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Review

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

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Key Words
Carbohydrate metabolism • Gluconeogenesis • Glucose transporter • Glycolysis • Yes-associated protein

Abstract
Yes-associated protein (YAP) is one of the Hippo pathway's two effectors, a pathway associated with organ size control. Research on YAP has focused on its oncogenic potential. However, in cancer cells, aside from inducing growth, YAP was also found to regulate glucose metabolism. The present review explores YAP's control of glucose metabolism and whether these findings are translatable to physiological conditions. According to current literature, YAP induces the transcriptional activity of most genes associated with glucose metabolism from enzymes to transport proteins. In glycolysis and gluconeogenesis, YAP upregulates all enzymes except for enolase and pyruvate kinase. Multiple research has also shown YAP's ability to regulate the expression of glucose transporter of the GLUT family. Additionally, glucose concentration, hypoxia, and hormones such as insulin and glucagon regulate YAP activity and depend on YAP to exert their biological activity. YAP is thus a central regulator of glucose metabolism, controlling both enzymes and proteins involved in glucose transport. YAP is also situated strategically in several pathways controlling glucose and was found to mediate their effects. If these results were consistent in physiological conditions and across glucose-associated metabolic disturbances, then YAP may become a prospective therapeutic target.

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Introduction

Yes-associated protein (YAP) is one of the Hippo pathway's two effectors, a pathway associated with organ growth and size. The other effector of this pathway is the Transcriptional coactivator with PDZ-binding motif (TAZ). Comprehensive reviews of this pathway are presented elsewhere [1, 2]. The first protein in this pathway, Warts, the human homolog of the large tumor suppressor protein (LATS), was first identified in *Drosophila* [3, 4] and subsequently found to be part of a vital growth-regulating pathway. The Hippo pathway consists of a cascade of two types of kinase, mammalian sterile-20-like kinases 1 and 2 (MST1/2) and LATS1/2 and their adaptor proteins, Salvador (SAV) and Mps-one binder (MOB), respectively. Phosphorylated MST1/2 activates LATS1/2 by phosphorylation. Active LATS1/2, in turn, inhibits the function of YAP and TAZ by phosphorylation, thereby sequestering them in the cytoplasmic compartment. Active and unphosphorylated YAP and TAZ can be transported to the nucleus, where they exert their transcriptional activity, mainly by binding to the TEA domain family of transcription factors (TEAD) [5].

Extensive research has been performed on YAP regarding its oncogenic potential. Mutations of LATS1/2, which result in YAP inhibition removal, were associated with a poorer prognosis in multiple cancer types [6-10]. Researchers have also found a correlation between YAP levels in certain types of cancer and patient mortality [11-13]. These findings revealed the Hippo pathway's growth-regulating ability and its importance in cancer pathology. However, YAP's role is not limited to its ability to induce growth and proliferation and its activities in other functions such as metabolism. Zhang, et al. [14] had showed that YAP/TAZ was associated with metabolic control in cancer cells, specifically its role in glycolysis, gluconeogenesis, and glutaminolysis.

Carbohydrates constitute an integral part of the metabolism in the human body. These macromolecules serve as one of the primary fuels that can be used in every human cell. Of all the carbohydrates, glucose is the most important in the human body [15]. It plays a central role in fuel metabolism and the synthesis of other carbohydrates such as nucleic acids. Given its central role, diseases or conditions involving glucose metabolism have far-reaching implications in the human body. Considerable research in cancer tissues has shown that YAP, aside from being an oncogene, also regulates glucose metabolism. Numerous studies have shown that the regulation of glucose mediates the oncogenic effects of YAP. These findings have shown that, at least pathologically, YAP affects glucose metabolism by regulating the transcription of the enzymes and proteins involved. However, since the results were obtained through studies on cancer cells, translating these findings into physiological conditions may be challenging. Against this background, there is potential for further research to elucidate YAP's roles in other conditions.

Depending on its intended role, there are several biochemical pathways for glucose metabolism. To generate energy, several pathways are available, such as glycolysis and the tricarboxylic acid cycle. Glucose is also used as a form of energy storage and can be converted into glycogen in the liver via a process known as glycogenesis. In short periods between food intake, the liver releases glucose from glycogen deposits in the liver. This process, called glycogenolysis, is essential for the maintenance of blood glucose levels. However, during a prolonged period without any nutrient intake, such as fasting or sleeping, the liver's glycogen is rapidly depleted. Since glucose is essential for various cell types, the liver synthesizes it from muscle proteins or triglycerides stored in the adipose tissue via a process known as gluconeogenesis.

In this review, we present that YAP pervasively regulates glucose metabolism on many different levels. YAP has been shown to control the expression of proteins involved in glucose transport, such as GLUT1 and GLUT3 [16, 17]. Additionally, several critical processes in glucose metabolism, such as glycolysis, and gluconeogenesis, have also been shown to be regulated by YAP [18-20]. YAP has also been shown to be regulated by energy status, such as conditions of high and low glucose. Additionally, YAP may mediate the effects of hormones

Table 1. The inclusion and exclusion criteria used during the systematic review

Inclusion Criteria	Exclusion Criteria
Population: Any species, both in vitro and in vivo	Review articles
Intervention: Any intervention	The study does not causally link YAP to aspects of glucose metabolism
Comparison: Any comparison	The study does not explore aspects of glucose metabolism
Outcome: • Any gene expression influenced by YAP • Any metabolism-related condition influencing YAP activity	

controlling glucose metabolism. This new perspective places YAP as a central regulator of glucose metabolism. However, further research is needed to fully explore YAP control aspects, such as YAP's insulin regulation.

Materials and Methods

Literature search

We conducted a search in the MEDLINE database through PubMed in April 2020 using the following search terms: "((carbohydrate metabolism [MeSH Terms]) OR (glucose metabolism [Title/Abstract])) AND ((YAP[Title/Abstract]) OR (Yes-associated protein [Title/Abstract]))." We searched relevant literature from the earliest possible date to April 2020. This search was repeated in September 2020 to identify relevant new publications.

Inclusion and exclusion criteria

Two investigators independently screened all titles and abstracts. The full text of the articles that were considered relevant was obtained if possible. The relevance of each study was assessed using the inclusion and exclusion criteria outlined in Table 1. Studies that did not meet the inclusion criteria were excluded, and the reasons for their exclusion are outlined in Supplementary Table 1 (for all supplementary material see www.cellphysiolbiochem.com). A third investigator resolved discrepancies in the investigators' findings.

Results

Articles identified in the systematic review

Through the MEDLINE database and a manual search, we identified 48 articles. The first screening process was performed using the title and abstract. After this screening, 37 articles were identified and subjected to a further review (Fig. 1). Six articles were excluded during the full-text review because most of them are on studies that examined the effects of an intervention on YAP but did not directly link YAP with glucose metabolism. One article was excluded since it did not explore aspects relevant to glucose metabolism. Thus, 30 articles were used in this systematic review. These articles were further classified to answer the research questions of what aspects of glucose metabolism are regulated by YAP and whether YAP is also regulated by glucose metabolism. A summary of the included studies and their findings is shown in Supplementary Table 2.

YAP regulates enzymes and proteins involved in glucose metabolism

Most of the articles found in our review explored YAP's ability as an upstream regulator of glucose metabolism. The affected aspects of glucose metabolism include glucose transport, glycolysis, and gluconeogenesis. YAP has been shown to regulate various genes associated with glycolysis consistently. Fig. 2 shows the enzymes in glycolysis and gluconeogenesis that were found to be controlled by YAP. Several studies have shown that, with the exceptions of enolase and pyruvate kinase, YAP upregulated almost all enzymes involved in glycolysis [18, 19, 21, 22]. Even the critical rate-limiting enzymes of glycolysis, such as hexokinase (HK) and phosphofructokinase (PFK) [18, 23-26], were shown to be under the control of YAP.

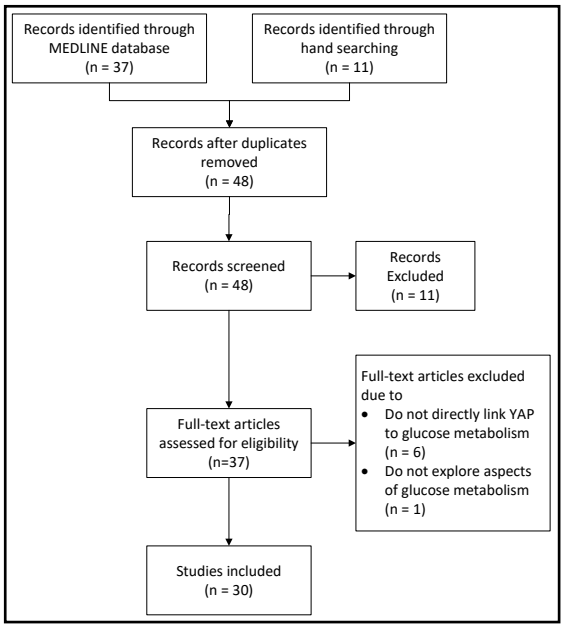

Fig. 1. PRISMA Diagram. PRISMA diagram outlining the systematic review pathway. Out of the 48 articles screened, 30 articles were used in the systematic review.

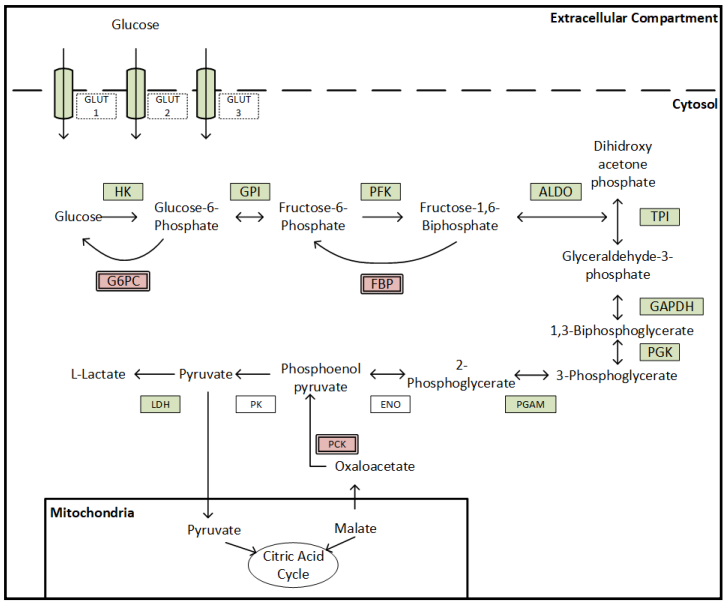

Fig. 2. Enzymes associated with glucose metabolism that is regulated by YAP. Shown above are the enzymes associated with the glucose metabolism pathway, specifically glycolysis and gluconeogenesis. Several glucose transporters that are regulated by YAP is also shown. YAP was found to upregulate almost all glycolysis enzymes and downregulate gluconeogenesis enzymes. The dashed line denotes the cell membrane, which separates the cytosolic and the extracellular compartment. The mitochondrial compartment is separated from the cytosolic compartment by the thick black box. Glycolysis enzymes are shown by the single black-bordered boxes. Gluconeogenesis enzymes are shown by the double black-bordered boxes. Glucose transporter protein is shown by the rounded rectangle at the edge of the cell membrane. Green color denotes the enzymes which are upregulated by YAP. Red color denotes the enzymes which are downregulated by YAP. ALDO: Aldolase, ENO: Enolase, FBP: Fructose-Bisphosphatase, GAPDH: Glyceraldehyde-3-phosphate dehydrogenase, GPI: Glucose phosphate isomerase, G6PC: Glucose-6-phosphatase, HK: Hexokinase, LDH: Lactate Dehydrogenase, PCK: Phosphoenolpyruvate Carboxykinase, PFK: Phosphofructokinase, PGAM: Phosphoglyceromutase, PGK: Phosphoglycerate kinase, PK: Pyruvate Kinase, TPI: Triosephosphate isomerase.

Interestingly, the enzymes hexokinase and phosphofructokinase were shown to regulate YAP activity directly [26, 27]. This finding directly coupled YAP with glycolysis. Confirming these findings, multiple studies have shown that glycolysis inhibition using 2-deoxyglucose (2DG) downregulated YAP target gene expression [19, 27]. *In vitro* study using mouse cardiomyocytes also confirmed the results, in which the administration of 2DG increased LATS1 phosphorylation and therefore inhibited YAP function [28]. Therefore, YAP regulated the enzymes associated with glycolysis and is also regulated by glycolysis.

Upregulation of the enzymes alone may not always lead to an increased glycolysis rate. However, the upregulation of enzymes by YAP is also accompanied by an increase in glycolysis rate, as shown by multiple studies measuring the extracellular acidification rate of the medium [16, 29]. Taken together, these findings are fascinating to translate into physiological conditions. If YAP can modulate glucose metabolism, drugs that exploit YAP's properties might be able to correct metabolic disturbances. Additionally, physiological conditions that modulate YAP might also alter glucose metabolism in tissues.

Unlike glycolytic enzymes, which have been consistently shown to be regulated by YAP, mixed results have been obtained for gluconeogenic enzymes. Hu, et al. [30] and Pocaterra, et al. [31] found that the overexpression of YAP *in vivo* using transgenic mice abolished the expression of *G6pc* and *Pck1,* even upon stimulation with glucagon and dexamethasone. The effects of YAP overexpression even improved glucose tolerance [30, 31] and decreased random blood glucose levels [30]. This finding is consistent because YAP also increases the expression levels of genes related to glycolysis and glucose transport proteins, which may increase glucose utilization in tissue. However, Sayedyahossein, et al. [32] found different YAP effects on gluconeogenesis-related genes, specifically *G6PC* and *PCK1*. They found that YAP knockdown through siRNA *in vitro* in skeletal muscle and liver tissues decreased *G6PC* and *PCK1* gene expression. These findings contrast with those of Hu, et al. [30] and Pocaterra, et al. [31]. However, since these studies were conducted in different subjects, the conflicting findings may result from different regulation of gluconeogenic genes by YAP in human tissues compared with those in mice. Further studies are needed to explain this discrepancy.

YAP has also been shown to influence glucose metabolism by upregulation of the GLUT family of glucose transporters. Glucose transporters are essential to glucose metabolism since they allow glucose transport across the cell membrane in a manner that relies not on passive diffusion alone. The importance of GLUT in metabolism is also reflected in many diseases caused by mutation or disruption of these proteins [33]. YAP has been shown to regulate GLUT1, GLUT2, and GLUT3 [16, 17, 19, 34]. However, there is a considerable variation in the findings reported in the literature, with several groups finding different GLUT isoforms to be regulated by YAP. However, such variation may be due to the differential expression of GLUT isoforms in different tissues [33]. Supporting our conclusion is that GLUT1, the most ubiquitously expressed of all GLUT isoforms, was found to be the glucose transporter most consistently upregulated by YAP/TAZ overexpression [21, 34-36].

YAP activity is influenced by energy status

YAP is highly influenced by energy status. High-glucose conditions were shown to activate YAP transcriptional activity. High-glucose induced the formation of advanced glycation end products and post-translationally modified many proteins, in this case, O-GlcNAcylation of YAP (Fig. 3A). *In vitro* studies have shown that high-glucose conditions induced the enzyme O-GlcNAc transferase [20, 37]. This enzyme post-translationally modifies YAP by adding N-acetylglucosamine on T241 [20]. YAP was then prevented from interacting with βTrCP and subsequently saved from degradation. Additionally, modification of YAP by OGT at S109 was also shown to inhibit its phosphorylation by LATS1/2, thereby releasing the control of the Hippo pathway over YAP [37].

Advanced glycation end products (AGE) formation due to high glucose was also shown to induce YAP activity. Studies have shown that methylglyoxal, a precursor of AGE, induced YAP nuclearization and transcriptional activity through the inhibition of LATS1 [38, 39]. Additionally, AGE also induced YAP activation through EGFR phosphorylation, although the

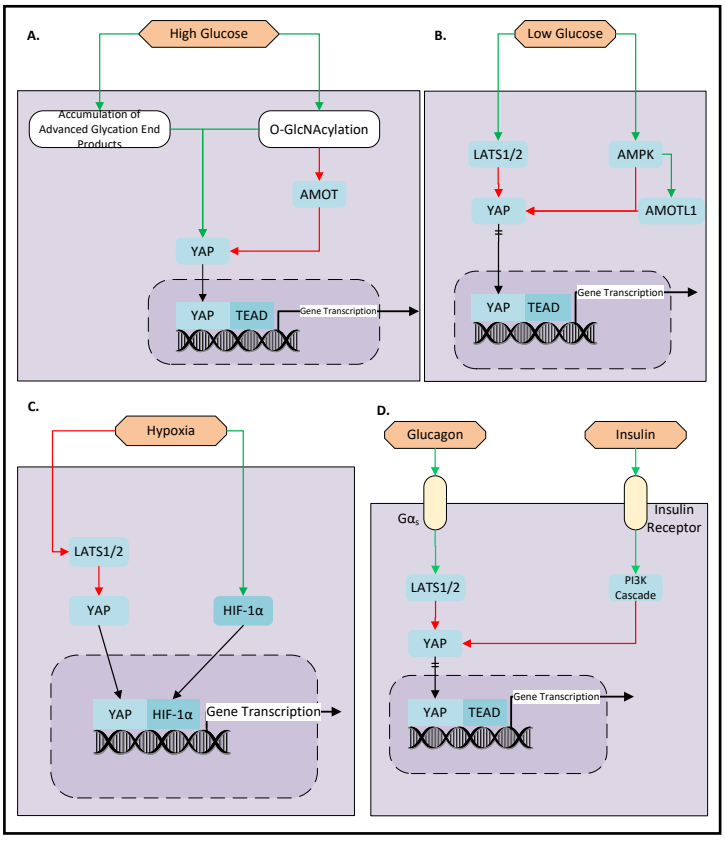

Fig. 3. The regulation of YAP concerning metabolic cues. A: High glucose condition induced the accumulation of advanced glycation end products (AGE) and O-GlcNAcylation through the enzyme O-GlcNAc transferase (enzyme not showed). Both AGE and O-GlcNAcylation increased the amount of unphosphorylated YAP. A detailed explanation of the mechanism is provided in the accompanying text. Additionally, the O-GlcNAcylation of AMOT also decreased AMOT's ability to bind YAP and sequester in the cytoplasm, thereby increasing the amount of nuclear YAP. B: Low glucose condition induced the activation of LATS1/2 and AMPK. Both kinases phosphorylated YAP and inhibited YAP's translocation to the nuclear compartment. Therefore, high glucose conditions increased the activity of YAP, and low glucose conditions inhibited it. C: The effects of hypoxia were shown to be partially mediated by YAP in addition to HIF-1α. Hypoxia inhibited the LATS1/2 function, which releases the control of the Hippo pathway on YAP. Therefore, allowing YAP to translocate to the nucleus to exert its transcriptional activity. Additionally, YAP was shown to bind HIF-1α and induce its stabilization and increase its half-life. YAP and HIF-1α formed a complex inside the nuclear compartment where it exerted its gene transcriptional activity. D: The effects of glucagon and insulin on YAP is shown. Glucagon induced LATS1/2 activation through binding with the G protein-coupled receptor (GPCRs) Gαs. Activation of LATS, in turn, increased YAP phosphorylation and inhibited its nuclear translocation. Insulin bind with the insulin receptor and, through the activation of the phosphatidylinositol-3-kinase (PI3K) pathway, phosphorylated YAP. Green arrows denote positive effects. Red arrows denote negative or inhibiting effects. Black arrows denote the translocation of protein between compartments. Black arrows with two dash denote inhibition of translocation. Light purple boxes with a solid black line represent the cellular compartment. Dark purple boxes with dashed lines represent the nuclear compartment. AMOT: angiomotin, AMPK: AMP-activated protein kinase, HIF-1α: Hypoxia Inducible Factor 1 Alpha, LATS1/2: Large tumor suppressor kinase 1/2, TEAD: TEA Domain Transcription Factor, YAP: Yes-associated protein.

study did not explore how EGFR phosphorylation affected YAP [38]. Therefore, high glucose through the formation of AGE and O-GlcNAcylation increased YAP activity, which might explain that diabetes is associated with an increased risk of liver cancer [40, 41]. However, one study did find a different effect of high glucose on YAP. Specifically, high glucose was shown to affect podocytes by downregulating its YAP expression resulting in apoptosis [42]. Therefore, different tissues may respond differently to increased glucose concentration. Further research is needed to clarify the role of YAP in different tissues and cells.

Energy stress also stimulates YAP activity, which involves several mechanisms. The post-translational modification of YAP during high-glucose conditions was dramatically reduced during glucose starvation *in vitro* [37]. This may mediate the deactivation of YAP by phosphorylation or degradation. However, there are other pathways linking energy stress and YAP (Fig. 3B). Energy stress is known to activate AMPK through its phosphorylation.

AMPK, in turn, was shown to deactivate YAP through direct YAP phosphorylation or the activation of LATS [16, 43]. However, it has been shown that AMPK and LATS phosphorylate YAP at different sites. Although the different phosphorylation sites at S127 (LATS) and S61 or S94 (AMPK) both downregulated classic YAP target genes [16, 43]. Additionally, AMPK was also shown to phosphorylate Angiomotin Like Protein 1 (AMOTL1), increasing its stability in the cytoplasm. AMOTL1 then binds YAP and sequesters it in the cytoplasm, thereby inhibiting its function [44].

YAP mediates the effect of hypoxia on glucose metabolism

Besides TEAD, YAP has also been shown to bind HIF-1α and promote its gene transcription effects (Fig. 3C). Its effects on HIF-1α link YAP with hypoxia, which is a well-known regulator of glucose metabolism. Hypoxia is known to induce genes related to glycolysis either physiologically, such as during strenuous exercise, or under pathological conditions such as cancer [45, 46]. Several studies have found that YAP mediated hypoxia's effects by binding and stabilizing HIF-1α [21, 47]. It would be interesting to determine whether these findings are translatable to other cells and tissues such as skeletal muscle and cardiac muscle cells, where hypoxia may be found under physiological conditions.

In vitro studies on liver cancer cells have shown that YAP binds to HIF-1α and maintains its stability [47]. Additionally, hypoxia also induced YAP translocation into the nucleus. This presumably occurs by reducing phosphorylated LATS, a key inhibitor of YAP in the Hippo pathway. The increase of nuclear YAP and subsequent binding to HIF-1α were shown to accelerate gene expression related to glycolysis. YAP and HIF-1α were shown to form a complex inside the cell nucleus, which promoted *PKM2*, *ALDOA*, *GLUT1*, *LDHA*, and *HK2* expression [21]. YAP is essential to this response to hypoxia, in that knockdown of YAP alone was able to suppress glycolytic gene expression [21, 47].

YAP expression is regulated by insulin and glucagon

YAP and TAZ were shown to regulate many aspects of glucose metabolism. It is reasonable to hypothesize that these Hippo pathway effectors will also be regulated by glucose-regulating hormones such as glucagon and insulin (Fig. 3D). Glucagon and epinephrine have been shown to regulate the Hippo pathway through binding with G protein-coupled receptors. Several G protein-coupled receptors have been found to regulate Hippo pathway signaling, such as $G\alpha_{12/13}$, $G\alpha_{q/11}$, $G\alpha_{i/o}$, and $G\alpha_{s}$ [48]. The signaling activity of most GPCRs was found to inhibit LATS1/2, increasing YAP/TAZ transcriptional activity. However, the coupling of glucagon and epinephrine with $G\alpha_{s}$ was shown to activate LATS1/2 by phosphorylation [48, 49]. The active LATS1/2 leads to YAP's phosphorylation and inhibition, leading to their cytoplasmic sequestration and degradation. Interestingly, the effects of glucagon in liver tissue are similar to those of YAP inhibition in liver tissue. *In vivo*, YAP overexpression in liver tissue was found to induce genes related to glycolysis and inhibit gluconeogenic gene expression [30, 31]. Therefore, glucagon's effects on glucose metabolism in the liver might be mediated, at least in part, by YAP inhibition. However, there is a need for intensive study to prove this conjecture and, if it is true, to determine how much glucagon depends on YAP.

Less research has been performed on insulin's effect on YAP/TAZ or the Hippo pathway than the findings for glucagon. However, Sayedyahossein, et al. [32] found that insulin, through an unknown mechanism, phosphorylated YAP and suppressed YAP transcriptional activity. This contrasts with previous findings linking glucagon to YAP inhibition [30]. In the context of glucose metabolism, insulin and glucagon have opposite effects on liver tissue. However, since both hormones were found to induce YAP inhibition, perhaps only one hormone's effects were mediated by YAP. Interestingly, Sayedyahossein, et al. [32] also found that inhibition of YAP decreases gluconeogenic gene expression, a finding that is in stark contrast to the findings of Hu, et al. [30] and Pocaterra, et al. [31]. However, this discrepancy might be due to different subjects being focused on in the research by Sayedyahossein, et al. [32] and Hu, et al. [30], namely, human tissue *in vitro* and mouse models *in vivo*, respectively. Further research is needed to establish YAP's role in the hormonal regulation of glucose metabolism, especially in the liver and muscle tissue.

Discussion

Our systematic review found that most studies about YAP reported to date explored its downstream effects. YAP was shown to regulate numerous enzymes associated with glycolysis. This regulation is very significant in cancer cells as the blockade of either YAP or the associated downstream glucose metabolism-related genes inhibits tumor growth. These findings are potentially exploitable for developing cancer treatments. If YAP can modulate glucose metabolism, drugs that exploit YAP's properties might be able to correct metabolic disturbances. Additionally, physiological conditions that modulate YAP might also alter glucose metabolism in tissues.

In a physiological state, YAP was shown to be regulated by physical exercise [50], which also increases glucose tolerance. It would be interesting to determine whether YAP mediates the beneficial effects of exercise in inducing glucose tolerance. Studies in liver cells have shown that the overexpression of YAP in liver tissues increases glucose tolerance and lowers the mice's baseline glucose level [30]. However, it is unknown whether physiological conditions such as exercise can increase YAP expression in the liver. Additionally, since exercise may increase YAP levels in the skeletal muscle tissue [50], it may increase glucose receptors and glucose tolerance after exercise. Further research on this issue is needed to prove our hypothesis.

The findings that YAP is regulated by energy status are interesting to translate to physiological conditions. However, it is unknown whether YAP is also similarly regulated under high and low glucose during conditions such as after consuming a meal or fasting. However, the increase in YAP and cell growth during high-glucose conditions is plausible during these conditions. During low-energy conditions, YAP would be inhibited, leading to a reduction of cell proliferation. These relationships between YAP and glucose condition were also seen in TAZ protein expression, YAP's homolog, although the results are different. In contrast to YAP, which is upregulated by high glucose, Wu, et al. [51] found that in bone tissue, high-fat and high-glucose environment suppresses TAZ and Runx2 protein gene expression. They postulated that these suppressions inhibited bone regeneration in mice [51]. Our current finding is interesting to explore as YAP's association with energy status might mediate cell growth. However, the Hippo pathway effectors were shown to have distinct functions in different tissues. Thus, further research is necessary to verify whether these findings can be generalized to different types of tissues and whether YAP and TAZ work synergistically or antagonizes each other's actions.

It is also worth considering whether the increase of YAP in high-glucose conditions is a purely pathological response or a dysregulated compensatory response. YAP overexpression in the liver was found to upregulate glucose transporter protein [37], which reduced blood glucose concentration and increased glucose tolerance [30, 31]. Although these effects are in turn associated with an increased risk of liver cancer [40, 41], perhaps the increase in YAP was supposed to be a regulatory mechanism to counteract high blood glucose. Further research should be done to prove whether this is the case.

Another notable finding is how AMPK signaling connects energy stress with YAP. AMPK signaling was shown to downregulate YAP activity during energy stress. Interestingly, AMPK is also regulated by metformin, a drug of choice for diabetes. The activation of AMPK by metformin mediates its beneficial effect on cancer cells [52, 53]. YAP was shown to be its main target [54, 55], consistent with the findings showing that AMPK regulates YAP activity [16, 43]. However, the effects of metformin on AMPK might also adversely affect tissue growth. A recent clinical trial showed that metformin is associated with lower muscle mass growth in elderly patients undergoing progressive resistance exercise training [56]. Although several conflicting findings have been obtained on the relationship between metformin and skeletal muscle mass [57, 58], further research is necessary to elucidate whether metformin use significantly affects tissue growth. This drug is ubiquitously used at all ages to treat insulin resistance. If coupled with aging, the drug potential effect of decreasing tissue growth may affect the quality of life.

We also found that YAP mediated, at least in part, the adjustment of glucose metabolism by HIF-1α. This finding is interesting as, besides inducing metabolic changes, YAP also promotes growth. Supporting this finding is that hypoxia is associated with increased growth and immune evasion in cancer cells [59, 60]. It would be interesting to further research whether the induction of hypoxic growth is mediated through YAP. The finding is also interesting if seen from the perspective of muscles such as cardiac and skeletal muscles, which may undergo hypoxia during intense exercise. Research by Nakada, et al. [61] found that hypoxia mediates the regeneration of adult cardiac muscle in mice. Therefore, further research may find new pathways in which muscles may undergo hypertrophy both from the associated mechanical work and through signaling associated with hypoxia.

There is a less clear understanding of insulin's effects on YAP metabolism compared with those of glucagon in the literature. However, it is reasonable to assume that the two hormones controlling glucose metabolism may also exert their effects through YAP. Primarily because TAZ, YAP's homolog, was found to influence insulin sensitivity. In adipose tissue, TAZ deletion increased insulin sensitivity by releasing its inhibitory properties on PPARγ [62]. Nevertheless, in muscle tissue, TAZ deletion was shown to decrease insulin sensitivity by downregulating *Irs1* expression [63]. Thus, YAP and TAZ may mediate distinct functions depending on the tissues expressing them. Further research is needed to ascertain YAP's roles concerning glucagon and insulin signaling, whether YAP's expression pattern is tissue-specific, and its interaction with TAZ. However, more literature is available for glucagon regarding its roles exerted primarily through GPCRs [49]. On the other hand, insulin has been less studied, and the present study showed its contrasting effect on YAP signaling. Therefore, exploring the role of insulin as a regulator of YAP may prove worthwhile.

Conclusion

Our review has revealed the myriad roles by which YAP regulates glucose metabolism. YAP controls several enzymes associated with glycolysis and gluconeogenesis. YAP also plays a central role in mediating hypoxia, energy status, and insulin and glucagon in adjusting glucose metabolism. We offer several hypotheses on how YAP may operate in physiological conditions. The translation of YAP's effects into physiological conditions may help expand our understanding of YAP's role as another oncogene and as a critical gene modulating metabolism and growth. Additionally, we have also shown that YAP may operate distinctly compared to TAZ and may produce different expression patterns in different tissues. If we can elucidate YAP expression patterns in different tissues, and these findings are consistent across different types of metabolic disturbance, YAP may become a prospective therapeutic target in conditions involving metabolic derangements associated with glucose.

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Author Contributions

A. Sanjaya, I. Setiawan, H. Goenawan, and R. Lesmana conceived the initial idea, the novelty and designed the search strategy for the review; A. Sanjaya retrieved the search results and tabulated the references; The results were reviewed and criticized by J. Gunadi

and Y. Limyati; A. Sanjaya resolved discrepancies between the reviewer's opinions. A. Sanjaya, R. Lesmana, and I. Setiawan drafted the initial paper; All authors contributed to the final version of the paper.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors declare no conflicts of interest exist.

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