10.1152/ajpgi.00077.2014.

Dynamic alterations in Hippo signaling pathway and YAP activation during liver regeneration

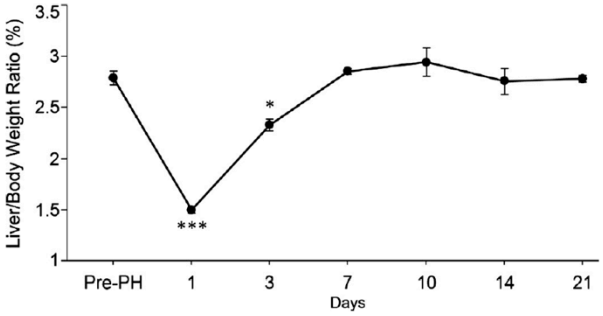
James L. Grijalva,[1] Megan Huizenga,[2] Kaly Mueller,[1] Steven Rodriguez,[2] Joseph Brazzo,[1] Fernando Camargo,[3] Ghazaleh Sadri-Vakili,[2] and Khashayar Vakili[1]

[1]Department of Surgery, Boston Children's Hospital, Boston, Massachusetts; [2]MassGeneral Institute for Neurodegenerative Disease, Massachusetts General Hospital, Boston, Massachusetts; and [3]Department of Stem Cell and Regenerative Biology, Boston Children's Hospital, Boston, Massachusetts

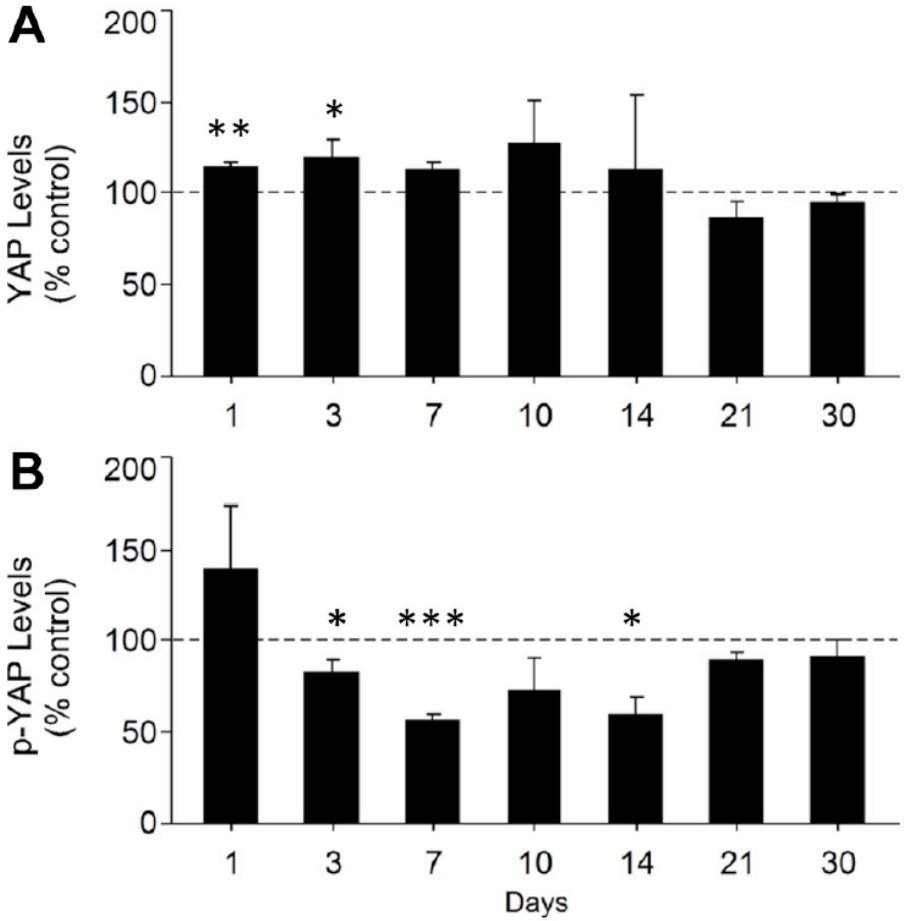
While Hyppo pathway is activated in quiescent livers, its inhibition leads to liver overgrowth and tumorigenesis

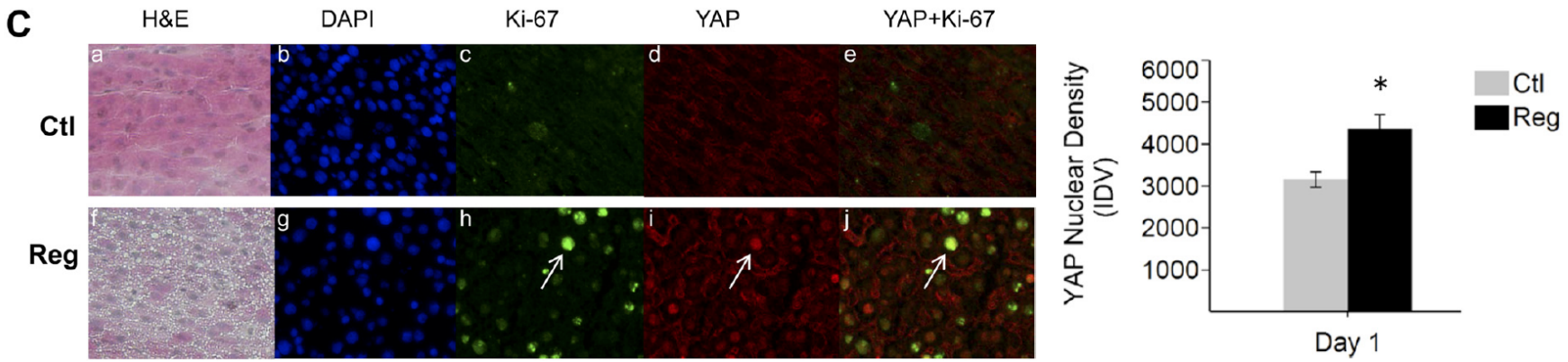
- 70% partial hepatectomy (PH) rat model.
- Increase in YAP activation by 1 day following PH.
- Decrease in the activation of core kinases Mst1/2 by 1 day as well as Lats1/2 by 3 days following PH.
- **Liver reaches its near normal size by 7 days following PH, which correlated with a return to baseline YAP nuclear levels and target gene expression, indicating reactivation of the Hippo signaling pathway.**

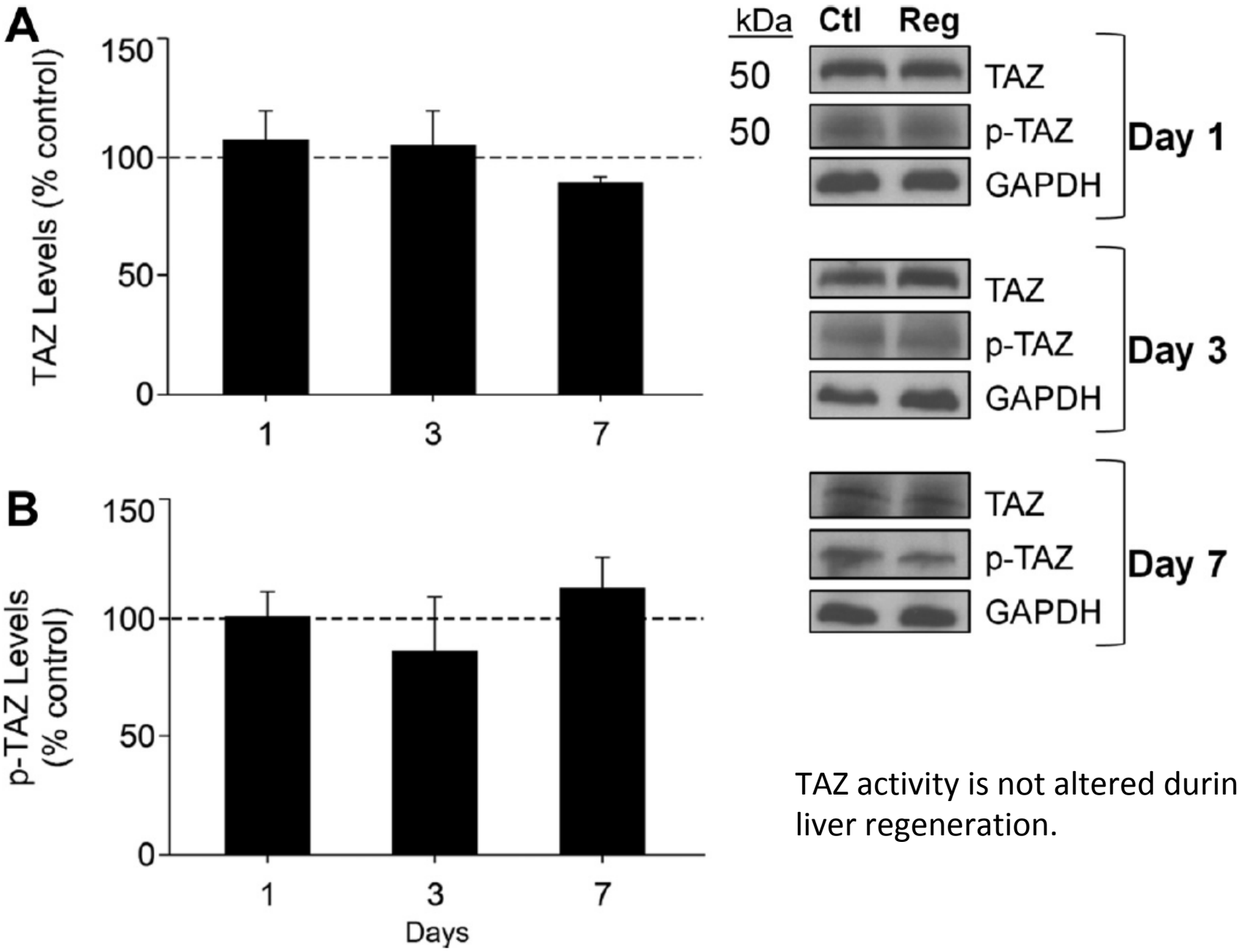
Dynamic changes in the Hippo signaling pathway and YAP activation during liver regeneration, which stabilize when the liver-to-body weight ratio reaches homeostatic levels



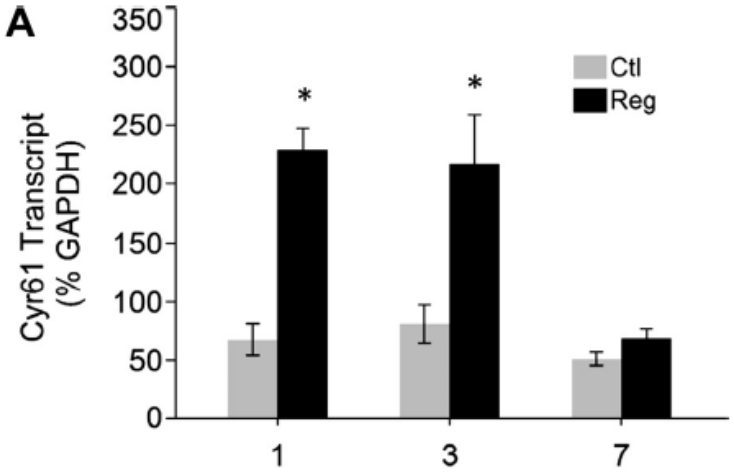
Activation of Yes-associated protein (YAP) is increased during liver regeneration.





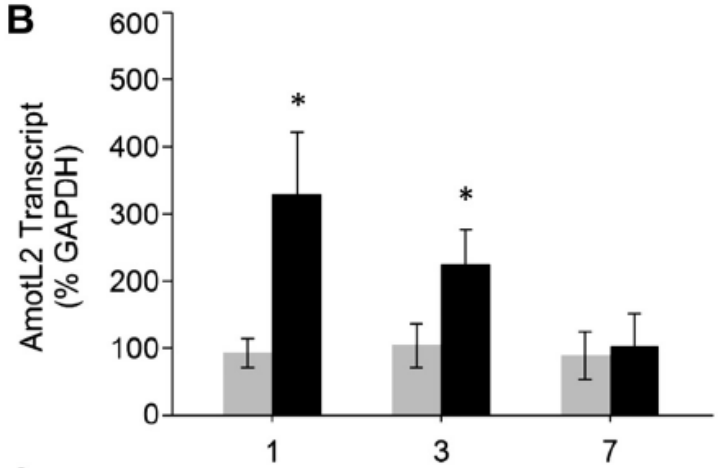


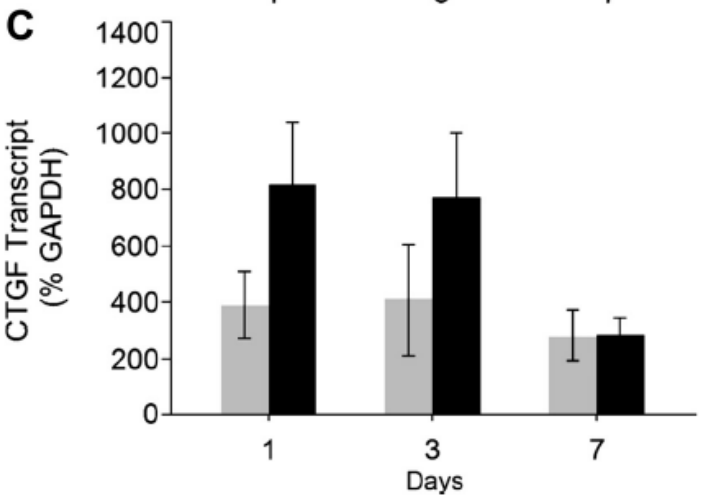
TAZ activity is not altered during liver regeneration.

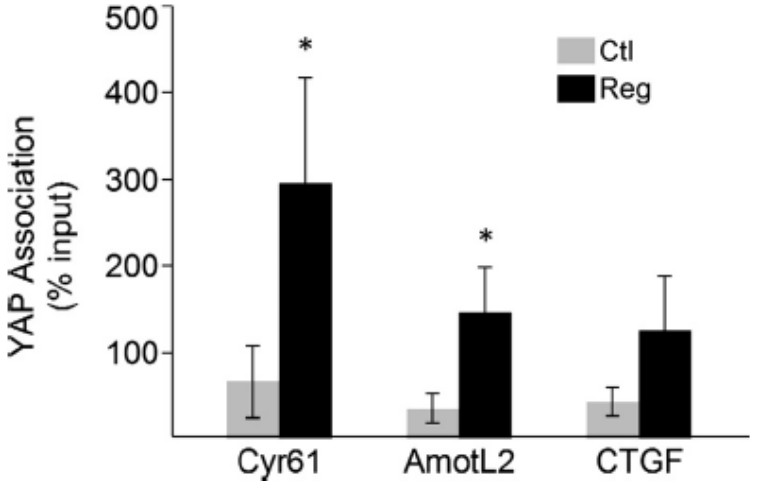


Expression of YAP target genes is increased during liver regeneration.

YAP is activated during liver regeneration.
The pattern of activation of YAP and inactivation of associated Mst1/2 and Lats1/2 kinases correlates with liver growth following PH.





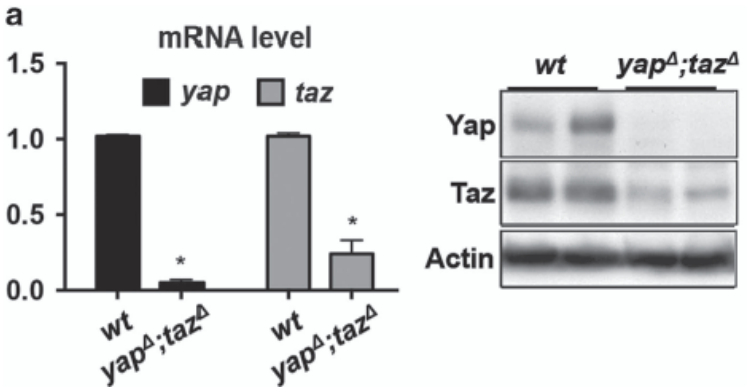


YAP associates with Cyr61 and AmotL2 promoter during liver regeneration.

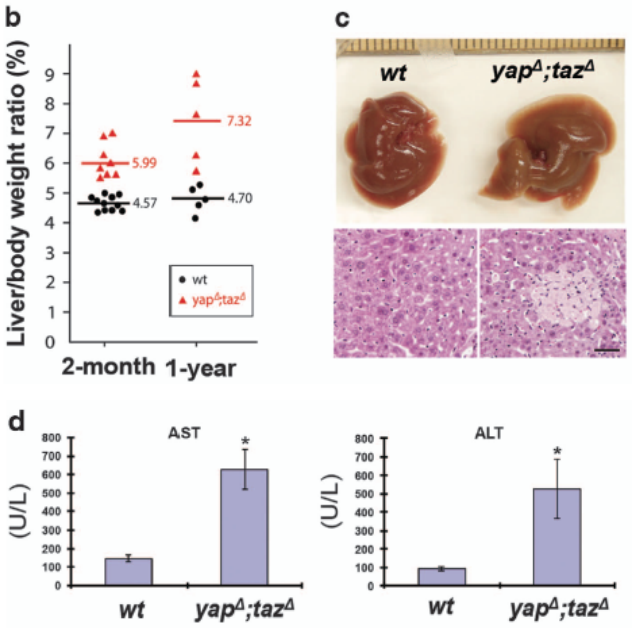
Experimental & Molecular Medicine (2018) 50, e423; doi:10.1038/emm.2017.205
Official journal of the Korean Society for Biochemistry and Molecular Biology
www.nature.com/emm

Hippo pathway coactivators Yap and Taz are required to coordinate mammalian liver regeneration

Li Lu[1,2], Milton J Finegold[3] and Randy L Johnson[4]

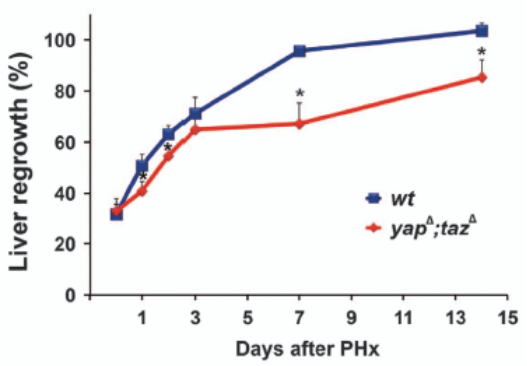


Mice lacking both Yap and Taz in hepatocytes and biliary epithelial cells were generated. Yap/Taz liver conditional knockout mice are viable and fertile.

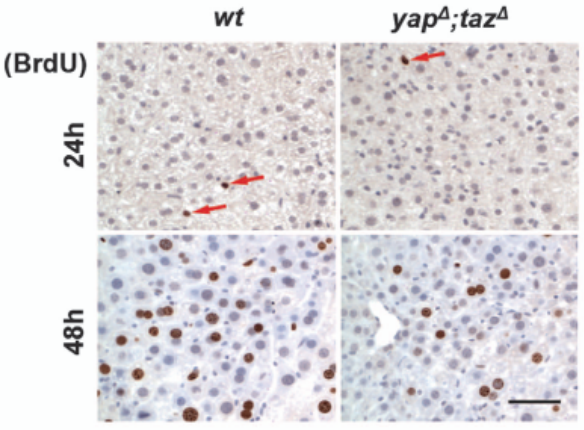


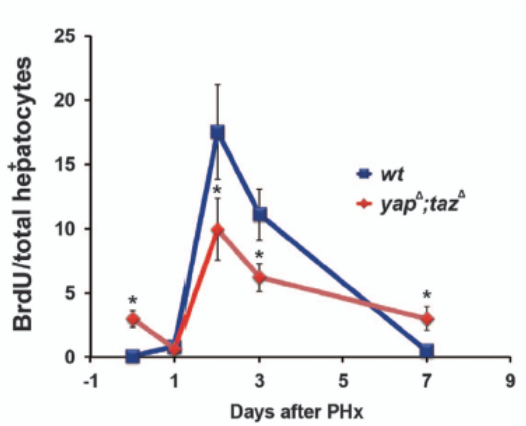
The liver to body weight ratio is enlarged.
The enlarged livers of Yap/Taz mutants had significantly Increased indicators of liver injury (elevated serum levels of alanine transaminase (ALT) and aspartate transaminase (AST).

Yap/Taz-mutant livers regenerated less efficiently following partial hepatectomy (PHx).



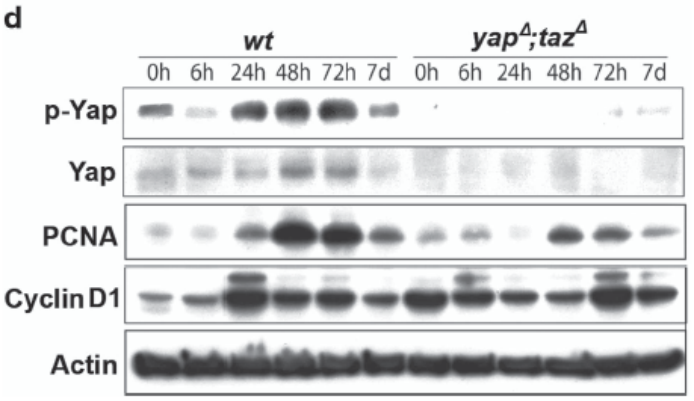
Liver regrowth is blunted in yapΔ/tazΔ liver at all time points.





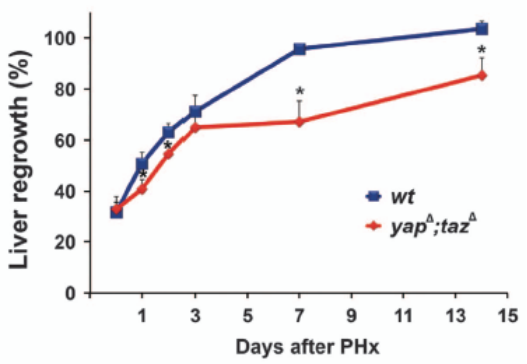
Diminished entry of yapΔ/tazΔ hepatocytes in to S-phase as assayed by BrdU incorporation.

Deficient hepatic cell cycle re-entry and progression in yapΔ/tazΔ liver by western analysis of the cell cycle markers.



Yap/Taz-mutant livers regenerated less efficiently following partial hepatectomy (PHx).

Yap and Taz are required to mount efficient regenerative responses and for achieving complete restoration of liver mass following PHx.



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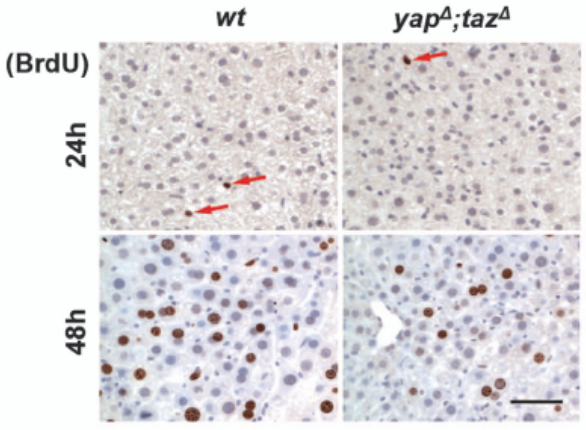

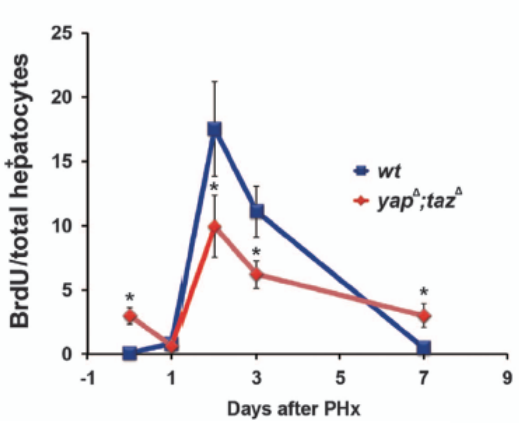

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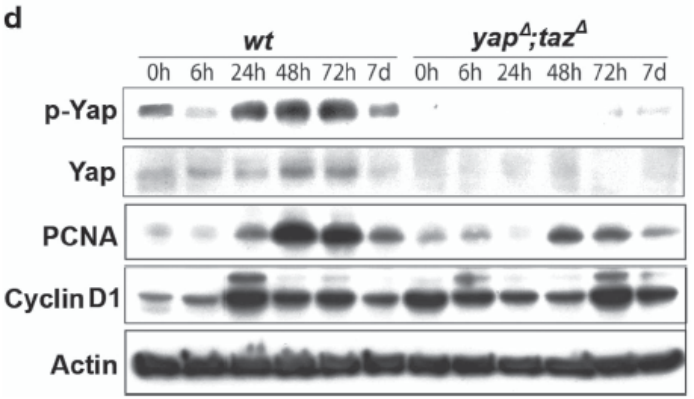
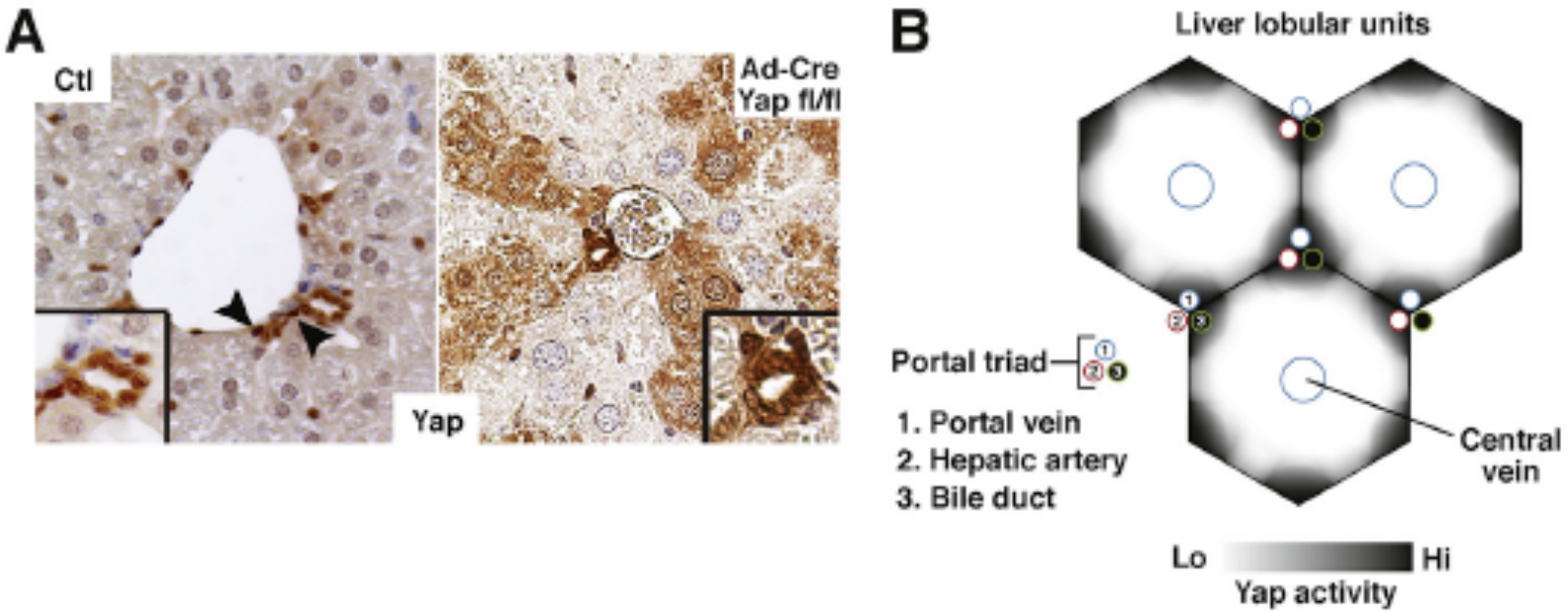
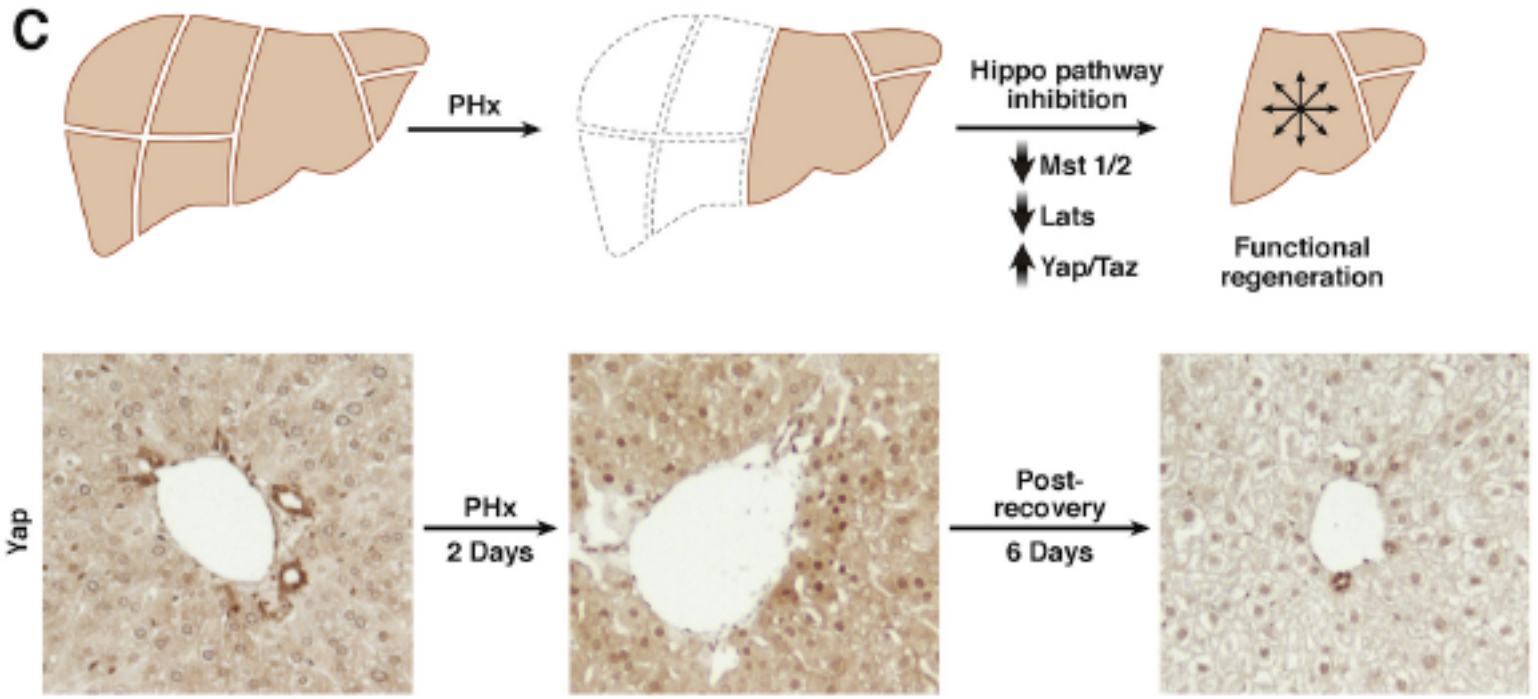


YAP expression during homeostasis and regeneration.



YAP is present in the epithelial cells of mouse liver (hepatocytes and biliary cells).
YAP expression and nuclear localization is more prominent in biliary cells (arrowhead) as compared with hepatocytes. Ad-Cre Yap fl/fl illustrates that YAP is present in hepatocytes as documented by mosaic Yap staining after deletion.
(B) Schematic of YAP activity in the liver. YAP activity is highest in the biliary cells/portal hepatocytes, diminishing in the hepatocytes toward the central vein.



Hippo/Yap activity dynamically changes after partial hepatectomy.
Yap levels increase with an associated decrease in MST1, MST2, LATS1, and LATS2 activity. These return to their normal levels as the liver reaches its appropriate size.

Partial hepatectomy in mice results in YAP enrichment and an increase in nuclear localization (day 2).
After 8 days of recovery, YAP expression is reduced to below baseline levels.

Open questions:

- ✧ What determines the zonation of YAP and TAZ expression in the liver?
- ✧ What is the consequence of Hippo pathway zonation?
- ✧ Does this pattern of signaling affect zonation defined by Wnt signaling?
- ✧ How do junction complexes differ in their regulation of YAP and TAZ?
- ✧ How is YAP activity maintained during homeostasis?
- ✧ What factors increase YAP activity after liver injury and then subsequently down-regulate it?

- ✧ Although YAP is often overexpressed in cancers, why are so few mutations found in the Hippo pathway?
- ✧ How does Hippo signaling interact with other biochemical pathways, such as NOTCH and WNT signaling?
- ✧ What are the downstream targets of YAP/TAZ that mediate their biological functions?

Hippo Signaling in the Liver Regulates Organ Size, Cell Fate, and Carcinogenesis

Gastroenterology 2017;152:533–545

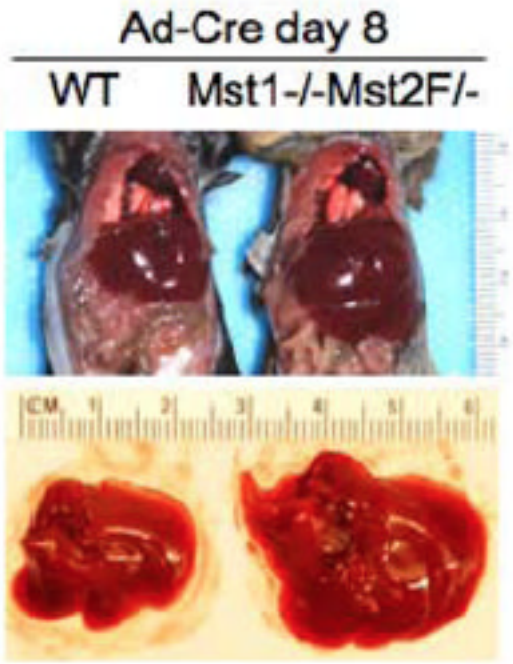
Sachin H. Patel,[1] Fernando D. Camargo,[1,2,3] and Dean Yimlamai[1,4]

The two faces of the Hippo signaling pathway:

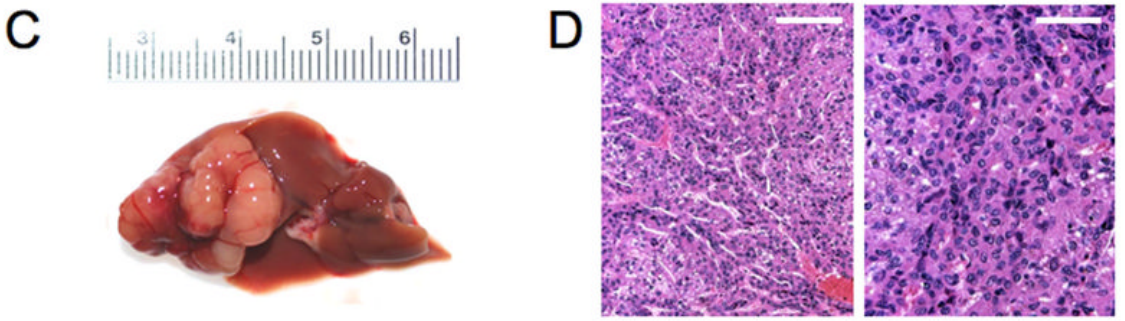
1.Regeneration

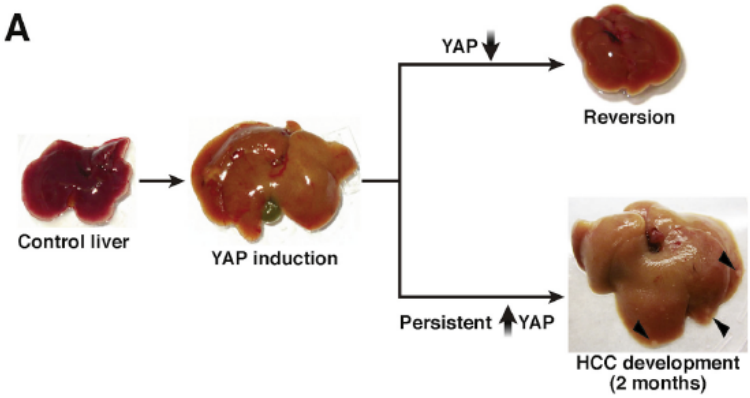
2. Cancer

The Hippo pathway in HCC

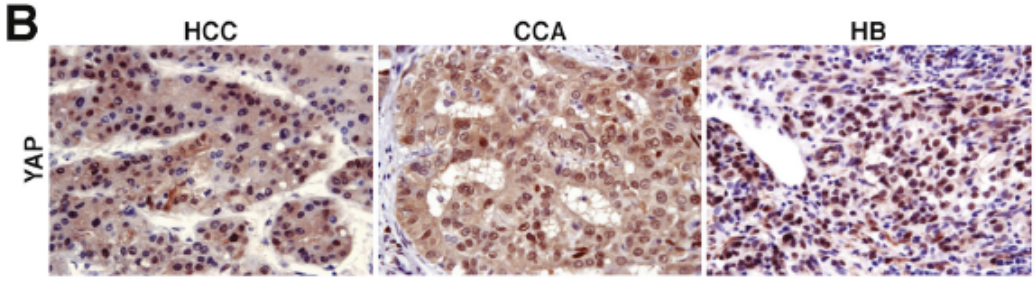


K.O. mice for the upstream regulators of YAP and TAZ
lead to an tumorigenic overgrowth of the liver



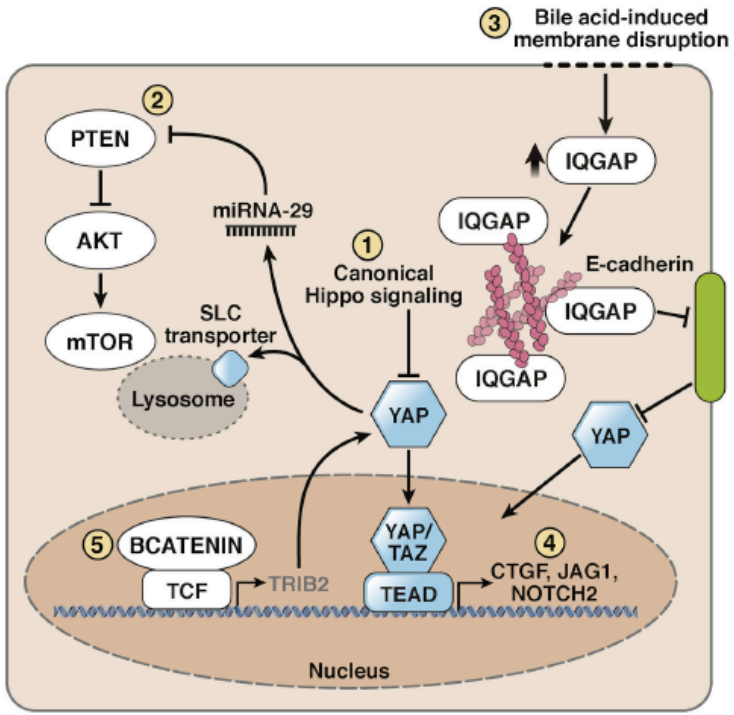


Liver-specific overexpression of YAP leads to massive hepatomegaly with livers approaching 4-5X their original size. Upon restoration of endogenous levels of YAP, the liver returns to its usual size. Persistent YAP activation for 2 months frequently results in HCC development (arrowheads).

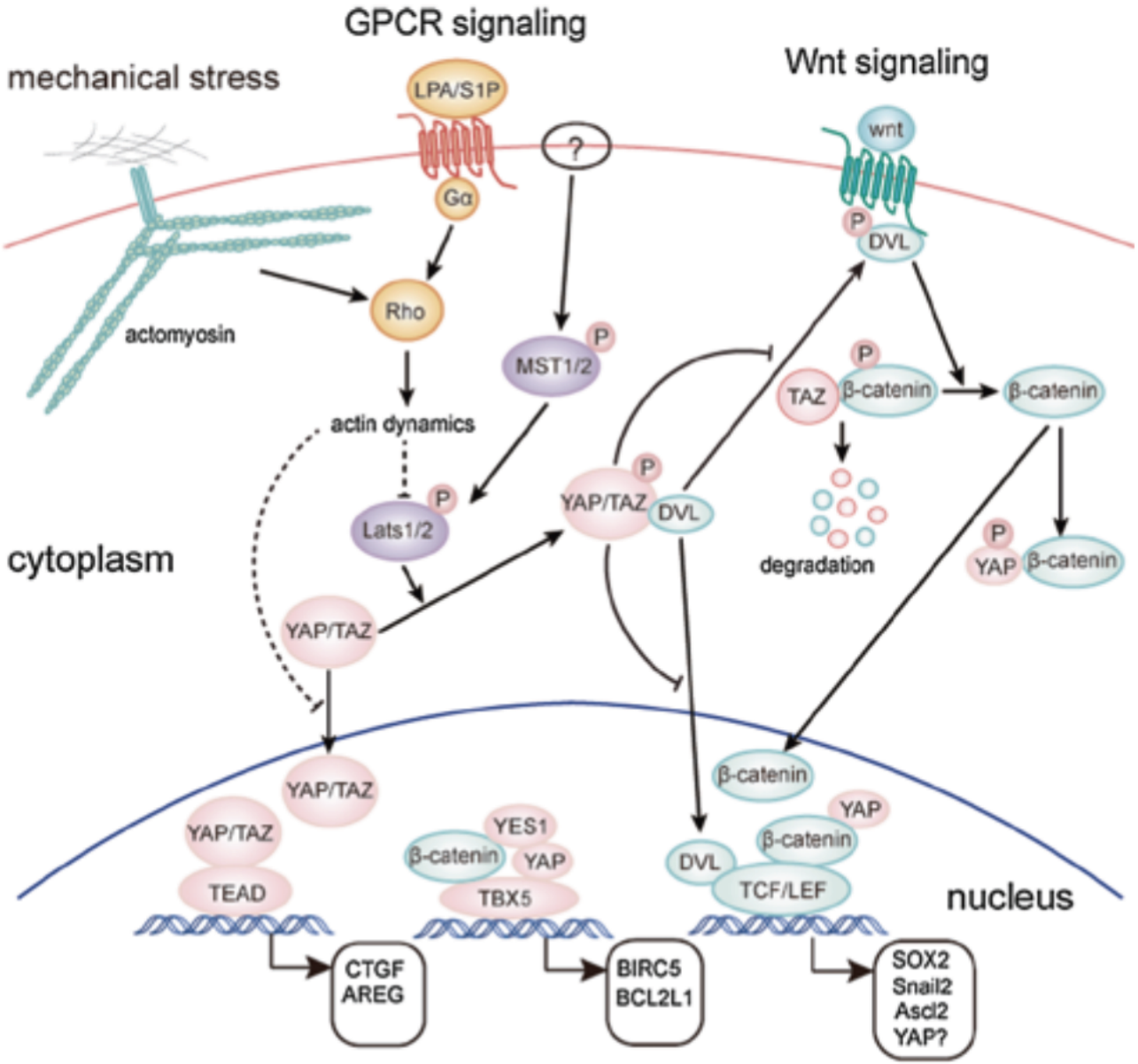


Increased overall YAP and nuclear YAP is a feature of several liver cancers.

YAP can mediate its tumorigenic effects either autonomously or through synergy with other pathways. YAP can be activated through canonical Hippo inactivation (1) or noncanonical membrane associated signaling (2).
YAP can also interact with the PI3KAkt mammalian target of rapamycin pathway through a microRNAmediated mechanism. Finally, YAP can interact with the NOTCH and Wnt pathways, as evidenced through upregulation of NOTCH ligands and receptors (4) and YAP's stabilization by the Wnt target gene TRIB2 (5).



YAP/TAZ are effectors of mechanical stress, GPCR signaling, and the Wnt signaling pathway



Mechanisms of YAP and TAZ regulation by mechanical stress, GPCR signaling, and the Wnt pathway as well as YAP/TAZ as modulators of the Wnt pathway are shown.