Supplementary Material

Elaborating the Physiological Role of YAP as a Glucose Metabolism Regulator: A Systematic Review

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Supplementary Table 1 Summary table of studies excluded during the full-text review and their reasons for exclusion

No.	Author	Species	Intervention	Reason for Exclusion
1	Yu, et al. [65]	*In vitro*: Mice C57BL/6J	Streptozotocin	The research did not establish a causal link between high glucose and YAP / Hippo pathway levels.
2	Li, et al. [66]	*In vitro*: Human renal mesangial cells Human podocyte cells	High glucose treatment Liraglutide siRNA against *Sirt3*	The research did not establish a causal link between high glucose and YAP / Hippo pathway levels.
3	Lei, et al. [67]	*In vivo*: C57BL/KSJ db/db mice *In vitro* Mouse Glomerular mesangial cells SV40 MES13	Quercetin	The study did not explore aspects of glucose metabolism.

4	Xing, et al. [68]	*In vivo*: Monkey choroid-retina RF/6A	Fufang Xueshuantong extracts shRNA against *YAP*	The study did not explore aspects of glucose metabolism.
5	Dixit, et al. [69]	*In vitro*: A172; U87MG; T98G	Chaetocin siRNA against *YAP*	The study did not explore aspects of glucose metabolism.
6	Fujisawa, et al. [70]	*In vitro*: Human hepatic stellate cells		The study did not explore aspects of glucose metabolism.
7	Li, et al. [71]	*In vitro*: 3T3-L1	Liraglutide siRNA against MST1	The study did not explore aspects of glucose metabolism.

The table is sorted according to the reason for exclusion. Only one main reason for exclusion is stated in this table.

Supplementary Table 2. Summary table of research findings included in the systematic review

No.	Author	Species	Intervention	Findings Summary	Groupings
1	Wang, et al. [16]	*In vitro* HEK293A; MDA-MB-231; SUM159	Glucose starvation and administration of 2DG. Administration of YAP5SA	Low glucose increased YAP phosphorylation at S127. Without energy stress, YAP translocated to the nucleus and increased the transcription of *CTGF*, *CYR61*, and *ANKRD1*. AMPK phosphorylated YAP at S61. Active YAP increased glycolysis, as shown by the lower pH value of the medium. Overexpression of YAP upregulates *GLUT3* expression.	Energy status
2	Mo, et al. [43]	*In vitro*: HEK293A; HEK293P;	Glucose starvation and 2DG treatment.	Glucose starvation activated LATS activity. Expression of active AMPK induced YAP phosphorylation.	Energy status

No.	Author	Species	Intervention	Findings Summary	Groupings
		HEK293T; H235; NIH3T3; C2C12; HeLa	AMPKα1 and AMPKα2 expression	Energy stresses induced the inhibition of YAP/TAZ through LATS and AMPK. AMPK phosphorylated YAP at S94.	
3	Zhang, et al. [20]	*In vitro*: Bel-7402; SMMC-7721	Glucose treatment OGT overexpression	O-GlcNAcylation increased YAP function. O-GlcNAcylation inhibited the interaction between βTrCP and YAP, thereby limiting its degradation. Glucose treatment increased *YAP* expression and endogenous YAP O-GlcNAcylation YAP overexpression upregulated *OGT*, *Nudt9,* and *SLC5A3* expression	Energy status
4	Nokin, et al. [39]	*In vitro*:	Methylglyoxal treatment	Methylgyoxal (MG) induced YAP nuclearization and transcriptional activity.	Energy status

No.	Author	Species	Intervention	Findings Summary	Groupings
		MDA-MB-231; MDA-MB-468; MCF7		MG significantly decreased the LATS1 protein level.	
5	Peng, et al. [37]	*In vitro*: HEK293T; HeLa; L3.6	shRNA against YAP YAP KO Cell line	The hexosamine biosynthesis pathway through O-GlcNAcylation directly promotes YAP activity and is dependent on extracellular glucose. O-GlcNAcylation of YAP activated its function by inhibiting interaction with LATS1. YAP-TEAD regulated the transcription of OGT and, therefore, O-GlcNAcylation.	Energy status
6	Liu, et al. [65]	*In vitro*:	High glucose	Although normally AMOT inhibited YAP function by decreasing YAP's nuclear	Energy status

No.	Author	Species	Intervention	Findings Summary	Groupings
		Bel-7402; SMMC-7721 *In vivo*: Mice models	Streptozotocin treatment *in vivo*	translocation, O-GlcNAcylation of AMOT increased YAP translocation during high glucose conditions. Streptozotocin treated mice highly expressed AMOT and YAP in the liver with bot located inside the nuclear compartment	
7	Huang, et al. [42]	*In vivo*: C57BL/Ksj, db/db diabetic mice *In vitro*: Immortalized mouse podocyte and renal	High glucose siRNA against *RhoA* and *YAP*	High glucose decreased total RhoA protein levels in mice podocyte. YAP expression levels in the nucleus were decreased both in high glucose treated podocyte and *RhoA* knockdown.	Energy status

No.	Author	Species	Intervention	Findings Summary	Groupings
		biopsies from diabetic nephropathy patients			
8	Enzo, et al. [27]	*In vitro*: MCF10A; MDA-MB-231	Administration of 2DG. siRNA treatment of PFK1 and YAP/TAZ	Reduction of glycolysis reduced YAP/TAZ activity. Knockdown of *PFK1* inhibits YAP/TAZ activity Inhibition of glycolysis reduced YAP/TEAD interaction	Glucose metabolism
9	Cox, et al. [35]	Zebrafish. Cancer Cell Line Encyclopedia	Transgenic *yap*$^{-/-}$ mutant embryos	*Yap*$^{-/-}$ mutants have a significantly lower level of *glut1* and *glut2*. Gene expression data revealed a strong positive correlation between *YAP1* and	Glucose metabolism

No.	Author	Species	Intervention	Findings Summary	Groupings
				GLUT1, with no correlation between *YAP1* and *GLUT2*.	
10	Li, et al. [34]	*In vitro*: SGC-7901	Ajuba overexpression YAP siRNA	Overexpression of Ajuba increased GLUT1 expression, and this effect is mediated through YAP.	Glucose metabolism
11	Zheng, et al. [22]	*In vitro*: MDA-MB-231	YAP5SA expression *BCAR4/GLI2* overexpression	BCAR4/GLI2 was a downstream target of YAP and mediated the increased glycolysis caused by YAP overexpression. YAP overexpression upregulated *HK2* and *PFKFB3*.	Glucose metabolism
12	Shen, et al. [66]	*In vitro*: MG63; MNNG-HOS; Saoa-2	Verteporfin treatment shRNA against *S1PR3*	YAP regulates the expression of *PGAM1* through c-Myc. Inhibition of YAP-TEAD interaction using Verteporfin failed to inhibit glycolysis.	Glucose metabolism

No.	Author	Species	Intervention	Findings Summary	Groupings
13	Kuo, et al. [19]	*In vitro*: HCT116; 116-LM; HT29	Administration of 2DG shRNA against YAP	GLUT3 protein overexpression upregulates YAP dependent target genes YAP knockdown or 2DG treatment decreased the expression of *GLUT3*, *HK1*, *GPI*, *PGK1*, and *ALDOA.*	Glucose metabolism
14	Mi and Kuang [67]	*In vitro*: Hep3B; HepG2	Melatonin treatment *YAP* plasmid transfection siRNA against *YAP*	*YAP* depletion downregulated GLUT3 protein and mRNA expression	Glucose metabolism
15	Song, et al. [24]	*In vitro*: CNE1; CNE2	Plasmid transfection	YAP, along with FOXC2, regulated HK2. Overexpression of FOXC2 or YAP increased HK2 protein and mRNA levels.	Glucose metabolism
16	Yan, et al. [25]	*In vitro*:	Verteporfin	YAP is a downstream regulator of hepatocyte growth factor.	Glucose metabolism

No.	Author	Species	Intervention	Findings Summary	Groupings
		AsPC-1; BxPC-3; CFPAC-1; Panc-1; MiaPaCa-2	Recombinant Human hepatocyte growth factor.	YAP overexpression increased *HK2* expression	
17	Mammoto, et al. [29]	*In vitro*: HUVE	Plasmid construct of YAP1, YAP1-S127A, and PGC-1α. shRNA against *PGC-1α* siRNA against *TEAD*	The knockdown of TEAD decreased the expression of PGC-1α mRNA and protein levels. YAP S127A overexpression increased PGC-1α mRNA and protein levels. Overexpression of YAP increased the extracellular acidification rate (ECAR) and glycolytic reserve.	Glucose metabolism
18	Cosset, et al. [17]	*In vitro*:	Verteporfin	YAP/TAZ knockdown decreased GLUT3 protein expression	Glucose metabolism

No.	Author	Species	Intervention	Findings Summary	Groupings
		U87MG; LN229; U251	shRNA against *YAP/TAZ*		
19	Wang, et al. [36]	*In vitro*: Hep-2	siRNA against TEAD	TEAD knockdown decreased GLUT1 protein expression	Glucose metabolism
20	White, et al. [18]	*In vitro*: SN12C	shRNA against YAP/TAZ	YAP/TAZ knockdown decreased *HK1, PFKFB4, HK2, PFKP, GAPDH, PGK1, PGAM1, LDHA1, PDHB* levels	Glucose metabolism
21	Wang, et al. [28]	*In vitro*: Neonatal mouse cardiomyocytes.	2DG treatment.	2DG treatment increased LATS1 phosphorylation and, thus, YAP phosphorylation and inhibition.	Glucose metabolism
22	Yin, et al. [26]	*In vitro*: AKR-2B	siRNA HK2 and siRNA YAP/TAZ	HK2 affected YAP / TAZ gene activity. And vice versa	Glucose metabolism

No.	Author	Species	Intervention	Findings Summary	Groupings
23	Menini, et al. [38]	*In vivo*: Transgenic mice *In vitro*: PaCa-2; Panc-1	Streptozotocin High glucose Methylglyoxal Nε-carboxymethyllysine FL-926-16 siRNA against YAP and EGFR	High glucose increased the accumulation of advanced glycation end products. *In vitro* studies showed that AGE precursors and preformed AGE increased cell proliferation by activating YAP1 MGO affected YAP by decreasing LATS1 protein levels. CML induced EGFR phosphorylation, and *EGFR* knockdown reversed YAP1 nuclear translocation.	Glucose metabolism
24	Chen, et al. [21]	*In vitro*: Hepa1-6; HepG2; Hep3B; HuH7	Gene knockdown using shRNA	*YAP* knockdown inhibited expression of *GLUT1*, *HK2*, *ALDOA*, and *LDHA*.	Glucose metabolism; hypoxia

No.	Author	Species	Intervention	Findings Summary	Groupings
				YAP knockdown abolished the effect of hypoxia-induced expression of *GLUT1*, *HK2*, *ALDOA*, and *LDHA*. YAP/HIF-1α complex formation was found in the cell nucleus.	
25	Hu, et al. [30]	*In vitro*: Primary mouse hepatocytes *In vivo*: Mice	Liver-specific YAP S127A expression.	Constitutively active YAP inhibits *G6PC* and *PCK1* expression YAP overexpression *in vivo* decreased random blood glucose levels and increase glucose tolerance. YAP altered the ability of PGC1α to bind gluconeogenic gene promoter	Glucose metabolism ; Insulin & Glucagon control
26	Pocaterra, et al. [31]	*In vivo*: C57BL/6 N	Transgenic mice with liver-specific	Inactivation of *Capzb* in mice hepatocytes increased YAP activity.	Glucose metabolism

No.	Author	Species	Intervention	Findings Summary	Groupings
			knockout of *Capzb, Yap1*, and *Wwtr1*	*Capzb* liver knockout produce the same metabolic phenotype as liver YAP overexpression, which is increased glucose tolerance and decreased *Pck1*, *G6pc*, and *Fbp1* expression	; Insulin & Glucagon control
27	Zhang, et al. [48]	*In vitro*: HepG2; Huh7	YAP siRNA	Hypoxia increased YAP translocation into the cell nucleus. The increase in glycolysis in hypoxic cells is abolished by YAP knockdown. YAP formed a complex with HIF-1α to bind to the PKM2 gene promoter and sustained HIF-1α stability.	Hypoxia

No.	Author	Species	Intervention	Findings Summary	Groupings
				YAP knockdown decreased the protein and mRNA expression of PKM2 during the hypoxic condition	
28	Li, et al. [68]	*In vitro*: MKN-45	Verteporfin treatment Plasmid transfection for YAP overexpression	Inhibition of YAP-TEAD interaction using Verteporfin significantly decrease the protein and mRNA levels of HK2 and PFK1 YAP overexpression upregulated *HIF-1α* in gastric cancer cells.	Hypoxia
29	Sayedyahossein, et al. [32]	*In vitro*: HepG2; C2C12	siRNA against YAP Insulin treatment	Insulin increased YAP phosphorylation, thereby inhibiting its function through the Pi3K signaling cascade.	Insulin & Glucagon control

No.	Author	Species	Intervention	Findings Summary	Groupings
				Insulin reduced the expression levels of *G6PC* and *PCK1,* and these effects are further pronounced by YAP knockdown	
30	Yu, et al. [49]	*In vitro*: Primary Mouse Hepatocytes	Glucagon treatment Serum starvation	LPA and S1P regulate YAP activity through their influence on the actin cytoskeleton. Glucagon stimulates YAP phosphorylation in primary mouse hepatocytes.	Insulin & Glucagon control

The table is sorted according to the categorical grouping. Articles with multiple categories meant the article's findings are used in more than one topic.

Abbreviations:

2DG: 2-deoxyglucose
AGE: Advanced glycation endproduct
ALDOA: Aldolase A
AMOT: Angiomotin
AMPK: AMP-activated protein kinase
ANKRD1: Ankyrin Repeating Domain 1
CML: Nε-carboxymethyllysine
CTGF: Connective tissue growth factor
CYR61: Cysteine rich angiogenic inducer 61
ECAR: Extracellular acidification rate
FBP1: Fructose-1,6-Bisphosphatase 1
FOXC2: Forkhead Box C2
G6PC: Glucose-6-phosphatase catalytic subunit
GAPDH: Glyceraldehyde-3-phosphate dehydrogenase
GLUT (1,2,3): Glucose Transporter (1,2,3)
GPI: Glucose-6-phosphate isomerase
HK (1,2): Hexokinase 1 & Hexokinase 2
LATS: Large tumor suppressor kinase
LDHA: Lactate dehydrogenase A
LPA: lysophosphatidic acid
MG: methylglyoxal
Nudt9: Nudix Hydrolase 9
PCK1: Phosphoenolpyruvate carboxykinase 1
PDHB: Pyruvate dehydrogenese E1 Subunit Beta
PFK1: Phosphofructokinase 1
PFKFB3: 6-Phosphofructo-2-Kinase 3
PFKFB4: 6-Phosphofructo-2-Kinase 4
PGAM1: Phosphoglycerate Mutase 1
PGC1-α: Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha
PGK1: Phosphoglycerate Kinase 1
PI3K: Phosphatidylinositol 3-kinases
PKM2: Pyruvate kinase M2
PFKP: Phosphofructokinase, Platelet
S1P: Sphingosine 1-phosphate
SLC5A3: Solute Carrier Family 5 Member 3
TEAD: TEA Domain Transcription Factor
YAP: Yes-Associated Protein