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Review

YAP/TAZ as mechanobiological signaling pathway in cardiovascular physiological regulation and pathogenesis

Rakibul Islam, Zhongkui Hong *

Department of Mechanical Engineering, Texas Tech University, Lubbock, TX 79409, USA

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ABSTRACT

Cardiovascular diseases (CVDs) persistently rank as a leading cause of premature death and illness worldwide. The Hippo signaling pathway, known for its highly conserved nature and integral role in regulating organ size, tissue homeostasis, and stem cell function, has been identified as a critical factor in the pathogenesis of CVDs. Recent findings underscore the significance of the Yes-associated protein (YAP) and the Transcriptional Coactivator with PDZ-binding motif (TAZ), collectively referred to as YAP/TAZ. These proteins play pivotal roles as downstream components of the Hippo pathway, in the regulation of cardiovascular development and homeostasis. YAP/TAZ can regulate various cellular processes such as cell proliferation, migration, differentiation, and apoptosis through their interactions with transcription factors, particularly those within the transcriptional enhancer associate domain (TEAD) family. The aim of this review is to provide a comprehensive overview of the current understanding of YAP/TAZ signaling in cardiovascular physiology and pathogenesis. We analyze the regulatory mechanisms of YAP/TAZ activation, explore their downstream effectors, and examine their association across numerous cardiovascular disorders, including myocardial hypertrophy, myocardial infarction, pulmonary hypertension, myocardial ischemia-reperfusion injury, atherosclerosis, angiogenesis, restenosis, and cardiac fibrosis. Furthermore, we investigate the potential therapeutic implications of targeting the YAP/TAZ pathway for the treatment of CVDs. Through this comprehensive review, our aim is to elucidate the current understanding of YAP/TAZ signaling in cardiovascular biology and underscore its potential implications for the diagnosis and therapeutic intervention of CVDs.

1. Introduction

Cardiovascular diseases (CVDs) are widely acknowledged as the primary cause of illness and mortality worldwide.[1] Despite advancements in understanding the molecular pathways underlying CVDs, there remains a pressing for more accurate and efficient diagnostic and therapeutic approaches.[1–3] CVDs, which comprise a range of conditions affecting the heart and blood vessels, include coronary artery disease (CAD), heart failure, stroke, arrhythmias, peripheral artery disease, and more. CVDs cause considerable suffering and financial burden, affecting individuals of all ages, genders, and races, each with different risk factors and consequences.[4] According to the World Health Organization, CVDs are responsible for approximately 17.9 million deaths annually, representing approximately 31% of all global deaths. Numerous risk factors contribute to the development of CVD, including high blood pressure, smoking, unhealthy diet, physical inactivity, obesity, diabetes, high cholesterol levels, age, gender, family history, and genetics. The consequences of CVD can be severe, potentially leading to complications such as heart attacks, stroke, heart failure, and reduced quality of life.[5]

Heart disease is the leading cause of death for most racial and ethnic groups in the United States of America (U.S.). One person dies every 33 s in the U.S. from CVD. In 2021 alone, approximately 695,000 people in the U.S. died from heart disease, accounting for one in every five deaths.[6] Heart disease imposes a staggering financial burden on the U.S., costing roughly $239.9 billion annually from 2018 to 2019.[7] Coronary heart disease remains the most common type of heart disease, claiming the lives of 375,476 individuals in 2021. Remarkably, about one in twenty people aged 20 and older are affected by CADs (about 5%). In 2021, approximately two in ten deaths from CAD occurred in individuals under the age of 65.[8] In the U.S., a heart attack occurs every 40 s, with roughly 805,000 people experiencing a heart attack each year.[9]

Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ) serve as transcriptional coactivators within the highly conserved Hippo signaling pathway. A considerable amount of

* Corresponding author.
E-mail address: zhongkui.hong@ttu.edu (Z. Hong).

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recent research has documented the significant impact of YAP/TAZ in the pathogenesis of CVDs, such as pulmonary hypertension, atherosclerosis, aortic disease, angiogenesis, and others.[10] YAP facilitated myocardial hypertrophy by regulating cardiomyocyte proliferation.[11] Additionally, in pulmonary arterial hypertension, YAP has demonstrated beneficial effects by inhibiting the proliferation of pulmonary smooth muscle cells (PASMCs) stimulated by Galectin-3.[12] Conversely, the overexpression of YAP/ TAZ holds the potential in alleviating the symptoms of myocardial infarction and myocardial-ischemia-reperfusion (I/R) injury.[13] Additionally, since the loss of YAP is implicated in irregular blood vessel branching, it can be inferred that YAP also plays a vital role in angiogenesis and has implications in the development of atherosclerosis.[14] Based on the findings of these research, YAP/TAZ exerts a significant influence on CVDs.

Furthermore, we delve into the emerging field of YAP-targeted therapeutics, presenting novel pharmacological drugs and molecular techniques aimed at regulating YAP activity. These advancements hold promise for potentially enhancing outcomes for patients with various cardiovascular disorders. In this review article, novel therapeutics, including verteporfin, VGLL4, XMU-MP-1, WWC-derived protein, and others were discussed. Verteporfin, in particular, emerges as a promising candidate for the treatment of CVDs due to its capacity to inhibit YAP nuclear localization, thereby preventing its interaction with TEAD.[15] VGLL4 offers a promising avenue for the treatment of lung cancers and CVDs by competitive binding with TEAD and interfering with the YAP-TEAD interaction.[16] Additionally, WWC proteins play a significant role in the treatment of cardiac fibrosis, inflammation, and hypertrophy by regulating YAP via the phosphorylation of LATS 1/2.[17]

This review paper seeks to stimulate future research endeavors aimed at developing more efficacious strategies to combat CVDs. By bridging knowledge gaps and highlighting potential therapeutic avenues, we aspire to contribute to the worldwide pursuit of improved cardiovascular health.

2. YAP/TAZ signaling as mechanobiological pathway

YAP/TAZ regulates the activity of several transcription factors, particularly the members of TEA domain (TEAD) family. The Hippo pathway modulates the activity of YAP/TAZ through a kinase cascade, which ultimately leads to their phosphorylation and cytoplasmic retention, thereby inhibiting their transcriptional activity.[10,18,19] The regulation of YAP/TAZ is complex and influenced by multiple factors, including cell–cell contact, mechanical cues, and extracellular signaling.[20,21] The core components of the Hippo pathway include Mammalian Sterile-20-like kinases 1 and 2 (MST1/2), Large Tumor Suppressor kinases 1 and 2 (LATS1/2), Mps One Binder kinase activator-like 1 (MOB1), the adaptor protein Salvador/Warts/Hippo, and the downstream effector Yokrie/YAP/TAZ.[22] The core components of Hippo signaling pathway and their functions are summarized in Table 1.

The conservation of Hippo pathway suggests that it plays key roles in a variety of biological processes required for organismal formation, growth, and maintenance. It controls organ size, tissue regeneration, cell proliferation, apoptosis, cell differentiation, and stem cell self-renewal. Disruption or dysregulation of the Hippo pathway can lead to developmental defects, tissue overgrowth, and contribute to the development of diseases such as CVDs, cancer, and others.

The upstream regulators of the Hippo pathway consist of cell polarity proteins (Crumbs, Scribble, and Merlin), G-protein-coupled receptors (GPCR), cell–cell adhesion molecules (E-cadherin), and extracellular matrix (ECM) components. The regulators detect cell density, cell shape, and mechanical stresses, then send signals to the main Hippo pathway components, affecting YAP/TAZ activity (Fig. 1). MST1/2 interacts with their regulatory component SAV1 or WW45, resulting in the formation of an active complex capable of phosphorylating and activating the kinase LATS1/2. MOB1 is responsible for facilitating LATS1/2 activity. Similarly, MST1/2 phosphorylate LATS1/2 to enhance their ability to bind within the LATS1/2-MOB1 complex. Subsequently, the transcriptional coactivator YAP/TAZ is phosphorylated by active LATS1/2. Phosphorylation of YAP leads to its nuclear exclusion, followed by ubiquitination and ultimately proteasomal degradation.[25–27]

In contrast, YAP/TAZ can translocate into the nucleus when the Hippo pathway is inhibited or inactivated.[28] In the nucleus, they interact with a variety of transcription factors, coactivators, and DNA-binding proteins (TEAD) to regulate the expression of target genes that are involved in cell proliferation, survival, differentiation, apoptosis, and organ development when they interact with these proteins.[29]

Mechanotransduction, the pivotal factor that impacts YAP/TAZ activation, refers to the mechanism through which cells perceive and react to mechanical stimuli coming from their surrounding microenvironment. It has been demonstrated that mechanical forces, such as substrate rigidity, ECM rigidity, shear tension, and cell contractility, modulate the activation of YAP/TAZ.[30] Different mechanosensors, including integrins, focal adhesions, cytoskeletal components, and the nucleus, enable cells to perceive mechanical cues. Mechanical forces and signals are transmitted by these mechanosensors to the Hippo pathway and YAP/TAZ. YAP/TAZ activation may result from higher mechanical tension or rigidity in the ECM or cellular cytoskeleton. In addition to modulating YAP/TAZ activity, mechanotransduction pathways, including Rho GTPases and cytoskeletal regulators, facilitate the transmission of mechanical signals to the Hippo pathway. YAP/TAZ activation may also be influenced by intercellular forces and cell–cell junctions. For instance, the tension generated by cell–cell contacts and the elongation of cell–cell junctions can influence the localization and activity of YAP/TAZ.[31,32]

The transmission of mechanical force through the cytoskeleton and integrins to actin filaments provides stiffness and reacts to stress. This mechanism involves the focal adhesion complex, which inhibits the function of YAP/TAZ via phosphorylation, resulting in their dissociation and degradation. Alterations in the integrin-actin signaling system may disrupt this regulation, demonstrating the integration of mechanical processes. LINC (Linker of Nucleoskeleton and Cytoskeleton) complexes in the nuclear periphery serve to connect the nucleus to the cytoskeleton and facilitate the transmission of external forces. This process relies on the presence of SUN2 and nesprins. The actin cytoskeleton plays a vital role in the activity of the LINC complex by facilitating the nucleocytoplasmic link, which is required for the activation of YAP/TAZ in response to matrix stiffness and actin stress fiber production.[33] Vascular

Table 1
List of the core components of Hippo signaling pathway and their functions.

Proteins		Functions	Reference
Mammals	Drosophila		
MST1/2	Hippo (Hpo)	It is the upstream regulator of LATS1/2.	23,24
WW45 (SAV1)	Salvador (Sav)	It facilitates the interaction between MST and LATS and promotes phosphorylation of LATS1/2.	
LATS1/2	Warts (Wts)	It inactivates YAP/TAZ by phosphorylation.	
YAP/TAZ	Yorkie (Yki)	Transcriptional co-activator.	
NF2	Merlin (Mer)	It is the upstream regulator of MST1/2.	
MOB1	Mats	It helps in activation and phosphorylation of LATS1/2.	
TEAD	Scalloped	It is the transcriptional factor that binds with YAP/TAZ to regulate the target gene expressions.	

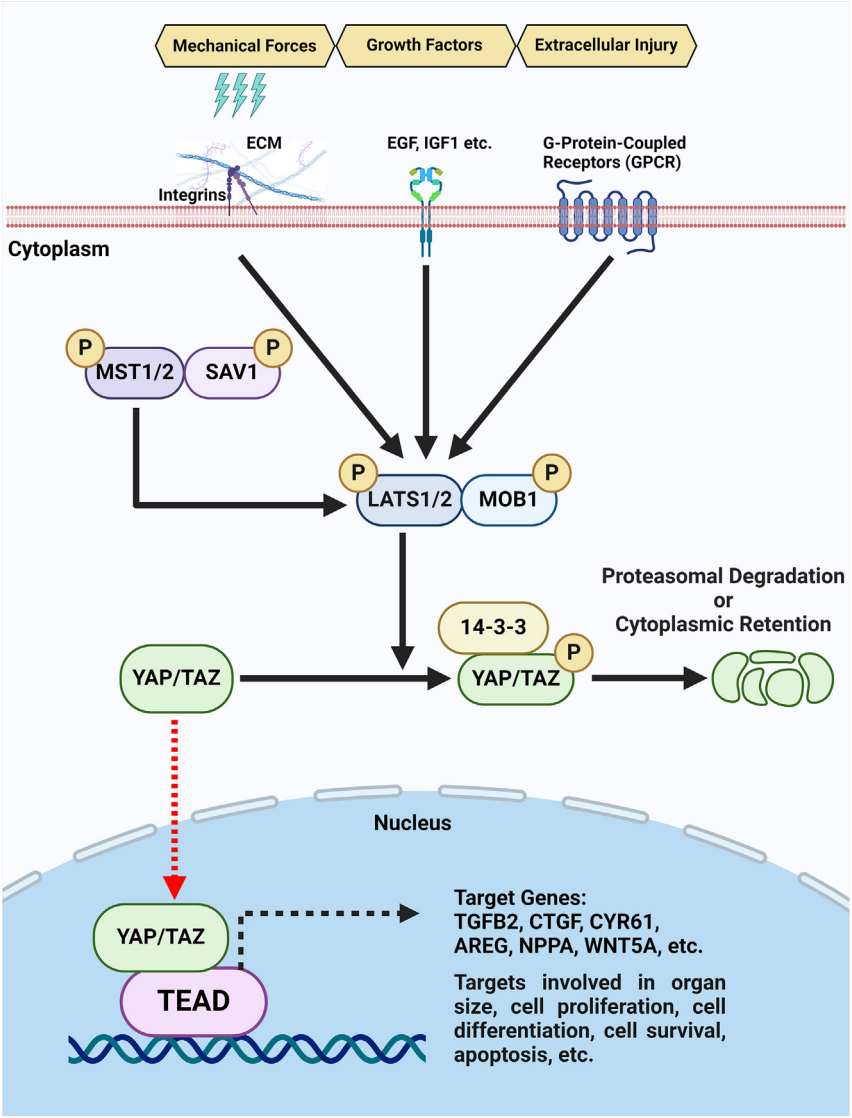

Fig. 1. Detailed mechanism of the YAP/TAZ signaling. When the signaling pathway is activated, the downstream effector, YAP/TAZ, becomes phosphorylated, leading to their cytoplasmic retention or proteasomal degradation. On the other hand, when the pathway is inactivated, the unphosphorylated YAP/TAZ translocates into nucleus, binds with the transcriptional factors (TEAD), and regulates the expression of target genes. Created with BioRender.com.

remodeling is influenced by the rearranging of the F-actin cytoskeletal network in vascular smooth muscle cells. When actin stress fibers are disrupted, YAP becomes delocalized, which suggests that actin organization controls mechanical responses via the Hippo pathway. The YAP/TAZ pathway preserves cellular quiescence and an anti-inflammatory condition when subjected to constant shear stress. However, it induces dysfunction, including endothelial activation, inflammation, and proliferation, in regions with low or disrupted flow.[34–36]

Another regulatory pathway of Hippo pathway involves GPCR signaling. GPCRs can either activate or inhibit the Hippo pathway depending on the specific G protein they interact with. The interaction underscores pathway's ability to respond to various extracellular signals, ultimately influencing cellular behaviors in accordance with the environmental cues.[37]

Ubiquitination plays a crucial role in regulating the Hippo pathway. This process targets specific components of the pathway for degradation by proteasomes, thereby influencing the stability and function of YAP/TAZ and LATS1/2. The incorporation of this post-translational modification provides an extra layer of control, ensuring precise regulation of pathway activity in response to the cell conditions.[38]

3. YAP/TAZ in cardiovascular diseases

YAP/TAZ signaling has been shown to play essential roles in various aspects of cardiovascular development, including heart formation, cardiac progenitor cell specification, and vascular development. In adult tissues, YAP/TAZ signaling contributes to the maintenance of cardiac homeostasis and the regulation of endothelial cell functions, such as angiogenesis and vascular barrier integrity.[39] Cell proliferation, apoptosis, cell migration, and ECM composition are crucial biological processes principally responsible for vascular remodeling.[40] Uncontrolled remodeling caused by hemodynamics, oxidative stress, or inflammation leads to endothelial cell activation, vascular smooth muscle cell (VSMC) migration, and death, facilitating ECM breakdown and compromising vascular structural integrity. However, YAP/TAZ

signaling in various CVDs, including myocardial infarction, cardiac remodeling, hypertension, cardiomyopathy, and other aortic diseases has a pivotal role to play (Fig. 2).[41]

3.1. Myocardial hypertrophy and heart failure

Myocardial hypertrophy is the adaptive reaction of the heart to increased workload, leading to an increase in heart muscle mass. It is a major risk factor for CVD, such as heart failure, arrhythmia, and sudden death. Myocardial hypertrophy can cause decreased blood pressure, enlargement of heart cells, apoptosis, reduced heart chamber flexibility, and impaired ability to pump blood, leading to a cycle of deteriorating heart function. Overall, myocardial hypertrophy is becoming increasingly significant in the field of CVD.[42] YAP/TAZ promotes glycolysis by increasing the expression of glucose transporter 1 (GLUT1), thereby aiding in support of compensatory ventricular hypertrophy in response to acute pressure overload. This process underscores the significance of metabolic reprogramming in the responses of the heart to stress. YAP/-TAZ activation leads to the accumulation of glycolytic metabolites, which induce ventricular hypertrophy.[43] However, Byun et al. demonstrated that the loss of YAP/TAZ impairs compensatory cardiomyocyte (CM) hypertrophy, leading to deteriorated cardiac function. YAP-CHKO mice exhibited reduced cardiac hypertrophy, increased cardiomyocyte apoptosis, and fibrosis, which correlated with worsened cardiac function one week after transverse aortic constriction (TAC). The loss of CM YAP hampers the activation of the cardioprotective protein Akt.[44] Wang et at. demonstrated that decreasing MST1 activity enhances the function of YAP, particularly in the regulation of genes such as Tnnt2 and Myh7, both of which are linked to hypertrophic cardiomyopathy (HCM). These findings are consistent with the evidence from previous research indicating that YAP promotes the growth of cardiac muscle cells and plays a crucial role in the adult heart function, including its involvement in facilitating heart hypertrophy. The involvement of YAP in the hypertrophic signaling pathway suggests its potential as a promising therapeutic target for interventions aimed at treating HCM. Regulating the activity of YAP holds promise as a potential approach to aid in the management or even reversal of the pathological hypertrophy observed in HCM.[11] The activation of YAP/TAZ has been implicated in the development of pathological cardiac hypertrophy and heart failure. Yang et al. demonstrated that miR-206 suppresses the expression of the tumor suppressor, Forkhead box protein P1 (FoxP1) and inhibits the action of FoxP1-UTR targets. These findings indicate that miR-206 is involved in the regulation of FoxP1 in cardiac cells, which has been identified as a target of YAP. The study suggests that YAP increases the expression of miR-206 in cardiomyocytes, and both miR-206 and YAP contribute to promoting cardiomyocyte hypertrophy. Additionally, the study demonstrated the impact of FoxP1 levels on the hypertrophic effects of YAP and miR-206.[45]

In summary (Fig. 3), YAP/TAZ proteins enhance glycolysis and support compensatory ventricular hypertrophy in response to acute pressure overload, increasing myocardial hypertrophy. Their activation increases glycolytic metabolites and cardiac muscle cell development, whereas their loss reduces hypertrophy and cardiac function. YAP/TAZ activity regulation may be a viable treatment for hypertrophic cardiomyopathy and associated heart diseases.

3.2. Myocardial infarction (heart attack)

A myocardial infarction (MI), often referred to as a heart attack, occurs when there is a reduction or cessation of blood flow in one of the coronary arteries of the heart. This lack of blood flow leads to tissue death (infarction) in the heart muscle. Nevertheless, the reperfusion process of reperfusion may induce cardiac damage. Exploring innovative therapies, such as the regulation of YAP, has the potential to mitigate such damage and enhance patient outcomes following PPCI for acute MI.[46] The study by Kang et al. explores the involvement of β-catenin in MI and its ability to decrease cardiomyocyte apoptosis via YAP-dependent pathways. Utilizing an MI rat model and H_2O_2-treated cardiomyocytes, researchers examined the impact of β-catenin on cardiac tissue and cell survival. The study revealed that diminished levels of β-catenin are associated with MI, while increasing its expression can decrease the extent of heart tissue damage, fibrosis, and apoptosis-induced cell death.[47] The study by Wang et al. delves into the therapeutic potential of IL-37 in mitigating MI in mice. It underscores the role of IL-37 in reducing tissue damage caused by a heart attack and improving heart function post-event. This is achieved by modulating the polarization of macrophages, shifting from a pro-inflammatory M1 state to an anti-inflammatory M2 state. By targeting macrophage programming and inflammation resolution, this effect, mediated by IL-37's inhibition of YAP-NLRP3 signaling, provides evidence that it may serve as a prospective therapeutic agent for the treatment of MI.[48] However, a study demonstrates that activating YAP specifically in the heart following a heart attack promotes heart regeneration by stimulating the proliferation of heart muscle cells, thereby enhancing heart function, and improving survival rates in a mouse model. Using transgenic and adeno-associated virus-mediated YAP expression, Lin et al. demonstrated that YAP activation does not cause hypertrophy or adverse effects on heart function. This underscores the

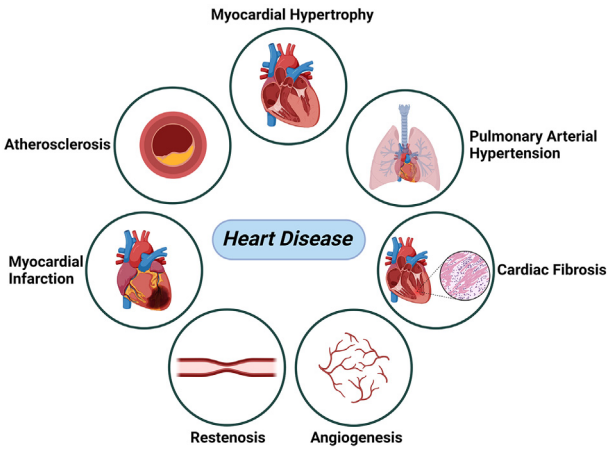

Fig. 2. Different types of heart disease that involve YAP/TAZ signaling pathway. Created with BioRender.com.

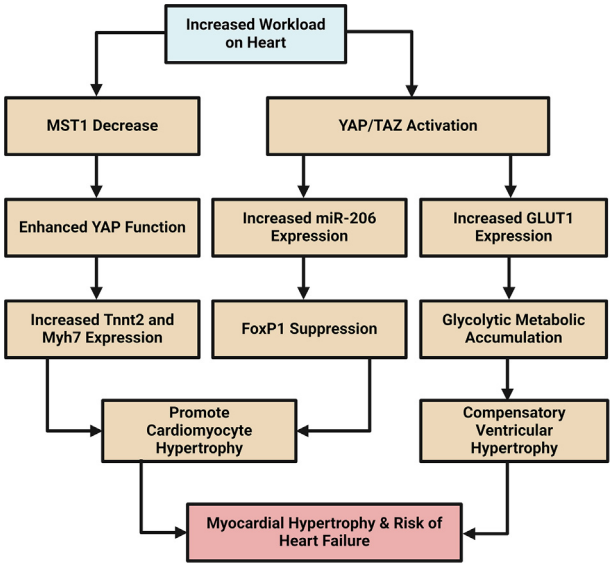

Fig. 3. Summary for the mechanism of Myocardial Hypertrophy.

therapeutic potential of YAP for heart repair following myocardial infarction.[49]

It is evident that after a myocardial infarction (MI), YAP/TAZ reduces cardiomyocyte apoptosis and boosts cardiac regeneration. Activating YAP in the heart enhances heart muscle cell proliferation without hypertrophy, suggesting it might improve cardiac function and survival post–MI. This makes YAP/TAZ an attractive target for novel MI therapies. The summarized mechanism underlying the YAP/TAZ and Myocardial Infarction is shown in Fig. 4.

3.3. Myocardial ischemia-reperfusion injury

Activation of YAP/TAZ activation has been demonstrated to confer protection to the heart against I/R injury by promoting cellular survival and angiogenesis. Matsuda et al. demonstrated the role of neurofibromin 2 (NF2), a tumor suppressor, in isolated cardiomyocytes and mouse myocardium, under normal conditions and in the presence of oxidative stress. NF2 expression was induced in cardiomyocytes exposed to H_2O_2 and in mouse hearts subjected to oxidative stress. Elevated NF2 expression facilitated the activation of MST1 and the inhibition of YAP, while depletion of NF2 attenuated these responses. In the presence of NF2, the activity of MST1 was found to be crucial in promoting apoptosis of cardiomyocytes. Cardiomyocyte-specific knockout mice lacking the NF2 gene were shielded from global I/R injury when studied ex vivo and exhibited improved restoration of heart function. The study also observed a nuclear interaction between NF2 and its activator myosin phosphatase target subunit 1 (MYPT-1) in cardiomyocytes. These findings suggest that YAP serves as a significant focal point of NF2 in the adult heart.[50] Additionally, YAP/TAZ signaling has been implicated in the regulation of cardiac fibroblast activation and fibrosis, key processes in the reparative response following myocardial infarction.[51]

One study investigates how shear stress reduces cell death in cardiac microvascular endothelial cells (ECs) during I/R injury through the YAP/miR-206/PDCD4 signaling pathway.[52] Shear stress increases YAP expression, enhances miR-206 levels, and reduces PDCD4 expression, leading to a reduction in cardiac microvascular EC apoptosis. YAP exerts a protective effect against ferroptosis, an intracellular iron-dependent form of cell death in myocardial I/R injury. Upregulation of YAP reduces iron-dependent cell death signals, thereby, ameliorating heart damage. In addition, YAP was found to increase the transcription of neural precursor cells expressed developmentally downregulated 4-like (NEDD4L) proteins, leading to the breakdown of the ferroptosis mediator protein ACSL4. This process inhibits ferroptosis and promotes cardiac performance. Fat mass and obesity-associated protein (FTO), m6A demethylase, reduces cell death and inflammation in heart muscle cells following damage from hypoxia and subsequent reoxygenation, with a specific focus on how it controls the stability and expression of YAP mRNA. It illustrates how FTO protects against myocardial damage by regulating YAP mRNA by removing m6A alteration, providing valuable information for future therapeutic approaches to I/R injury.[53,54] Additional recent discoveries demonstrate the therapeutic capabilities of YAP. For instance, Xue examined how adipocyte enhancer binding protein 1 (AEBP1) exacerbates MIRI by inhibiting IκBα.[55] Zhu et al. investigated how YAP contributes to the activation of autophagy in hepatic ischemia-reperfusion. Their findings demonstrate that YAP prevents damage by promoting autophagy through JNK signaling, thereby inhibiting hepatocyte apoptosis.[56] Resveratrol can also reduce damage caused by I/R by blocking necroptosis through the regulation of the Hippo pathway. This highlights the protective impact achieved by promoting YAP's movement into the cell nucleus.[57] This intervention proposes a potential treatment approach to decrease I/R damage by elucidating how the Hippo pathway regulates cardiomyocyte necroptosis and protects the myocardium.

From the above discussion, it is conclusive that YAP/TAZ activation protects the heart against I/R damage by increasing cell survival, angiogenesis, and lowering apoptosis. YAP/TAZ regulates cardiac

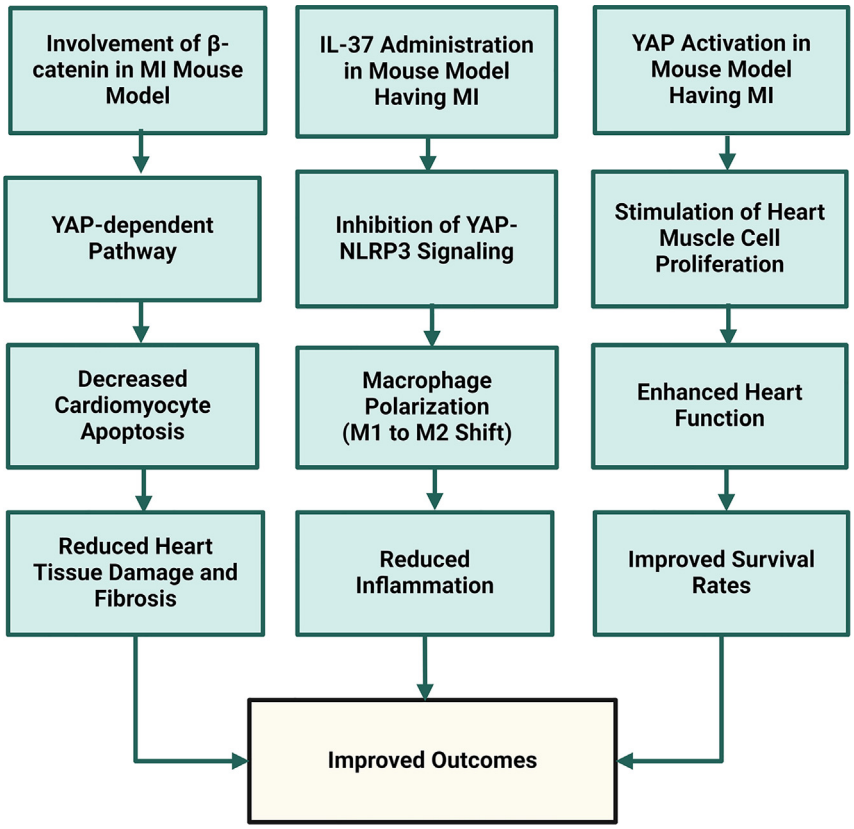

Fig. 4. Summary for the mechanism of Myocardial Infarction.

fibroblast activation and fibrosis, aiding heart repair and demonstrating its therapeutic potential. Moreover, YAP also reduces ferroptosis and necroptosis, which helps reduce heart damage and improve cardiac function after I/R injury. The summarized mechanism is shown in Fig. 5.

3.4. Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a progressive illness characterized by elevated blood pressure in the pulmonary arteries, which can develop at any age.[58] This condition is a form of pulmonary hypertension that primarily impacts the arteries in the lungs and the right side of the heart. PAH is characterized by the constriction, obstruction, or deterioration of the pulmonary arteries, leading to increased resistance to blood flow in the lungs. This elevated resistance places strain on the right ventricle of the heart, requiring increased effort to pump blood through the lungs, ultimately leading to right heart failure.[59,60] Despite its reputation for being incurable, numerous scholars are working to discover novel therapeutic options for this disease and YAP/TAZ emerges as a strong contender, showing promising outcomes.[61–63]

In their recent study, Wang et al. provided evidence that Sphingosine-1-phosphate (S1P) facilitates the proliferation of PASMCs through the induction of Notch3 expression mediated by YAP. Chen et al. arrived at the same conclusion. They demonstrated that deficiency of Sphingosine Kinase 1 (SPHK1) in VSMCs prevents hypoxia-induced pulmonary hypertension via YAP signaling.[64,65] Zuo et al. examined the pharmacological effects of luteolin on PAH induced in rats by monocrotaline (MCT).[66] The researchers established that luteolin partially ameliorates PAH by inhibiting the HIPPO-YAP/PI3K/AKT signaling pathway. The study conducted by Acharya et al. illustrated that pulmonary hypertension (PH) in rats can be reduced through the concurrent pharmacologic inhibition of YAP and glutaminase 1 using inhaled microparticles encapsulated in poly(lactic-co-glycolic) acid.[67] Bertero et al. also demonstrated in their research that the activation of glutaminolysis and anaplerosis, dependent on the YAP/TAZ pathway, is a key mechanism by which vascular stiffness might promote cellular proliferation in PH.[68] The key protein of the YAP signaling pathway, LATS1, is found to be inactivated in certain cells and small remodeled pulmonary arteries in idiopathic PAH, as revealed by specific tests. This inactivation is linked to several molecular changes, including the activation of mTOR-Akt, accumulation of HIF1a, and other pathways, ultimately leading to increased cell proliferation and survival. Crucially, LATS1 inactivation and the subsequent increase in YAP levels also boost fibronectin production, which in turn increases levels of integrin-linked kinase 1 (ILK1) and induces pulmonary vascular remodeling.[69] All these investigations confirm the crucial involvement of YAP in the molecular etiology of PAH and related vascular complications.

In summary (Fig. 6), YAP/TAZ promotes pulmonary artery smooth muscle cell proliferation and vascular remodeling, which contributes to the development of pulmonary arterial hypertension (PAH). YAP/TAZ signaling pathways, influenced by Sphingosine-1-phosphate and the HIPPO-YAP/PI3K/AKT axis, promote pulmonary artery cell proliferation and resistance in pulmonary arteries. That is why targeting YAP/TAZ may offer innovative PAH and vascular complications treatments.

3.5. Angiogenesis

Angiogenesis is the biological process by which new blood vessels develop from existing ones formed during the initial stage of vasculogenesis. This process is essential for supporting tissue growth, development, wound healing, and tissue repair in the body. Angiogenesis involves the proliferation and migration of endothelial cells along blood vessels, leading to the formation of new capillaries and bigger blood vessels. YAP/TAZ exerts a significant effect on angiogenesis. Long non-coding RNAs (lncRNAs), which regulate angiogenesis, have implications in conditions such as atherosclerosis, hypertension, and vascular retinopathies.[70] YAP/TAZ plays a crucial role in the migration, growth, and junction formation of ECs, thereby affecting the development of new blood vessels and the maturation of protective barrier. A study demonstrates that the deletion of YAP results in vascular abnormalities, including irregular branching of blood vessels and impaired barrier function. Furthermore, YAP/TAZ regulates EC actions by remodeling the actin cytoskeleton, upregulating MYC signaling activity, and coordinating metabolic processes. This underscores their potential as therapeutic targets for vascular disorders.[39] Another study reveals that Angiopoietin-2 (ANG-2), a transcriptional target of YAP, significantly influences the angiogenic activity of ECs in both laboratory settings (*in vitro*) and in living organisms (*in vivo*). This discovery underscores the crucial role of YAP in angiogenesis, providing insights into EC functioning and the mechanisms underlying vascular remodeling.[71]

The above findings extensively advocate that YAP/TAZ promotes

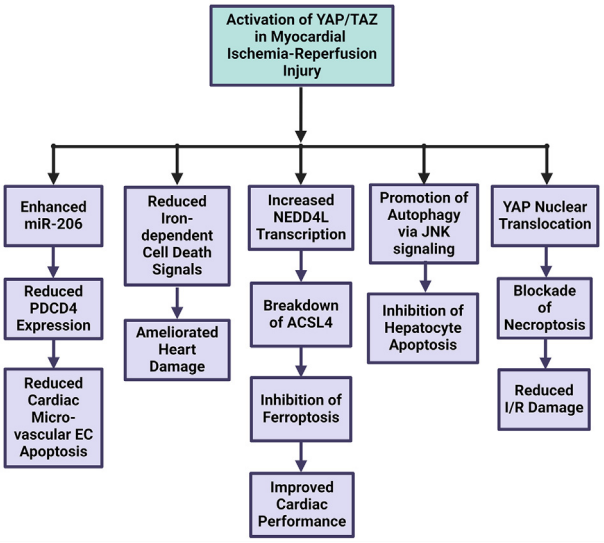

Fig. 5. Summary for the mechanism of Myocardial Ischemia-Reperfusion Injury.

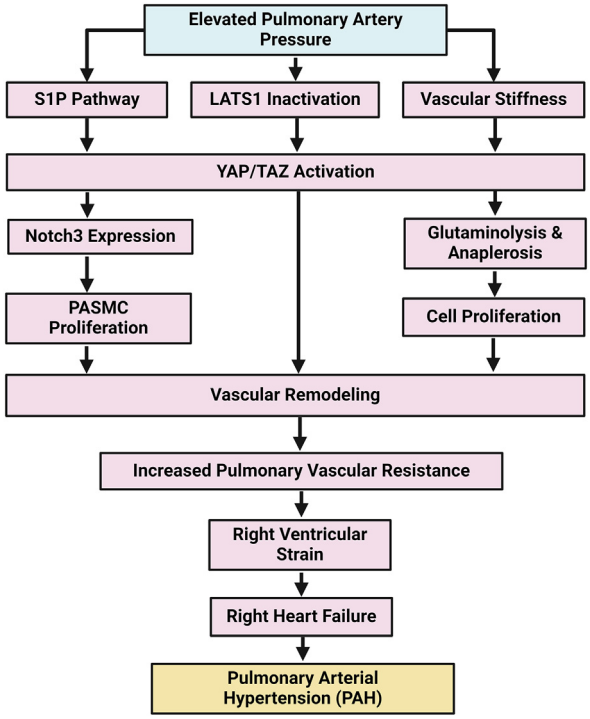

Fig. 6. Summary for the mechanism of Pulmonary arterial hypertension.

endothelial cell proliferation, migration, and junction formation, essential for blood vessel growth. These proteins modify the actin cytoskeleton, enhance MYC signaling, and coordinate metabolic activities in endothelial cells. YAP/TAZ's function in angiogenesis suggests they might cure vascular diseases and improve tissue repair. The summarized mechanism is shown in Fig. 7.

3.6. Restenosis

Restenosis is defined as the re-narrowing or re-occlusion of a blood vessel subsequent to a prior intervention aimed at addressing a blockage or narrowing. This condition can significantly affect the effectiveness of vascular interventions by impeding or completely obstructing blood flow, often requiring further treatments or interventions to restore vessel patency. YAP can be regulated by mechanical cues such as ECM stiffness and fluid shear stress. Damkham et al. emphasized YAP's impact on mesenchymal stem cells (MSC) and pluripotent stem cells (PSCs) underscoring YAP's sensitivity to mechanical stimuli. This sensitivity is crucial considering the mechanical stress associated with vascular interventions, which ultimately contributes to restenosis.[72]

Osteoprotegerin (OPG) exacerbates in-stent restenosis by activating YAP via αVβ3/FAK signaling, leading to VSMC proliferation and migration. In aortic VSMCs, OPG induces YAP dephosphorylation and activation through the phosphorylation of focal adhesion kinase (FAK) and actin cytoskeleton remodeling, mediated by OPG's interaction with integrin αVβ3.[73] Sometimes blood vessel damage can trigger the expression of YAP, coinciding with the synthetic phenotype of VSMCs and promotes SMC proliferation and migration while concurrently reducing the expression of contractile gene. Therefore, targeting YAP presents a promising approach for treating vascular occlusive disorders by attenuating abnormal VSMC proliferation and migration, thereby mitigating the risks of restenosis.[74] Li et al. investigated Adiponectin as a possible therapeutic target for restenosis, emphasizing its protective effects against endothelial dysfunction, inflammation, and VSMC proliferation, which are the key factors contributing to restenosis. Moreover, the study by Huang et al. demonstrates that a drug-eluting stent specifically designed to target SP-1 effectively reduces restenosis by activating the YAP-mediated pathway in VSMCs. This approach underscores the therapeutic potentials of regulating YAP to inhibit VSMC growth, a pivotal factor in restenosis.[75,76]

In summary (Fig. 8), targeting YAP/TAZ presents a promising therapeutic strategy to mitigate abnormal VSMC proliferation and reduce the risk of restenosis due to its a crucial role in promoting VSMC proliferation and migration in response to mechanical stress and signaling pathways

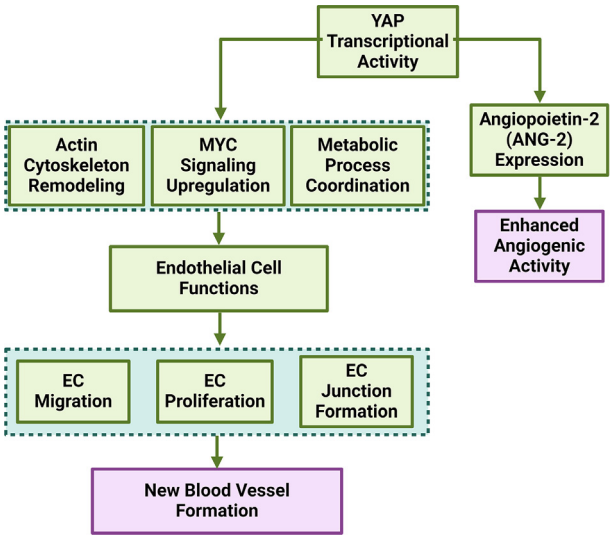

Fig. 7. Summary for the mechanism of Angiogenesis.

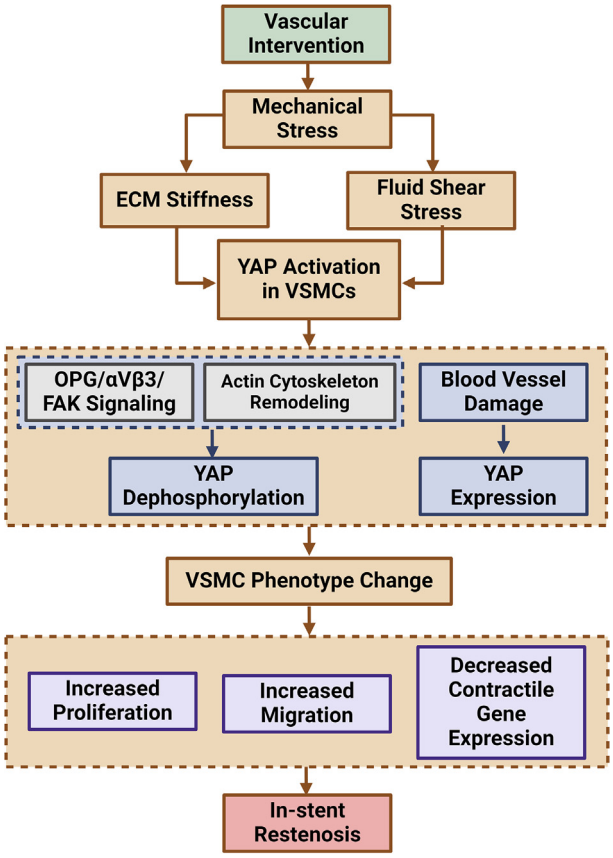

Fig. 8. Summary for the mechanism of Restenosis.

such as αVβ3/FAK, ultimately contributing to the re-narrowing of blood vessels after interventions.

3.7. Atherosclerosis

Arteriosclerosis is a chronic disease characterized by the thickening and stiffening of arteries, caused by the buildup of fatty deposits, cholesterol, cellular waste, calcium, and other substances within the artery walls. This accumulation can lead to reduced blood flow through the affected arteries.[77] As time progresses, arteries may undergo arterial calcification, a process that leads to their hardening. The potential of targeting YAP signaling as a therapeutic approach for atherosclerosis has been recognized, given its effects on cell proliferation and autophagy in the vascular system.[78] YAP plays a pivotal role in the chronic inflammatory condition associated with atherosclerosis, modulating various processes such as impaired lipid metabolism, dysfunctional ECs, and activated VSMCs. YAP-related pathways are activated by changes in flow patterns and matrix stiffness, leading to the development of arterial plaques. Moreover, YAP's involvement extends to consequences including arterial calcification and intraplaque bleeding, demonstrating its diverse role in the initiation and progression of atherosclerosis.[79]

Mechanical stresses exerted on the circulatory system affect both the structure and physiological functions of the heart. Unidirectional shear flow exerts a protective effect against atherosclerosis through the Integrin-YAP/TAZ-JNK cascade pathway.[2] This pathway reduces atherosclerosis by inhibiting YAP/TAZ activity, leading to decreased inflammation and monocyte attachment. Modifying YAP specifically in ECs affects plaque formation in ApoE$^{-/-}$ mice, indicating that targeting YAP/TAZ could be a promising therapeutic approach for treating atherosclerosis. Another study demonstrates that Methotrexate (MTX) protects against atherosclerosis by inhibiting YAP/TAZ activity in ECs subjected to disturbed flow. MTX reduces inflammatory reactions and

monocyte attachment through the AMPK-YAP/TAZ pathway, demonstrating a new approach for preventing and treatment of atherosclerosis.[80] In contrast, another study investigates how laminar flow exerts a positive effect on ECs in protecting against atherosclerosis by regulating YAP activity.[81] Laminar flow inhibits YAP activation by inducing LATS1/2-dependent phosphorylation, which in turn decreases the production of pro-atherogenic genes. This underscores a new mechanism for flow-mediated protection against atherosclerosis.

A study proposes that oxidized low-density lipoprotein (ox-LDL) induces vascular EC dysfunction by promoting the expression of miR-496, which subsequently suppresses YAP.[82] This process leads to significant death and impairment in human umbilical vein endothelial cells (HUVECs), indicating a possible genomic mechanism by which ox-LDL influences atherosclerosis by affecting YAP expression and signaling. YAP interacts with TRAF6 to suppress NF-κB activation, thereby attenuating endothelial activation and vascular inflammation.[83] A separate study demonstrates that the lack of tissue factor pathway inhibitor-1 (TFPI-1) in VSMCs exacerbates atherosclerosis in ApoE$^{-/-}$ mice.[84] This phenomenon is attributed to increased proliferation and migration of VSMCs, which is facilitated by decreased phosphorylation of angiomotin (AMOT) and YAP. These results suggest that TFPI-1 exerts a protective effect against atherosclerosis by regulating VSMC activity via the AMOT/YAP pathway. Consequently, there may be a negative correlation between TFPI-1 expression levels and the development of atherosclerosis. A different research study demonstrates that utilizing monocyte membrane-coated nanoparticles (MoNP) to deliver verteporfin significantly decreases YAP/TAZ expression. This downregulation subsequently reduces inflammatory gene expression and macrophage infiltration in cultivated ECs and mouse arteries exposed to atherogenic factors. Moreover, the lesion-targeted verteporfin nanodrug significantly reduces plaque formation in mice without inducing any observable histopathological changes in vital organs.[85]

It is irrefutable that YAP/TAZ is integral to the progression of atherosclerosis, influencing processes like cell proliferation, autophagy, inflammation, and arterial calcification. By lowering inflammation, monocyte attachment, and plaque formation, targeting YAP/TAZ might effectively treat atherosclerosis. The summarized mechanism is shown in Fig. 9.

3.8. Cardiac fibrosis

Cardiac fibrosis (CFs) is characterized by an abnormal accumulation of fibrous connective tissue in the heart. This process can occur due to injury, aging, or disease, leading to heart muscle stiffness, reduced cardiac function, and potentially heart failure. Fibrosis leads to an abnormal accumulation of the collagen and other ECM components in the heart, disrupting its structure and function, which impairs its ability to contract and relax effectively.[86–89] Recent studies have provided insights into the mechanisms by which YAP/TAZ significantly contributes to the development and progression of cardiac fibrosis. Garoffolo et al. discovered a novel method that impedes the molecular translation of mechanical signals, demonstrating how YAP influences fibrotic programming in cardiac stromal cells by regulating TGF-β1, a key profibrotic cytokine.[90] Another study demonstrates that increased matrix stiffness triggers the activation of cardiac fibroblasts, culminating in fibrosis, with YAP activation playing a pivotal role in mediating this mechanism. In response to a stiff matrix, CFs exhibit increased YAP expression and nuclear localization, leading to heightened cell activation. Knockdown of YAP reduced the fibrogenic response of cardiac fibroblasts, while YAP overexpression amplified fibroblast activation, indicating the critical role of YAP in regulating the fibroblasts activation induced by matrix stiffness.[91] Liu et al. discovered that Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) was upregulated in high-glucose cardiac fibroblasts and diabetic cardiomyopathy (DCM) mice, leading to enhanced collagen formation, inflammation, and cell proliferation. MALAT1 was demonstrated to inhibit the Hippo-YAP pathway and promote the translocation

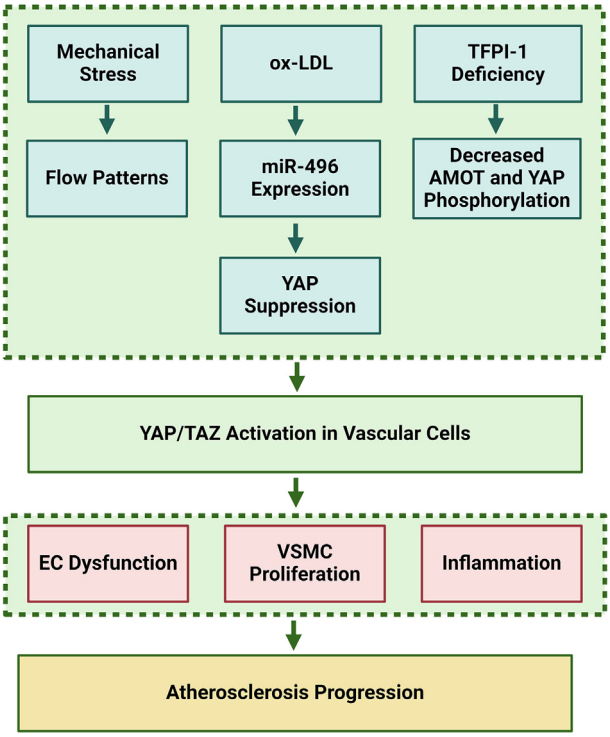

Fig. 9. Summary for the mechanism of Atherosclerosis.

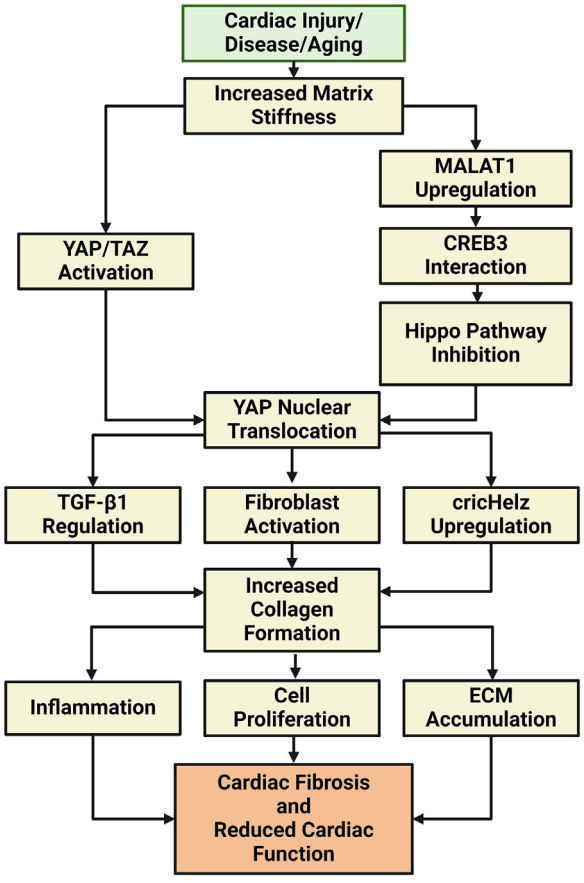

Fig. 10. Summary for the mechanism of Cardiac Fibrosis.

of YAP into the cell nucleus by interacting with CREB3. Suppression of MALAT1 reversed these effects, resulting in improved cardiac function and reduced fibrosis in DCM animals.[92] In their study, Mia et al. demonstrated that the activation of YAP/TAZ in cardiac fibroblasts following myocardial infarction leads to fibrosis and inflammation. Specifically deleting YAP/TAZ in fibroblasts reduces fibrotic and inflammatory responses, ultimately enhancing cardiac function.[93] Additionally, the circular RNA circHelz is upregulated in CFs and TGF-β-treated cardiac fibroblasts, exacerbating CFs via interacting with YAP. Conversely, reducing circHelz levels alleviates fibrosis in myocardial infarction rats and activated cardiac fibroblasts.[94] Both Xiao et al. and Francisco et al. reported similar results demonstrating that YAP knockout mice exhibit reduced CFs and dysfunction after myocardial infarction.[95,96]

In summary (Fig. 10), increased matrix stiffness and factors like high glucose and TGF-β1 enhance YAP activity which causes cardiac fibroblast activation and fibrotic programming, leading to fibrosis and inflammation. These outcomes suggest that targeting YAP/TAZ in cardiac fibroblasts can be a potential therapeutic approach to reduce fibrosis and improve cardiac function.

4. Therapeutic potential of targeting YAP/TAZ in cardiovascular diseases

Currently, scholars are advocating YAP/TAZ as a promising therapeutic intervention for a range of diseases, given its effectiveness in regulating fundamental physiological processes including cell proliferation, differentiation, tissue regeneration, and embryonic development. Moreover, ongoing studies are aimed at identifying effective inhibitors or effectors of YAP/TAZ for treating various diseases. This cascade of protein phosphorylation, serving as a novel therapeutic strategy, has garnered considerable attention from numerous researchers. Thus far, several commercially available pharmaceuticals such as Verteporfin, VGLL4, Flufenamic Acid, have been identified for targeting YAP/TAZ. Moreover ASO (ION537), IK-930, and VT3989, are currently in phase 1 of development as YAP inhibitors. Additionally, Fan et al., Qi et al., Fitamant et al., and other researchers have utilized AS-1, WWC-derived protein (SuperHippo), siRNA/shRNA, and other non-commercially available approaches for YAP inhibition.[97–99]

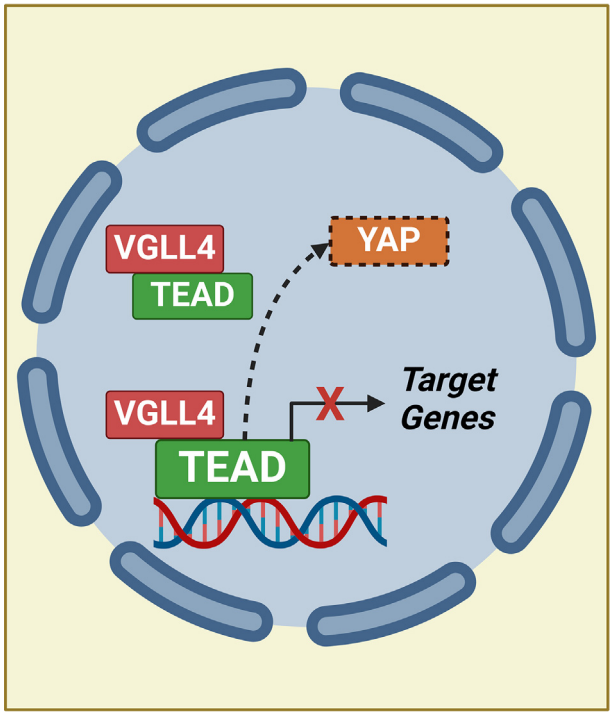

Fig. 11. The mechanism of VGLL4 inhibiting YAP involves competitive interaction with TEAD, inhibiting the YAP-TEAD interaction. Created with BioRender.com.

4.1. Vestigial-like family member 4

Vestigial-like family member 4 (VGLL4) is a protein belonging to the VGLL family that may interact with TEAD. VGLL4 diminishes YAP's activity by decreasing the interaction between TEAD and YAP, as well as by reducing TEAD degradation. It achieves this by competitively interacting with TEAD, a key transcriptional mediator. VGLL4's Tondu domain bears resemblance to the YAP binding domain of transcriptional regulators. This structural similarity enables VGLL4 to compete with TEAD for binding, thereby preventing YAP from initiating TEAD-mediated transcription (Fig. 11).[100,101] Consistently, Zhang et al. also observed that VGLL4 competes directly with YAP for binding to TEADs, thereby suppressing YAP activity. Overexpression of VGLL4 in cancer cells leads to reduced cell proliferation, migration, and invasion.[102] Acetylation of VGLL4 regulates its function and influences YAP-TEAD signaling. Acetylation at specific sites may diminish VGLL4's ability to interact with TEAD, thereby affecting cell growth and control of organ size.[103] VGLL4 inhibits the expression of YAP target genes and pro-cancer collagen genes, leading to reduced tumor development.[104] Additionally, VGLL4 enhances osteoblast differentiation by counteracting TEADs, which suppresses YAP via a mechanism distinct from its typical pathway. These findings suggest that VGLL4 serves a multifaceted role in both inhibiting cancer growth and stimulating differentiation across cell types.[105] PH induces an upregulation of VGLL4 acetylation and expression, which in turn impacts STAT3 signaling. Knockdown of VGLL4 reduces PH and pulmonary artery remodeling, while overexpressing exacerbates PH. These findings suggest that inhibiting VGLL4 acetylation may mitigate the effects of PH.[106]

4.2. Verteporfin

Verteporfin (VP) is a drug commonly used in photodynamic treatment to address irregular blood vessel formation in eye disorders such as wet

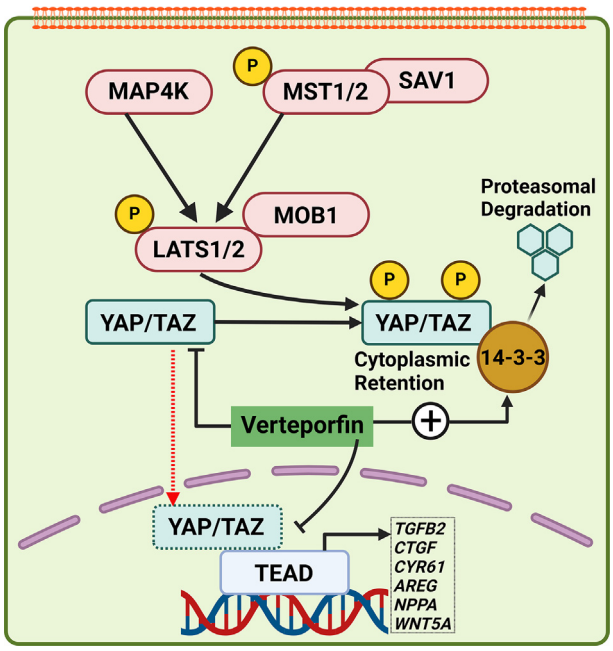

Fig. 12. The detailed mechanism of VP as a YAP inhibitor involves multiple steps. VP blocks the YAP signaling pathway by (a) reducing the expression level of YAP/TAZ, (b) inhibiting the interaction between YAP/TAZ and TEAD, and (c) upregulating the level of 14-3-3σ proteins, which are responsible for YAP degradation. Created with BioRender.com.

age-related macular degeneration (AMD). A recent study has explored VP's capacity to suppress YAP in the Hippo signaling pathway, which is implicated in heart disease and cancer, suggesting potential therapeutic uses beyond its traditional application in ophthalmology (Fig. 12).[107] One research indicates that VP induces levels of cytosolic 14-3-3σ, a protein responsible for sequestering YAP in the cytoplasm, thereby inhibiting nuclear YAP expression. This mechanism impedes the transcriptional activation of downstream targets by YAP, suggesting that VP may serve as a promising therapeutic strategy for cancers.[15] Gibault et al. showed that, in cancer therapy, VP treatment notably reduce the levels of YAP/TAZ expression, which in turn inhibits the YAP/TAZ-TEAD interaction.[108] In another study, the combined administration of VP and CB-839, a Glutaminase 1 inhibitor, was evaluated by inhaled poly(lactic-co-glycolic) acid (PLGA)-encapsulated microparticles for the treatment of PH. This strategy aims to target both YAP and GLS1 concurrently by delivering medications directly to the lungs, aiming to reduce general adverse effects and enhance treatment effectiveness. The administration of VP and CB-839 via PLGA microparticles resulted in a significant enhancement of PH indicators in rats.[67]

According to the findings of one research, VP has the ability to mitigate the deleterious effects of hypertension-induced kidney disease, including proteinuria, inflammation, and fibrosis in mice.[109] VP efficiently inhibits the activation and proliferation of hepatic stellate cells (HSCs) by blocking the YAP-TEAD complex. Additionally, it enhances the apoptosis of HSCs, suggesting a promising therapeutic strategy to ameliorate hepatic fibrosis.[110] VP is employed as a YAP inhibitor to treat lung fibrosis by reducing TGF-β or BLM-induced mitochondrial reactive oxygen species (mtROS) in human lung fibroblasts. It also diminishes the expression of fibronectin and alpha-smooth muscle actin.[111] In another study, VP is utilized to counteract the anti-inflammatory effects of intracerebral hemorrhage (ICH) damage.[112] Additionally, it reduces IL-6 and TNF-α levels via modulating the NF-κB and JAK/STAT signaling pathways, thereby inhibiting lipopolysaccharide (LPS)-induced inflammation in RAW 264.7 cells, a macrophage cell line.[113] An innovative method utilizing monocyte membrane-coated nanoparticles as a drug carrier for precise delivery of VP, a YAP/TAZ inhibitor, to atherosclerotic plaques has demonstrated promising outcomes. This method successfully decreases YAP/TAZ expression, leading to a reduction in inflammatory gene expression and macrophage infiltration in mouse arteries, showing promise as a targeted therapy for atherosclerosis.[85]

4.3. Angiotensin II

Angiotensin II (Ang II), the major regulatory peptide of the renin–angiotensin system (RAS), is widely recognized for its physiological mediator that restoring circulatory integrity, its function as a growth factor regulating cell growth and fibrosis, and its involvement in crucial inflammatory processes.[114] Ang II stimulates YAP and TAZ, two transcription factors linked to fibrosis. This activation relies on RhoA and enhances the expression of genes related to fibrosis, which contributes to fibrosis in the cardiovascular system. Blocking YAP/TAZ signaling reduces Ang II-induced fibrosis.[115] Ang II stimulates YAP/TAZ activation in the heart and aorta, leading to increased size and scarring of the heart and blood vessels. The activation occurs via the Rho kinase/ERK1/2 pathway in VSMCs. This finding confirms the previous research and suggests that Ang II's ability to activate YAP might make it a potential therapeutic target for CVDs.[116]

4.4. CA3

One study suggests that CA3 could serve as a potential YAP inhibitor, specifically targeting radiation-resistant, Cancer Stem Cell (CSC)-enriched esophageal adenocarcinoma cells. CA3 strongly inhibits YAP-TEAD transcriptional activity, leading to suppression of tumor cell development, induction of apoptosis, and reduction of CSC features such as tumor sphere formation and ALDH1+ cell fraction. Additionally, CA3 synergizes with 5-FU to decrease esophageal adenocarcinoma cell proliferation, indicating its potential for treating CSCs and treatment-resistant cancers by targeting the YAP pathway.[117]

4.5. Flufenamic acid

An analogue of flufenamic acid, LM98, demonstrates a high affinity for TEAD. In this investigation, LM98 was designed to inhibit TEAD with the aim of targeting cancer. LM98 binds strongly with TEAD, preventing its autopalmitoylation and thereby diminishing the transcriptional activity of YAP-TEAD.[118] Additionally, flufenamic acid has demonstrated great potential in reducing arrhythmia by reducing the frequency of early afterdepolarizations (EAD) in mice.[119]

4.6. XMU-MP-1

A study demonstrated the cardioprotective effects of XMU-MP-1, an MST1 inhibitor, against myocardial I/R injury in mice. The study investigated the fundamental molecular mechanisms involved and found that therapy with XMU-MP-1 reduces tissue damage caused by lack of blood flow, decreases cell death, preserves cardiac function, and alleviates dysfunction of mitochondria in the heart muscle of mice experiencing I/R injury. In addition, XMU-MP-1 promotes the polarization of M2 macrophages and prevents inflammation. This study demonstrates that both the administration of XMU-MP-1 and the absence of MST1 activate the AMPKα pathway in the myocardium, which is crucial for the beneficial effects in preventing I/R injury.[120] Triastuti et al. and Okuyama et al. both concluded that XMU-MP-1 decreases the activity of the kinases MST1 and MST2, which play a crucial role in the Hippo pathway. This inhibition results in the activation of YAP, leading to cell proliferation, survival, and control of organ size.[121,122]

4.7. AS-1

The Toll/interleukin-1 receptor (TIR)/BB-loop mimetic AS-1 has been demonstrated to impede cardiac hypertrophy by blocking the signaling pathway reliant on myeloid differentiation primary response gene 88 (MyD88) and mediated by the interleukin-1 receptor (IL-1R). The AS-1 therapy successfully restored phosphorylation and expression of LATS1, a key molecule in YAP signaling pathway, in both laboratory settings (*in vitro*) and living organisms (*in vivo*). AS-1 therapy inhibited the activation of cell division, specialization, and collagen production in neonatal rat cardiac fibroblasts (NRCFs) in response to mechanical stress. AS-1 also ameliorated the condition of hypertrophic cardiac myocytes and attenuated cell apoptosis by diminishing the release of signaling molecules from stretched cardiac fibroblasts. Consequently, AS-1 therapy in mice exhibited a protective effect against transverse aortic constriction (TAC)-induced cardiac hypertrophy, myocardial fibrosis, and heart failure.[97]

4.8. WWC-derived protein

The WWC protein family, comprising WWC1 (KIBRA), WWC2, and WWC3, play a vital role in the Hippo signaling pathway, influencing cell proliferation and regulation of organ growth. Numerous studies have investigated its conservation across different species, its capacity to form homo- and heterodimers, and its role in collectively inhibiting cell proliferation by modulating YAP transcriptional activity. In mice, the loss of WWC protein expression leads to liver hypertrophy, inflammation, fibrosis, and carcinoma, underscoring the pivotal role that WWC proteins play in regulating cell proliferation, organ size, and tumor suppression.[123,124] SuperHippo, a protein derived WWC, mitigates tissue overgrowth, inflammation, and fibrosis associated with liver cancer in mice by inhibiting the YAP/TAZ activity. This protein interacts with LATS1/2, leading to their phosphorylation.[98] The potential therapeutic drugs targeting YAP/TAZ and their working mechanism are summarized in Table 2.

Table 2
Summary of the potential therapeutic drugs targeting YAP/TAZ and their working mechanism.

Participant	Disease/Condition	Mechanism	Remarks	Reference
VGLL4	Gastric Cancer	Competes directly with YAP for binding to TEAD.	Commercially available.	102
	Heart Development	Acetylation of VGLL4 affects its capacity to interact with TEAD.		103
	Osteoblast Differentiation	Competes directly with YAP for binding to TEAD.		105
Verteporfin	Human Tumor	Verteporfin induces levels of cytosolic 14-3-3σ, a protein responsible for YAP's cytoplasmic retention and subsequent proteasomal degradation.	Commercially available.	15
	Pulmonary Hypertension	simultaneous delivery of verteporfin and CB-839 using inhaled PLGA-encapsulated microparticles enhances pulmonary vascular remodeling.		67
	Hypertensive-Renal Injury	It nullified all the kidney damage (such as renal fibrosis, inflammation, albuminuria, etc.) done by Angiotensin II.		109
	Atherosclerosis	Inhibits inflammatory gene expression and macrophage infiltration in mouse arteries.		85
XMU-MP-1	Myocardial Hypertrophy and Ascending Aortic Expansion	It regulates the activity of MST 1/2, which is one of the core components of the Hippo signaling pathway.	Commercially available.	121,122
CA3 (CIL56)	Solid Tumor	It inhibits the YAP-TEAD interaction.	Commercially available.	117
Angiotensin II	Cardiac Fibrosis	It directly promotes YAP activation and increases Ang II-induced fibrosis.	Commercially available.	115
Flufenamic Acid	Breast Cancer	Due to the high affinity to TEAD, flufenamic acid binds strongly with TEAD and inhibits YAP-TEAD activities.	Commercially available.	118
AS-1	Myocardial Hypertrophy	It interacts with LATS1/2 and induces its phosphorylation.	Commercially not available.	97
WWC-derived Protein	Liver Cancer	This protein interacts with LATS1/2 and induces its phosphorylation.	Commercially not available.	98
	Hepatic Cell Differentiation and Tumorigenesis	Loss of WWC protein expression results in liver hypertrophy, inflammation, fibrosis, and carcinoma.		123,124

5. Conclusion and future prospects

The growing global prevalence of CVDs poses a significant health concern, necessitating comprehensive understanding and innovative treatment strategies. This review elucidates the pivotal role of the YAP signaling pathway in both the pathogenesis and progression of various CVDs, emphasizing its potential as a promising therapeutic target. As the incidence of CVDs continues to rise, it becomes increasingly imperative to unravel their complex molecular etiology. The involvement of YAP signaling pathway is evident across diverse CVDs, including myocardial hypertrophy, infarction, atherosclerosis, and cardiac fibrosis. By emphasizing YAP's regulatory mechanisms and intricate interactions with signaling cascades, we underscore its crucial involvement in orchestrating cellular activities relevant to the pathogenesis of CVDs.

Despite the promising advancements in YAP-targeted therapies, there exist several obstacles and prospects that require consideration. A thorough understanding of context-dependent signaling dynamics is essential, given the complexities inherent in YAP regulation and its diverse downstream effectors. This underscores the imperative for personalized therapeutic strategies. Moreover, rigorous validation, and optimization of these strategies, coupled with meticulous evaluation of their safety profiles and long-term outcomes, are indispensable for translating preclinical findings into clinically effective interventions. Most of the newly developed therapeutic drugs targeting YAP have primarily been tested on cancer cells. However, there is only a limited amount of literature addressing their effects on CVDs. Consequently, a significant knowledge gap exists due to the insufficient data to evaluate their efficacy in the context of CVDs. Resolving the challenges associated with the relationship between novel therapeutics and CVDs will require extensive future investigation in this field.

Overall, the YAP/TAZ signaling pathway represents a promising target for understanding the pathogenesis of CVDs and developing innovative therapeutic interventions. Further investigations are necessary to elucidate the precise molecular mechanisms and downstream effectors of YAP/TAZ in different cardiovascular disorders. Expanding our knowledge of YAP/TAZ signaling may pave the way for the development of personalized and effective treatments for various CVDs.

Ethical approval

This study does not contain any studies with human or animal subjects performed by any of the authors.

CRediT authorship contribution statement

Rakibul Islam: Writing – original draft, Conceptualization. **Zhongkui Hong:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Zhongkui Hong reports financial support was provided by Texas Tech University. Zhongkui Hong reports a relationship with National Science Foundation that includes: funding grants. Zhongkui Hong reports a

relationship with National Institutes of Health that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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