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The role of YAP/TAZ in energy metabolism in the heart

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Abstract

The heart requires a high amount of energy, in the form of adenosine triphosphate (ATP), to maintain its viability and pump function. Anaerobic glycolysis and mitochondrial oxidative phosphorylation are the main metabolic pathways by which ATP is generated, utilizing fatty acids (FAs), glucose, lactate, and ketone bodies as primary substrates. Previous studies have demonstrated that, in response to stress, the heart undergoes alterations in metabolism, ranging from changes in substrate utilization to mitochondrial function, collectively called metabolic remodeling. However, the molecular mechanism mediating metabolic remodeling in the heart remains unclear. Yes-associated protein 1 (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ), which are major downstream effectors of the Hippo signaling pathway, play an important role in the regulation of heart size and cellular homeostasis of cardiomyocytes through the regulation of various transcriptional factors under both physiological and pathophysiological conditions. Recent findings in various organs and cell types have revealed that YAP and TAZ play an important role in energy metabolism. Here we summarize what is currently known about YAP/TAZ in the regulation of metabolism of various substrates and mitochondrial function in various organs and cell types and discuss the potential role of YAP/TAZ in mediating metabolic remodeling of the heart during stress and heart failure.

Keywords

the Hippo pathway; YAP; TAZ; glycolysis; metabolic remodeling; heart failure

1. Introduction

The heart has a large metabolic demand due to continuous contraction, requiring that a large amount of adenosine triphosphate (ATP) be generated (1). ATP is produced at high rates so that the heart can quickly respond to a sudden increase in hemodynamic overload. Fatty acid (FA), glucose, lactate, and ketone bodies are the primary substrates for ATP production (2, 3). There are two fundamental mechanisms for ATP synthesis: anaerobic *glycolysis* and aerobic *oxidative phosphorylation*. Under baseline conditions, more than 95% of ATP is

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Conflict of interests

The authors declare no conflict of interest.

produced from oxidative phosphorylation in mitochondria and the remaining 5% from glycolysis in the cytosol in the healthy adult heart. Under baseline conditions, 60–90% of acetyl-CoA, which is utilized in the tricarboxylic acid (TCA) cycle, comes from β-oxidation of FAs, and 10–40% from oxidation of pyruvate, derived from glycolysis and lactate oxidation (1, 4). In the fetal heart, low levels of circulating FAs and high levels of glucose and lactate allow the heart to generate approximately 50% of ATP from glucose and lactate (5, 6). Heart failure (HF) is a condition in which the pump function is insufficient for responding to systemic metabolic demand. Despite recent progress in medical treatment, HF is a major cause of mortality in developed countries (7). HF is accompanied by significant changes in metabolism in the heart, termed metabolic remodeling, ranging from changes in substrate utilization to mitochondrial dysfunction. Metabolic remodeling during HF can be either the cause or the effect of reduced cardiac contractility and either adaptive or maladaptive (3, 8, 9). Compared to glucose oxidation, FA oxidation requires more oxygen for the production of an equal amount of ATP. Together with the increased circulating level of FAs during HF, the use of FA promotes oxygen consumption, which in turn causes a proton leak from the electron transport chain and mitochondrial dysfunction due to oxidative damage. Thus, the downregulation of FA oxidation commonly observed in failing hearts may be an adaptive response. However, FA oxidation progressively declines with mitochondrial dysfunction, which in turn leads to decreases in ATP production and further decreases in cardiac contraction (10). Thus, decreases in FA oxidation can be maladaptive during HF. Intervening in the process of metabolic remodeling may allow improvement of cardiac function in HF patients. However, the signaling mechanism through which metabolic remodeling takes place in the failing heart remains poorly understood.

The Hippo signaling pathway is an evolutionarily conserved signaling pathway, regulating organ size and tumorigenesis. Yes-associated protein 1 (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ), which are the two major terminal effectors with partially overlapping functions in the Hippo signaling pathway, play a crucial role in tissue homeostasis through regulation of proliferation, hypertrophy, survival and death in the heart (11, 12). In general, activation of the upstream components of the Hippo pathway, including Mst1 and Lats2, inhibits cell proliferation and induces cell death, including apoptosis, whereas inactivation of the Hippo pathway and consequent activation of YAP/TAZ promote both proliferation and survival in many cell types. Since cell growth during tumorigenesis and organ enlargement are accompanied by changes in metabolism, an emerging hypothesis is that the Hippo pathway may also control metabolism. In fact, increasing lines of evidence suggest that YAP/TAZ plays an important role in energy metabolism in many cell types (13, 14). This review summarizes the role of YAP/TAZ in energy metabolism in various cell types and discuss the potential role of YAP/TAZ in mediating metabolic remodeling in the heart.

2. The Hippo signaling pathway

The Hippo pathway, an evolutionarily conserved signaling pathway, generally serves as a key regulator of organ size through regulation of both apoptosis and proliferation (11). Major components of the Hippo pathway include an upstream protein kinase cascade comprising mammalian sterile 20-like kinase 1 and 2 (MST1/2), large tumor suppressor 1

and 2 (LATS1/2), the scaffold protein Salvador (SAV, also known as WW domain-containing adaptor 45 (WW45)), and Mps one binder kinase activator 1A and B (MOB1A/B), and downstream effectors, including YAP and TAZ. In response to stress, such as oxidative stress, endoplasmic reticulum stress, and cytokines, MST1/2 interacts with SAV1 and activates LATS1/2, thereby phosphorylating and inhibiting YAP/TAZ (Figure 1) (15). YAP/TAZ, phosphorylated by the upstream Hippo pathway components, are bound by 14-3-3 and retained in the cytosol (16), where they undergo degradation through the ubiquitin proteasome system (17). YAP Ser127 and TAZ Ser89 are key phosphorylation sites for phosphorylation-induced inhibition by LATS. When the Hippo pathway is inactivated, active YAP/TAZ translocate to the nucleus and interact with multiple transcription factors, such as TEADs, TBX5, SMADs, p73, p63, ERBB4, EGR-1, Erb4, FOXO1, FOXOM1, HIF1α/β, KLF5, FOS, C/EBPα, CREB, OCT4, GLI, TTF-1, PAX3/8, PPARγ, MyoD, and RUNXs (12). TEAD is one of the most well characterized transcription factors mediating the function of YAP/TAZ through expression of genes promoting cell survival, proliferation, and metabolism (14, 18). YAP and TAZ exhibit 60% homology in their amino acid sequences and many of their functions are redundant. Although they also have non-redundant function, thus far, differential effects of YAP and TAZ upon metabolism have not been demonstrated.

The Hippo signaling pathway plays an important role in regulating cardiac development (11). Mouse hearts with Nkx2.5-Cre-mediated embryonic deletion of Hippo signaling components, including Sav, Mst1 or Lats2, exhibit Yap activation, thickened ventricular walls, enlarged ventricular chambers and elevated cardiomyocyte proliferation with no effect on cell size (19). Consistent with this result, Yap gain-of-function is sufficient to promote hyperplasia with cardiomyocyte proliferation but does not induce cardiac hypertrophy in the infant mouse heart (20). In contrast, mouse hearts with Tnnt-Cre-mediated embryonic deletion of Yap exhibit hypoplasia with reduced cardiomyocyte proliferation and eventual embryonic lethality (20). Interestingly, YAP and TAZ have both distinct and overlapping functions in cardiac homeostasis before and after birth (21). Postnatal cardiac-specific knockout of Sav with Myh6-Cre does not affect mouse heart size or cardiomyocyte proliferation at baseline (12). Postnatal cardiac-specific knockout of Yap, but not Taz, with Myh6-Cre in mice induces cardiomyocyte apoptosis, fibrosis and hypertrophy, resulting in cardiomyopathy with premature death (22, 23). In addition, double cardiac-specific knockout of Yap and Taz with Myh6-Cre causes extremely severe and lethal cardiac structural abnormality at birth (23), suggesting that Yap and Taz have non-overlapping functions.

In the adult heart, the Hippo signaling pathway is activated during stress, such as myocardial infarction, ischemia/reperfusion injury, and oxidative stress, leading to suppression of YAP/TAZ (22, 24, 25). YAP promotes an anti-apoptotic effect, compensated hypertrophy, cardiomyocyte proliferation, and myocardial regeneration after cardiac injury or during HF (22, 26). In the mouse heart, YAP is activated transiently, peaking around 7 days, after transverse aortic constriction (TAC), thereby contributing to cardiomyocyte proliferation and hypertrophy, most likely compensatory mechanisms, during the acute phase of pressure overload (12, 26). The activity of the upstream kinases, including Mst1 and Lats2, is increased during the chronic phase of pathological hypertrophy, and, thus, YAP/TAZ is inactivated during cardiac remodeling after myocardial infarction and the chronic phase of

HF (12). Reactivation of YAP/TAZ after myocardial infarction may allow cardiac regeneration and improve cardiac function in HF patients (27). It should be noted, however, prolonged activation of YAP in the long-term pressure-overloaded heart induces cardiomyocyte dedifferentiation and HF (12). Thus, although the Hippo pathway and its terminal effectors YAP and TAZ play an essential role in the pathogenesis of HF, their functions appear to be stress- and time-dependent. Currently, the role of the Hippo pathway in metabolic remodeling during HF is poorly understood.

3. The role of YAP/TAZ in regulating metabolism pathways in the heart under physiological and pathophysiological conditions

3.1 Carbohydrate metabolism

The glycolytic pathway starts with glucose, which is sequentially converted to two molecules of pyruvate and two molecules of nicotinamide adenine dinucleotide (NADH) and produces two molecules of ATP from each molecule of glucose. In the healthy adult heart, a relatively small amount (10–40%) of acetyl-CoA derives from pyruvate (4). The contribution of glycolysis to overall ATP production increases when mitochondrial dysfunction develops during myocardial ischemia (10, 28). In moderately ischemic hearts, anaerobic glycolysis is beneficial because glycolytically generated ATP contributes to the maintenance of intracellular Ca^{2+} homeostasis in cardiac excitation-contraction coupling (29). It should be noted, however, that glycolysis is also activated in the presence of normal levels of oxygen, termed *aerobic glycolysis* or the Warburg effect (30). Glycolytic conversion of glucose to lactate is often observed in cancer cells in the presence of oxygen. Glycolysis produces less ATP per unit of glucose than oxidative phosphorylation. However, glycolysis not only produces ATP in a low oxygen environment but also supports cell growth through production of macromolecules, such as nucleotides through the pentose phosphate pathway, properties that would benefit tumor growth and cardiac hypertrophy (31) in any oxygen environment. Recent evidence suggests that glucose promotes cardiac hypertrophy through activation of mTOR by the KLF15-branched chain amino acid catabolism pathway (32).

Since YAP/TAZ are involved in cell proliferation and tissue regeneration and that glucose metabolism is intimately involved in cell growth responses, one can speculate that YAP may be involved in both anaerobic and aerobic glycolysis. Previous studies have shown that several oncogenes, including c-Myc, hypoxia-inducible factor 1α (HIF-1α) and tumor suppressors, including p53, are involved in the transcriptional regulation of glycolysis (33). Increasing lines of evidence suggest that YAP/TAZ positively regulate glycolysis and glucose metabolism during organ growth as well as in cancer cells. For example, YAP stimulates nucleotide biosynthesis through activation of glucose uptake in zebrafish (34). Hypoxia-induced YAP activation stimulates glycolysis in hepatocellular carcinoma cells through stabilization of HIF-1α (35). YAP upregulates expression of hexokinase 2 and 6-phosphofructo-2-kinase-2,6-bisphosphatase 3 through lncRNA breast cancer anti-estrogen resistance 4 (BCAR4) and Hedgehog signaling (36). YAP-induced stimulation of glycolysis and nucleotide biosynthesis plays an essential role in mediating cell growth responses (34, 36). YAP may promote survival of tumor cells in the cancer microenvironment through

activation of the aerobic glycolytic pathway and consequent activation of anti-apoptotic signaling pathways (37).

YAP and TAZ are positively regulated by phosphofructokinase 1 (38), whereas YAP is negatively regulated by AMP-activated protein kinase (AMPK) (39). Thus, both aerobic glycolysis and the availability of an energy source (glucose) positively regulate YAP/TAZ, thereby promoting a positive feedback mechanism.

We have shown previously that upregulation of YAP/TAZ occurs one week after TAC, which contributes to the development of compensatory hypertrophy and survival of cardiomyocytes (12, 26). HIF-1α is critically involved in the preservation of cardiac function after TAC without affecting cardiac hypertrophy (40). c-Myc activation in response to TAC and ischemia/reperfusion increases glucose uptake/utilization in adult cardiomyocytes, thereby contributing to preserved cardiac function (41). These findings suggest that YAP/TAZ may also promote glycolysis in cardiomyocytes in response to hypertrophic stimuli.

Which target of YAP is involved in stimulating glycolytic activity? YAP promotes glycolysis in hepatocellular carcinoma cells by upregulating pyruvate kinase muscle isozyme 2 through stabilization of HIF-1α (35). YAP upregulates expression of glut1 in the zebrafish liver (34). Glucose transport into cardiomyocytes is mediated primarily through insulin-mediated glucose transporter GLUT4 and, to a lesser degree, through GLUT1 in the healthy adult heart (3). The demand for more ATP (triggered by cell growth) accelerates glucose uptake and utilization in hypertrophied cardiomyocytes (42). Upregulation of Glut1 has been observed in hypertrophied hearts (43). GLUT1 overexpression increases basal glucose transport in the heart (44) and protects the heart against pressure overload-induced cardiac hypertrophy and dysfunction. It would be interesting to investigate whether YAP regulates glucose uptake during the development of cardiac hypertrophy.

Type II diabetes is characterized by insulin resistance and hyperglycemia, and the prevalence of hypertension is higher in diabetic patients than in non-diabetic patients (45). We have shown recently that YAP, which is activated in the mouse heart in response to high fat diet consumption and in heart failure patients with diabetes, contributes to the development of heart failure in the presence of pressure overload, such as high blood pressure (46). In pancreatic β-cells, YAP plays a key role in cell proliferation, stress adaptation and resistance to apoptosis in the presence of diabetes (47). Type II diabetes has been proposed as a major risk factor in the progression of liver cancer (38). The hexosamine biosynthesis pathway (HBP) is an important glucose metabolic pathway to generate uridine diphospho-N-acetylglucosamine (UDP-GlcNAc), which is used by O-linked β-N-acetylglucosamine (O-GlcNAc) transferase (OGT) to catalyze O-GlcNAcylation (48). Under high glucose conditions, including diabetes, O-GlcNAcylation of YAP, but not TAZ, mediates high-glucose-induced liver tumorigenesis through interaction with TEAD and CREB (49). It is possible that O-GlcNAcylation of YAP may modulate YAP-dependent responses in the heart.

3.2 FA Metabolism

The rate of FA uptake in the heart is determined by the concentration of non-esterified FAs in the plasma (50). FAs enter cardiomyocytes through either passive diffusion or protein-mediated transport across the sarcolemma assisted by FA translocase (FAT) and a plasma membrane FA binding protein (FABP). Non-esterified FAs bound to FABP are activated by esterification to fatty acyl-CoA by fatty acyl-CoA synthetase (FACS). Long-chain fatty acyl-CoA can be esterified to triglyceride, an important source of FAs in cardiomyocytes. Alternatively, long-chain fatty acyl-CoA is converted to long-chain fatty acylcarnitine by carnitine palmitoyltransferase I (CPT-I). The resultant long-chain fatty acylcarnitine is eventually transported into mitochondria, and undergoes β-oxidation, thereby producing acetyl-CoA that enters the TCA cycle.

Whether YAP affects FA metabolism remains unclear. YAP is activated in lymph node-metastatic tumors, leading to the upregulation of genes involved in FA oxidation (51). Although this appears different from the Warburg effect, this would suggest that acetyl-CoA and NADH derived from FA oxidation inhibit PDH and drive FA utilization over glucose when activation of YAP occurs. If this mechanism holds true in the heart, downregulation of YAP during HF may contribute to activation of PDH and concomitant downregulation of FA oxidation. Further investigation is required to test this hypothesis. We have proposed recently that inactivation of YAP during the chronic phase of pressure overload prevents de-differentiation of cardiomyocytes, and, thus, it may be adaptive (12, 52). Whether changes in the activity of YAP during the course of pressure overload contributes to the changes in FA metabolism remains to be elucidated.

In hepatocytes, YAP directly interacts with sterol regulatory element binding proteins (SREBP-1 and SREBP-2), thereby promoting lipogenesis and cholesterol synthesis by activating fatty acid synthase and 30-hydroxylmethyl glutaryl coenzyme A reductase (53). YAP is activated in the heart in response to high fat diet consumption in mice (46), a condition in which PPARα is activated (54). Thus far, direct interaction between YAP/TAZ and PPARα has not been demonstrated. Whether YAP contributes to changes in FA metabolism during the early phase of type II diabetes remains to be elucidated. Palmitic acid, the most common saturated FA, suppresses endothelial cell proliferation and migration through inhibition of YAP/TAZ (55).

3.3 Tricarboxylic acid (TCA) cycle

The TCA cycle acts as the biochemical hub and consists of eight sequential reactions in mitochondria (56). This cycle oxidizes acetyl-CoA derived from carbohydrates, lipids, and proteins and generates NADH, flavin adenine dinucleotide ($FADH_2$), and ATP. NADH and $FADH_2$ are in turn fed into the electron transport chain for ATP production. Another important task of the TCA cycle is providing precursors for the biosynthetic pathways.

In hypertrophied rat hearts, the rate of palmitate entry into oxidative metabolism was reduced 23% compared to in normal hearts despite similar TCA cycle flux rates (57). Glucose oxidation through pyruvate dehydrogenase does not increase, however, despite the fact that glycolysis is elevated. This reduced rate may be balanced by a compensatory

increase in the anaplerotic flux into the TCA cycle through increased carboxylation of glycolytic pyruvate by malic enzyme (58). Several studies have confirmed this hypertrophy-associated anaplerotic change in the hearts (59, 60). Inhibition of this anaplerotic change may improve cardiac function in the failing heart by normalizing myocardial triacylglyceride content (61).

The TCA cycle intermediate succinate accumulates after ischemia/reperfusion, contributes to the production of reactive oxygen species (ROS) at Complex I through reverse electron transport, and exacerbates ischemia/reperfusion injury (62). Attenuation of succinate accumulation decreases infarct size in vivo (63). Mitochondrial structure and function, including ROS production, are controlled by YAP signaling pathways (64). However, the role of YAP/TAZ in the regulation of the TCA cycle is poorly understood.

Glutamine is one of the most abundant non-essential amino acids in the plasma. Glutaminolysis, an anaplerotic pathway, converts glutamine into α-ketoglutarate and replenishes it for use in the TCA cycle and generation of ATP. Cancer cells and stem cells often rely on glutaminolysis in order to maintain an effective TCA cycle for proliferation (65). Activation of YAP elevates the level of glutamine by inducing expression and the transcriptional activity of glutamine synthetase, resulting in liver enlargement in zebrafish (66). In pulmonary hypertension, stiffening of the extracellular matrix mechanically activates YAP/TAZ, which in turn modulates metabolic enzymes, including glutaminase, in order to coordinate glutaminolysis and glycolysis in vascular cells. Activation of glutaminolysis plays an essential role in mediating proliferation and migration of pulmonary vascular cells (67). Pulmonary hypertension activates glutaminolysis in heart cells as well, which in turn contributes to the development of cardiac hypertrophy, capillary rarefaction, and decreased cardiac contractility. Stimulation of glutaminolysis is mediated though activation of cMyc-Max as a consequence of right ventricular ischemia (68); the involvement of YAP/TAZ remains to be elucidated.

Glutamine uptake in cancer cells relies on neutral amino acid transporter solute carrier family 1 member 5 (SLCA5) (69). Receptor tyrosine kinase EphA2-dependent activation of YAP/TAZ enhances glutamine metabolism by promoting the expression of SLC1A5 (70). Cooperation between mTORC1 and YAP/TAZ mediate amino acid metabolism through upregulation of SLC38A1 and SLC7A5 expression (71). Amino acids supply TCA cycle intermediates, thereby protecting the heart against stress (72). Thus, YAP/TAZ may also protect the heart through regulation of amino acid metabolism.

3.4 Mitochondrial function

Mitochondria are central intracellular organelles that mediate oxidation of carbohydrates and FAs and produce NADH and $FADH_2$. High-energy electrons from NADH and $FADH_2$ are transferred through the electron transport chain (ETC) located on the mitochondrial inner membrane. Energy from these electron transfer reactions makes a proton gradient across the inner mitochondrial membrane, which is then used for ATP synthesis. Mitochondria are dynamic organelles that continuously undergo fusion and fission (73). Mitochondrial fission is controlled by dynamin-related proteins (DRP1), while mitochondrial fusion is driven by mitofusins (Mfn1 and Mfn2) and OPA1 (74). These biological processes play critical roles

in maintaining mitochondrial function when cells experience metabolic or environmental stresses (75, 76). Furthermore, mitochondrial dysfunction is now recognized as one of the key mechanisms promoting HF (9). A mitochondria-specific form of autophagy (named mitophagy), by which damaged mitochondria are degraded, plays an essential role in maintaining healthy mitochondria and protecting the heart against pathological stress through multiple pathways (77–79). However, excessive mitophagy caused by YAP deficiency leads to downregulation of ETC complexes I-IV and provides insufficient ATP in hepatocellular carcinoma, suggesting that Hippo/YAP signaling potentially regulates the electron transfer reactions in mitochondria (80).

Cell growth responses are generally accompanied by appropriate mitochondrial biogenesis (81), suggesting that YAP/TAZ-induced cell proliferation and hypertrophy may also be accompanied by mitochondrial remodeling and biogenesis. Remarkably, overexpression of Yki/YAP induces larger mitochondria in human and Drosophila cells, through transcriptional upregulation of *opa1* and *Marf*, genes mediating mitochondrial fusion (64). YAP negatively regulates mitochondrial fission in myoblasts and neuroblastoma cells (82, 83) and promotes Mfn2-mediated mitophagy in gastric cancer cells (84). In addition, YAP-mediated suppression of mitochondrial fission inhibits apoptosis and migration of human rectal cancer cells (85). Whether YAP/TAZ directly regulate genes involved in mitochondrial dynamics, and if so, which transcription factor is involved remain to be elucidated. We have shown previously that Mst1 is activated in mitochondria through a K-Ras-Rassf1A-dependent mechanism. Mst1 phosphorylates Bcl-xL, thereby inducing mitochondria-mediated apoptotic cell death in cardiomyocytes during ischemia/reperfusion (86). It is possible that other molecules in mitochondria are also phosphorylated by Mst1 and, thus, the function of mitochondria may be directly regulated by non-canonical activation of the Hippo pathway in the heart.

4. Conclusions

Studies regarding cardiac metabolism in normal and failing hearts have uncovered important alterations in metabolic substrates during HF; however, molecular mechanisms mediating metabolic remodeling remain unclear. As we discussed in this review, YAP/TAZ are likely to regulate metabolism during cardiac stress. Unfortunately, however, the interplay between YAP/TAZ and metabolism has been studied primarily in cancer cells (Figure 2), where YAP/TAZ transcriptionally regulate glucose metabolism, thereby conferring the ability to effectively produce ATP in a stressed environment and generating macromolecules for cell growth. Whether YAP and TAZ regulate metabolism of other substrates, including FAs and ketone bodies, remains poorly understood. Further studies are required to elucidate the role of YAP/TAZ in mediating metabolic remodeling during cardiac stress and HF.

YAP and TAZ are transcription co-factors and, thus, their function is mediated through interaction with downstream transcription factors. We have shown recently that the function of YAP/TAZ is stimulus-specific since distinct transcription factors are induced in response to distinct stresses (87). Although TEAD1 is one of the most well characterized target transcription factors for YAP/TAZ, we have shown that other transcription factors, including FoxO1, can also mediate the effect of YAP/TAZ (24). In addition, YAP/TAZ may affect gene

expression through epigenetic mechanisms, including chromatic remodeling (88). Identifying the specific transcription factors mediating the effect of YAP/TAZ would allow a better understanding of the effect of YAP/TAZ upon metabolism in response to cardiac stress.

Recently, specific chemical inhibitors of the components of the Hippo pathway have been developed (89, 90). These compounds may be useful for controlling cardiac metabolism, either alone or in combination with other compounds, to modulate the function of metabolic pathways for the treatment of HF.

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Abbreviations

AMPK	AMP-activated protein kinase
ATP	adenosine triphosphate
BCAR4	breast cancer anti-estrogen resistance 4
CPT-I	carnitine palmitoyltransferase I
DRP1	dynamin-related protein
ETC	the electron transport chain
FA	fatty acid
FABP	FA binding protein
FACS	fatty acyl-CoA synthetase
$FADH_2$	flavin adenine dinucleotide
FAT	FA translocase
HBP	the hexosamine biosynthesis pathway
HF	heart failure
HIF-1α	hypoxia-inducible factor 1α
LATS1/2	large tumor suppressor 1 and 2
Mfn	mitofusin
MOB1A/B	Mps one binder kinase activator 1A and B

MST1/2	mammalian sterile 20-like kinase 1 and 2
NADH	nicotinamide adenine dinucleotide
O-GlcNAc	O-linked β-N-acetylglucosamine
OGT	O-GlcNAc transferase
ROS	reactive oxygen species
SAV	the scaffold protein Salvador
SLCA5	solute carrier family 1 member 5
SREBP	sterol regulatory element binding protein
TAC	transvers aortic constriction
TAZ	transcriptional coactivator with PDZ-binding motif
TCA cycle	the tricarboxylic acid cycle
UDP-GlcNAc	uridine diphospho-N-acetylglucosamine
WW45	WW domain-containing adaptor 45
YAP	Yes-associated protein 1

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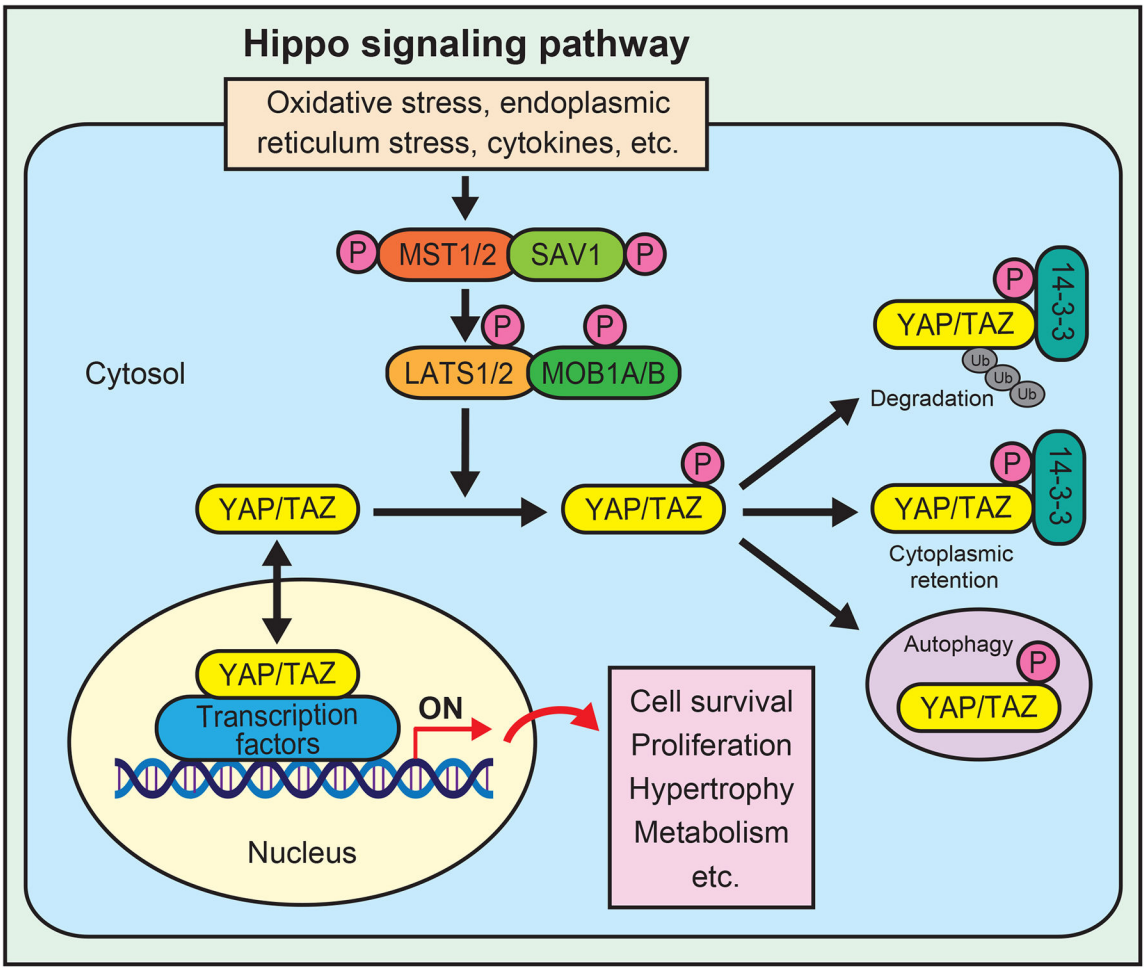

Figure 1.

Schematic representation of the Hippo signaling pathway. In response to activation of upstream signaling, MST1/2 interacts with SAV1 and phosphorylates LATS1/2 and MOB1A/B. LATS1/2 in turn phosphorylates and inhibits YAP/TAZ by causing cytoplasmic retention and degradation. Unphosphorylated YAP/TAZ translocates into the nucleus and act as transcription coactivators by interacting with various transcription factors, resulting in cell survival, proliferation, hypertrophy, and changes in metabolism.

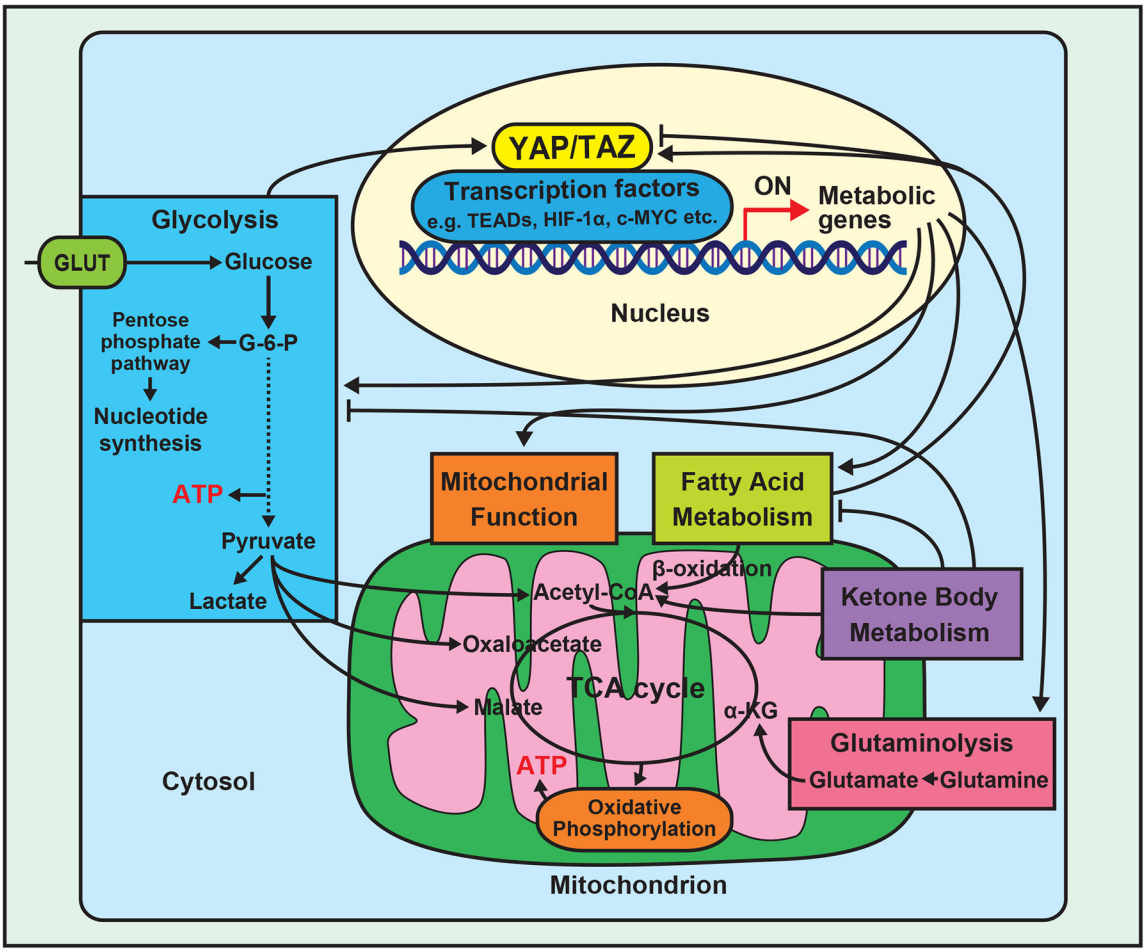

Figure 2.
Summary of the relationship between YAP/TAZ signaling and energy metabolism pathways.