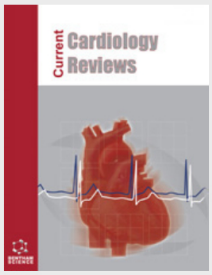

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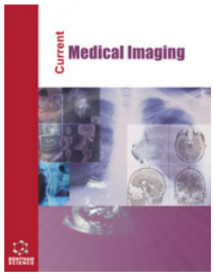

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MINI-REVIEW

Potential Role of Exercise in Regulating YAP and TAZ During Cardiomyocytes Aging

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Abstract: Adaptation of cardiac muscle to regular exercise results in morphological and structural changes known as physiological cardiac hypertrophy, to which the Hippo signaling pathway might have contributed. Two major terminal effectors in the Hippo signaling pathway are Yes-associated protein (YAP) and its homolog transcriptional coactivator with PDZ-binding motif (TAZ). The latest studies have reported the role of YAP and TAZ in different life stages, such as in fetal, neonatal, and adult hearts. Their regulation might involve several mechanisms and effectors. One of the possible coregulators is exercise. Exercise plays a role in cardiomyocyte hypertrophic changes during different stages of life, including in aged hearts. YAP/TAZ signaling pathway has a role in physiological cardiac hypertrophy induced by exercise and is associated with cardiac remodelling. Thus, it can be believed that exercise has roles in activating the signaling pathway of YAP and TAZ in aged cardiomyocytes. However, the studies regarding the roles of YAP and TAZ during cardiomyocyte aging are limited. The primary purpose of this review is to explore the response of cardiovascular aging to exercise *via* signaling pathway of YAP and TAZ.

Keywords: Aging, cardiomyocyte, cardiac hypertrophy, exercise, YAP, TAZ.

1. INTRODUCTION

Adaptation of cardiac muscle to regular exercise results in morphological and structural changes known as physiological cardiac hypertrophy, that is characterized by increased wall thickness and cell sizes without increasing cardiomyocyte numbers [1]. During the process, the Hippo signaling pathway might contribute to physiological cardiac hypertrophy, proliferation**,** and survival [2].

The Hippo signaling pathway or the Salvador/ Warts/ Hippo (SWH) pathway was first found in fruit flies (*Drosophila melanogaster*) in 1930 by identifying genes that, when knocked out, resulted in cancer-like overgrowth [3]. Since 1995, several studies have found several growth-inhibiting genes that influenced each other and finally formed the core of the Hippo signaling pathway [4]. The Hippo signaling pathway is highly conserved from *Drosophila* to mammals [5].

The core components in the Hippo signaling pathway are the upstream kinase MST 1/2 (also known as STK 4/3), with two scaffolding proteins Salvador (SAV) and MOB 1A/1B. These components will activate its downstream kinase LATS 1/2 [6, 7]. Two major terminal effectors in the Hippo signaling pathway are Yes-associated protein (YAP) and its homolog, transcriptional coactivator with PDZ-binding motif (TAZ). Activation of MST 1 and LATS 2 inhibits proliferation, while activation of YAP and TAZ promotes proliferation in many cell types, including cardiomyocytes [8].

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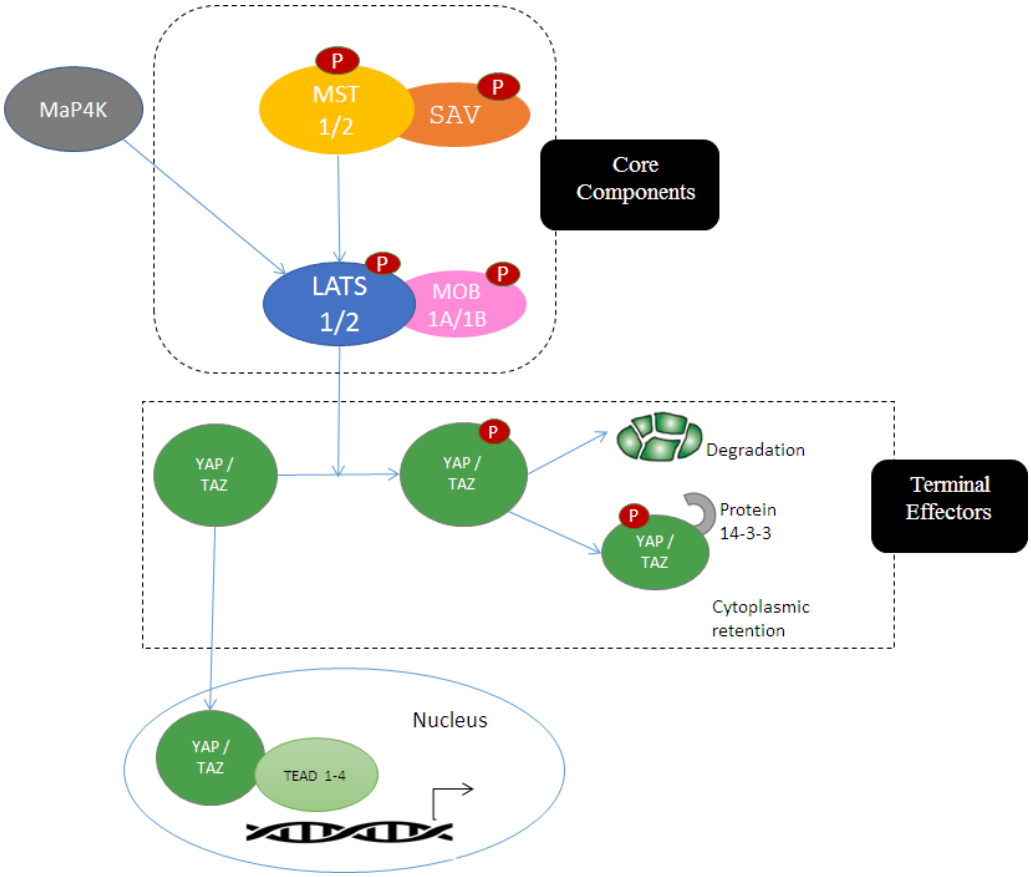

Fig. (1). A Simple schematic for the hippo pathways signaling cascade. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

In 2014, an alternative kinases that can phosphorylate LATS 1/2, namely MAP4K 4/6/7 isoform (Mitogen-activated protein kinase kinase kinase kinase), was reported [9, 10]. Phosphorylated LATS kinases by MST kinases or MAP4K4 then inhibit the transcriptional cofactors YAP and TAZ through phosphorylation of their multiple HXRXXS motifs (S denoting serin phosphorylase) [11, 12]. Phosphorylation of YAP on Ser127 causes YAP to bind to the 14-3-3 proteins in the cytoplasm. This binding sequesters YAP and TAZ in the cytoplasm and prevents transcriptional activity [12]. Additionally, YAP and TAZ can be inhibited and placed near the cellular membrane by Angiomotin protein families (AMOT) [13].

When YAP and TAZ are phosphorylated (at S381 and S311 respectively) by LATS 1/2, casein kinase 1 will further phosphorylate YAP and TAZ to create a phosphodegron motif. These phosphorylation sequences recruit the E3 ubiquitin ligase β-transducin protein, which leads to YAP and TAZ degradation by the proteasome in the cytoplasm [14]. YAP and TAZ as coactivators do not have a DNA binding site. To activate their transcription program, they need to bind with transcription factors, such as TEADs proteins. Unphosphorylated activated YAP and TAZ proteins translocate to the nucleus and interact with TEAD proteins (TEAD 1-4), inducing transcription (Fig. **1**) [15].

The involvement of YAP and TAZ signaling pathways in physiological cardiac hypertrophy might be coregulated by mechanisms and effectors as shown in Fig. (**1**). One of the most likely inducers of physiological cardiac hypertrophy is exercise.

However, there is little information about the regulation of exercise on YAP and TAZ signaling in cardiomyocyte adaptation, especially under the influence of aging. The primary purpose of this review is to explore the response of cardiovascular aging to exercise *via* signaling pathway of YAP and TAZ.

2. REGULATION ON YAP AND TAZ SIGNALING ON CARDIOMYOCYTES IN DIFFERENT STAGES OF LIFE

The mammalian heart consists of cardiomyocytes, forming an important muscular organ that works like a pumping system to distribute around 5 litres of human blood per minute [16]. In post-natal period, cardiomyocyte will lose the ability to proliferate, as shown in both mice and humans [17]. Thus, after that, the heart's growth will be achieved by increased cardiomyocyte size, known as hypertrophy [16]. There is limited information regarding the mechanism that correlates the proliferation, hypertrophy, and physiological adaptation process in cardiomyocytes. One of the possible mechanisms involved in proliferation and growth is the Hippo signaling pathway.

During the fetal period, several studies showed that the Hippo signaling pathway plays an important part in fetal heart growth and maintains its size [18-20]. In the studies by

Von Gise *et al.* and Xin *et al.* deleted YAP in cardiomyocytes resulted in disruption of cardiomyocyte proliferation, creating fatal heart hypoplasia with overly thin myocardium [18, 19]. On the other hand, overexpression of specific activated YAP in cardiomyocyte will increase cardiomyocyte proliferation, bringing forth an overgrowth of cardiomyocytes in mouse models [18]. However, overexpression of YAP in mice also caused bleeding and dramatic myocardial overgrowth, leading to obliteration of the heart chamber and embryonic death [19]. SAV 1, MST 1/2, and LATS 2 gene knockout studies in embryonic mice heart evoked an increase in cardiomyocyte proliferation, expanded trabecular network, and thickening of the ventricular myocardium, which subsequently led to cardiomegaly, with intact cardiac muscle structures and no change in cell size [20, 21].

During the neonatal period, cardiac growth is accomplished by increasing cardiomyocyte sizes, which is known as hypertrophy [16]. The process is well recognized as a shifting model from proliferation to hypertrophy. This shift is associated with a physiological decrease in YAP expression [22]. On the contrary, YAP overexpression is found to expand the neonatal cardiomyocyte cell cycle activities and promote regeneration, and the deletion of cardiomyocyte specified YAP will inhibit neonatal heart regeneration [18, 19].

Table 1. Hippo pathways in age-related cardiomyocyte protection.

No.	Hippo Pathway	Research Subjects	Study Type	Findings	Author, Year
1	YAP, Fetal	SAV cKO, LATS 2 cKO and MST 1/2 cKO mouse hearts	*In vivo*	Hippo pathway has roles in cardiomyocyte proliferation	Heallen *et al.*, 2011 [20]
2	YAP, Fetal, Neonatal	Cultured cardiomyocyte, and intact fetal and neonatal mouse hearts.	*In vitro* and *in vivo*	YAP regulates cardiomyocyte proliferation but not in physiological hypertrophic growth	von Gise *et al.*, 2012 [19]
3	YAP, Adult	Cardiac-specific inactivation of YAP using α-MHC Cre recombinase transgenic mice; transduced cardiomyocytes with YAP1 or LacZ adenovirus	*In vivo*	YAP causes increased cardiomyocyte apoptosis, and YAP expression induces cardiomyocyte hypertrophy	Del Re *et al.*, 2013 [23]
4	YAP, Adult	Cardiac-specific activation of YAP using adeno-associated virus subtype 9 (AAV9) after MI	*In vivo*	YAP improves cardiac function without causing hypertrophy and enhances survival	Lin *et al.*, 2014 [24]
5	YAP, Adult	Transgenic mice	*In vivo*	YAP will increase miR 206 abundantly, as a mediator in silencing FoxP1 in hypertrophy and survival of cardiomyocytes	Yanfei Yang, Dominic P. Del Re, Noritsugu Nakano, Sebastiano Sciarretta, Peiyong Zhai, 2015 [25]
6	YAP, Adult	Transgenic mouse conditionally overexpressing active YAP (YAP5SA)	*In vivo*	YAP induces a proliferative state of cardiomyocytes to induce hyperplasia.	Monroe *et al.*, 2019 [26]
7	YAP, Adult	Eighteen Wistar rats	*In vivo*	Aerobic exercise suppresses B myosin, LATS expression and further suppresses the Hippo pathway leading to a decrease of apoptosis of left ventricular cardiomyocytes	Tabrizi A, Soori R, Choobineh S, Gholipour M., 2020 [27]
8	YAP, Adult	Fourteen male Wistar rats	*In vivo*	Endurance exercise increases YAP expression level and causes cardiomyocyte hypertrophy in healthy rats	Gholipour, M. Tabrizi A., 2019 [28]
9	TAZ, Fetal	Mutant mouse embryos	*In vivo*	TEF 1 has roles in cardiac growth at the embryonic stage	Chen Z, Friedrich GA, Soriano P., 1994 [29]
10	YAP and TAZ, Fetal	Deletion of YAP in the embryonic mouse heart	*In vivo*	IGF activation relates to cardiac growth, shown by the increased number of β-catenin activity	Xin *et al.*, 2011 [18]
11	YAP and TAZ, Neonatal	Neonatal rat cardiac myocytes	*In vivo*	YAP can stimulate the TAZ-activated TBX5-dependent transcriptional complex.	Murakami *et al.*, 2005 [30]
12	LATS, Adult	Eighteen male Wistar rats	*In vivo*	Aerobic exercise training diminishes LATS suppression by reducing the expression of MAP4K, preventing the propagation of apoptosis induced by hypertrophy in the cardiomyocytes	Tabrizi *et al.*, 2019 [31]
13	TEAD	Transgenic Mice expressing HA-tagged TEAD-1 under the control of the muscle creatine kinase (MCK) promoter	*In vivo*	TEAD-1, MyHC protein alters cardiomyocytes	Tsika *et al.*, 2010 [32]

During adulthood, cardiac hypertrophy can occur, whether physiologically or pathologically. Physiological adaptation usually occurs when oxygen demand exceeds its pumping function, such as in exercise or pregnancy [33]. On the other hand, pathological adaptation usually happens in many chronic diseases such as chronic hypertension. Even though the cellular signaling pathway and gene transcription pathway of cardiac hypertrophy differ between physiological and pathological processes, all of them are involved in protein synthesis [34]. Astonishingly protein synthesis in the adult heart is scant. This finding possibly reflects the relatively low turnover cell activity in the adult heart [16]. Monroe *et al.* (2019) reported that overexpression of activated YAP in adult cardiomyocytes led to increased proliferation, resulting in a thicker ventricle wall and elevated heart function. It was also noticed that overexpression of YAP 5SA could return adult cardiomyocytes into fetal cell state by increasing embryonic heart enhancers in the adult heart [26].

Xin *et al.* reported that there were differences in the response of myocardial injury to 4 weeks old wild-type transgenic mice and αMHC-YAPS112A, in which the adult transgenic αMHC-YAPS112A mice showed an elevation in regenerative response after myocardial injury in a similar way to those from the neonatal period, compared with the wild-type littermate control group [35]. Lin *et al.* also reported that activation of heart-specific YAP in adult rat hearts induced cardiomyocyte proliferation, increased heart function, and reduced cell death after myocardial injury [24].

Unlike YAP, TAZ's role in the heart has not yet been vastly studied. However, the combination of TAZ and YAP deletion in the cardiomyocyte will lead to dose-dependent heart failure. This failure is also associated with increased cardiomyocyte proliferation and decreased apoptosis [18]. The TEAD family of transcription factors interacts with YAP and TAZ by binding with N-terminal TEAD binding domain in YAP and TAZ. TEAD 1 loci disruption by retroviral gene trap results in the thinning of ventricular wall formation, widening of pericardial space, bradycardia, and embryonic death [29]. It is highlighted that overexpression of TEAD 1 in the mouse heart will induce cardiomyopathy and heart failure, demonstrating that TEAD 1 plays a significant role in developing a healthy heart [32].

The studies have reported the role of YAP and TAZ on cardiomyocytes in fetal, neonatal, and adults that can be seen in Table **1**. However, the role of YAP and TAZ in aging cardiomyocytes has yet to be determined.

2. POTENTIAL ROLE OF EXERCISE IN REGULATING YAP AND TAZ DURING CARDIOMYOCYTE AGING

Physiological cardiac hypertrophy is a normal response of cardiac muscles to chronic exercise, characterized by enlargement of cardiomyocyte's size [36]. These changes may enhance the function of the heart [27]. However, in many chronic diseases, the heart will undergo pathological hypertrophy, which often correlates with cardiomyocyte loss and heart injury [33, 37]. Excessive sympathetic activity causes pathological hypertrophy and adversely affects the heart, such as hypertrophy, apoptosis, and fibrosis [38]. Pathological hypertrophy-induced heart failure is one of the highest causes of death in the world [32].

It has been shown that regular exercise will have a cardioprotective effects towards heart muscle injuries in a pleiotropic way [31, 39]. It will also inhibit heart muscle fibrosis and cardiomyocyte apoptosis [40]. Several pathways have been known as hypertrophic mediators in the hearts, such as insulin-like growth factor1, thyroid hormone, PI3K (phosphoinositide 3-kinase), Akt, AMP-activated protein kinase and mTOR (mammalian target of rapamycin) pathways, protein kinase C, and mitogen-activated protein kinase signaling [37].

The Hippo pathway has been recognized as a potential key factor in regulating cardiomyocytes [41]. Exercise activates mechanical tension to influence the phosphorylation and activity of the Hippo pathway core kinases, adaptor proteins, and effectors (YAP and TAZ) [13]. Exercise has a role in cardiomyocytes during different stages of life, and YAP and TAZ signaling pathway has a role in exercise. Thus it can be hypothesized that exercise has roles in activating the signaling pathway of YAP and TAZ in cardiomyocytes throughout the different stages of life, including in aged cardiomyocytes.

Exercise in aging induces the activation of AMP-Activated Protein Kinase (AMPK) through the increases in AMP/ATP requirement [42]. AMP-Activated Protein Kinase (AMPK) is the critical sensor of the cellular energy that will act as the negative feedback in energy homeostasis [42]. AMPK activates two pathways, which are LATS dependent and LATS independent pathway. LATS dependent kinases pathway is regulated by AMPK that subsequently phosphorylates YAP and TAZ and increases Hippo pathway LATS 1/2 activities through AMOTL1, creating inhibition of YAP and TAZ (Fig. **2**) [42]. DeRan *et al.* discovered that AMPK phosphorylates AMOTL1 and thus increasing LATS1 activity [43]. Activated AMOTL1 can hinder YAP directly as well as stimulation towards LATS [44]. The latest study considers AMPK as the negative regulator of YAP and TAZ activity [43, 45, 46]. Several conditions that trigger stress such as lack of energy in exercise, dictate phosphorylated YAP activation, especially LATS independent kinases [43]. Mo J.-S *et al.* stated that AMPK directly bound YAP and identified YAP S94 as the primary phosphorylation site [45]. This observation was vital because S94 residue is essential in the YAP-TEAD interactions. It implied that AMPK activation might phosphorylate YAP directly or through the LATS pathway. Wang *et al.* found that AMPKl directly binds YAP and phosphorylated primarily through S61, S94, and T119 residues [46]. Subsequent phosphorylation of YAP and TAZ by AMPK prevents their translocation to the cell nucleus, thereby leading to the inactivation of target genes, some of which are involved in cell proliferation, including cardiac muscle causing cardiac hypertrophy [45, 47]. The inactivation of YAP and TAZ will cause apoptosis and cytoplasmic retention resulting in cardiac degeneration [48]. We hypothesize that in aged cardiac muscle during exercise, these external stimuli may act through the core Hippo pathway kinases (MST 1/2, MAP4K, LATS 1/2) to regulate the activity of YAP, TAZ, and TEAD to promote protein synthesis and cardiac growth.

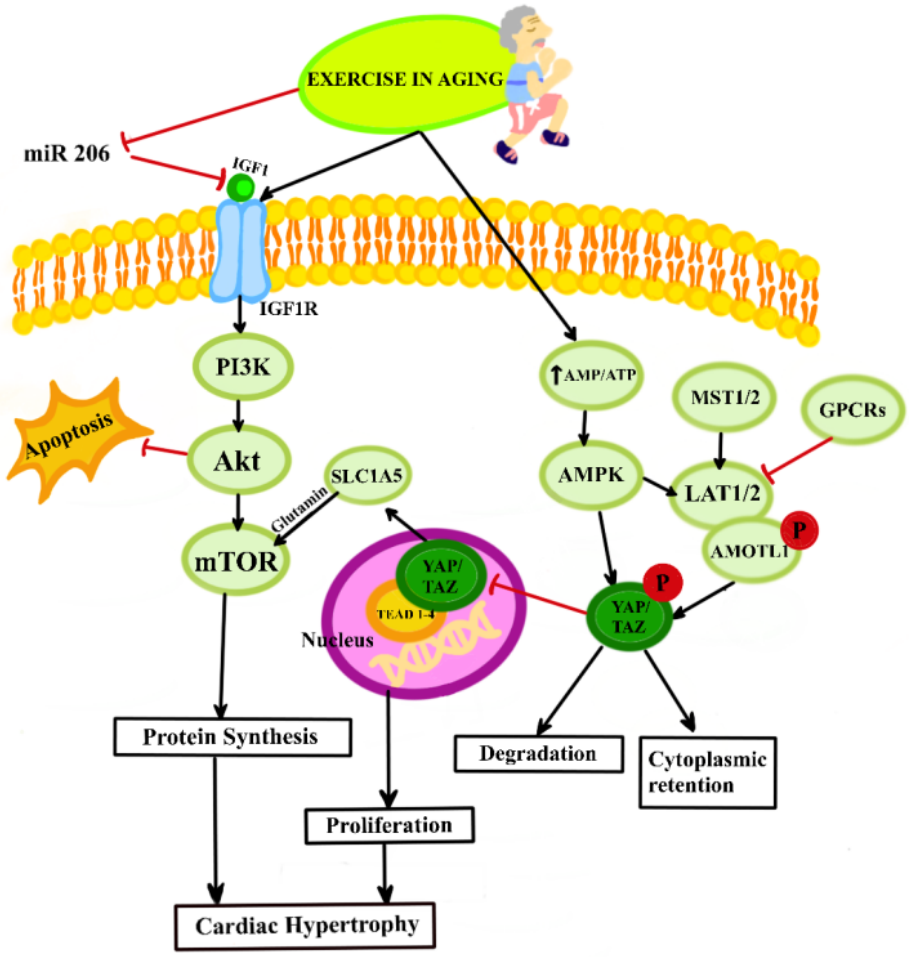

Fig. (2). Schematic showing the regulation of exercise on YAP and TAZ in cardiomyocytes adaptation and aging. Black lines are stimulation, and red lines are inhibition. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

MST was first known as the activating factor of the Hippo kinase cascade and as an early signal to activate LATS in mammals [10, 49]. Today, it is known that the kinases that control LATS activation are not just MST as MST gene elimination does not truly inactivate LATS [50]. The recent studies revealed that, similar to MST, MAP4K also had roles in LATS activation. In cardiomyocytes, MAP4K will activate LATS to inhibit hypertrophy [6]. It can be concluded that MST and MAP4K work synergically in controlling LATS to some extent. Some of the stimuli that can activate the two factors are stress-energy and intracellular density [10]. It was shown that MST gene expression induces an increase in cardiomyocyte apoptosis [23].

LATS is one of the central signaling components known for cell proliferation inhibition and cell apoptosis [51] and also known as the primary mediator and controller in the kinase cascade. LATS downregulation will lead to YAP activation that provokes higher tumorigenesis in rat models [50]. In the heart, LATS controls cardiomyocyte response, including hypertrophy, apoptosis, and autophagy [32]. As a response to injury, the heart will phosphorylate LATS through activation of MST, which stimulates cardiomyocyte apoptosis. On the other hand, inhibition of LATS will lead to cellular hypertrophy [52]. By inactivating MST and LATS, Lin *et al.* in 2014 noticed an elevation in the heart's size [24]. Similar results were found in another study, where LATS gene knockout in adults led to cardiomyocyte proliferation [52].

Elevated YAP expression may lead to cardiomyocyte hypertrophy, according to some studies [23, 53]. Meanwhile, in heart failure cases, an elevation in YAP regulation will lead to cardiomyocyte proliferation [52, 54].

Some studies have shown a correlation between aerobic exercise and left ventricular hypertrophy [10, 55]. Other studies also showed that a lot of pathways stimulated by exercise might have contributed to the Hippo pathway regulation [7, 55]. Elster *et al.* showed exercise also increases the proliferation of fibroblast in myocardial infarct through the Hippo pathway [44]. Thus, it can be hypothesized that exercise regulates YAP as Hippo pathway components and YAP acts as a mediator in exercise adaptation [56].

Numerous molecular mechanisms explaining cardiomyocyte hypertrophy in aged hearts showed similar intracellular mechanisms resulting in pathological changes happening in hypertensive heart diseases and heart failures [57]. Combination of both chronically stimulated neurohor-

monal system, such as adrenergic, endothelin, and renin-angiotensin-aldosterone; and increased workload, plus biomechanical stretch at the remaining cardiomyocyte, can stimulate some growth factor pathway, such as mitogen-activated protein kinases, histone deacetylase, calcineurin / activated T cell factor, and insulin-like growth factor-I (IGFI) –phosphatidylinositol 3-kinase (PI3K) – Akt – mTOR pathway [34], A lot of these pathways still need to be determined, whether the aging process directly regulates them, or only relatively contribute to the cardiac hypertrophy [58].

Several hypertrophy mechanisms are highly relevant to those of the aged heart. Unlike young animals, where aerobic exercise usually ends with several stages of hypertrophy, old animal projects showed vast variability in the heart growth response. In many of the studies, aerobic exercise could reverse aged-based hypertrophy [58-61].

Several studies show that physical exercise and age are two essential factors in modulating the phenotype of exercise-mediated aged heart. However, the diversity of the results of these studies leads to the unclear molecular mechanism of exercise-mediated cardiac growth between young and older hearts. For example, a study with older animals given higher intensity training protocols showed repressed age-related heart hypertrophy [61]. It is hypothesized that the cytoprotective effect of exercise will lengthen old cardiomyocyte lives *via* inhibition of reactive pathological hypertrophy, as the study showed decreasing of apoptotic index in older heart rats [58-60]. Since the caspase proapoptotic pathway can directly induce pathological cardiomyocyte growth in adults, the result of this study suggests an alternative mechanism for inhibiting physical activity-induced apoptotic pathways, which in the end, may inhibit the pathological growth of elder hearts [62]. However, whether these changes will result in lower cell death rates and decreased pathological growth is yet to be determined.

IGF-1/PI3K/Akt pathway might correlate with the cardioprotective effect that could potentially lengthen aged cardiomyocyte lives. Cardiac IGF-1 overexpression, PI3K, and Akt1 were all proven to lengthen cardiomyocytes living in TAC (Transverse Aortic Constriction) exposed adult cardiomyocyte, or ischemic cardiomyocyte [63]. Several studies showed that aerobic exercise increased Akt phosphorylation in elder rat's hearts to which are described as follows [60, 64, 65]. Lai C.H, *et al.* studied ten 3-month-old rats, ten 12-month-old rats, and six 18-month-old rats. Each age group was divided into two groups: controlled aged rats and exercise aged rats. The aim of this study was to find a correlation between apoptotic and survival pathways of IGF1, IGF1R, PI3K, and Akt. The results showed that there were no significant level changes in IGF1, IGF1R, and PI3K signals. However, Akt levels were significantly lower in the exercise group [60]. Iemitsu M. *et al.* studied three groups of rats: young sedentary, old sedentary group, and old with exercise (8 weeks of swimming) group. The results showed that the old exercise group had the highest Akt phosphorylation and Akt phosphorylation to Akt ratio compared to the young sedentary group. The old sedentary group had the lowest result [64]. Lin C.H *et al.* studied four groups of rats for 4 weeks: control, exercise, resveratrol treatment, exercise and resveratrol treated. Results showed that appropriate exercise would increase the PI3K-Akt pathway through protein analysis [65]. All these studies showed that aerobic exercise could lower Akt levels. This could explain that the probability of the restored Akt level of activity in elder hearts was enough to increase cell longevity and decrease pathological growth but not enough to develop physiological growth [61].

The diversity of exercise-induced heart growth responses between young and elder animals might result from a difference in substance between the two, with constitutively activated apoptotic hypertrophy and pathological pathways. In one of the studies, though the exact mechanism is unknown, Akt signal might inhibit mitogen kinases that led to pathological heart hypertrophy, which may directly suppress pathological growth in elder hearts [66].

Besides the Akt signal, it is essential to notice that exercise also modulates other growth that may be relevant to aging hearts. A study using acute treadmill exercise showed stimulation of neuregulin in skeletal muscle, which had an anti-apoptotic effect on cardiomyocytes through end tyrosine kinase and PI3K/ Akt [67]. A different study showed that exercise could also decrease skeletal muscle and heart myostatin in humans with pathological hypertrophy [68]. Even though the exact role of myostatin and its closest homolog growth differentiation factor 11 (GDF 11) are yet to be established, they may have a function with Akt. Myostatin can promote cardiomyocyte growth through Akt activation as shown *in vitro* study [69].

Even though pathological and physiological pathways are overlapping pathways and crosstalk are exhibited and exposed in Fig. (**2**). For instance, while activated calcineurin/ core factor of T cell contributes to pathological hypertrophy, in other cases, calcineurin also mediates cardioprotective effect in some physiological growth [70]. Exercise may contribute to these dynamically controlled different signalling pathways, which also correlate with age-related cardiomyocyte hypertrophy. However, the exact contribution still needs to be explored.

Several studies correlate GPCRs with Hippo signaling pathways [42, 71-73]. Adrenaline/epinephrine suppresses YAP and TAZ through GPCRs synergically with GαS and protein kinase A [71]. GPCRs may indirectly inhibit LATS 1/2 as well, but the exact mechanism is unclear (Fig. **2**) [42]. On the other hand, angiotensin II and other ligand signals activate YAP and TAZ through GPCRs Gα 12/ 13 and Gαq/11 [72]. Other transduction signal that mediates physiological heart hypertrophy is the IGF 1 - PI3K - Akt pathway. Meanwhile, pathological hypertrophy is mediated by the Gαq pathway and activated by Ang II/ Angiotensin II, ET1/ Endothelin I, and catecholamine. Pathological hypertrophy also correlates with an increase in PI3K, MAPK, PKC, PKD, and calcineurin [74].

These results form the basis for further study to determine whether GPCRs – Hippo signaling pathways are involved in mediating the adaptation process of cardiac hypertrophy [74].

An interesting concept is that these inhibitions of pathological hypertrophic changes in cardiac muscle may involve YAP and TAZ. However, the optimal type, duration, and

intensity of the exercise that will trigger the best cardiac muscle adaptation process in aging mammals are yet to be determined. The process may potentially also involve optimal adaptation *via* autophagy and activation of growth factor, as has been shown by Gunadi *et al*. in their research [75].

CONCLUSION

Adaptation of cardiac muscle to regular exercise will lead to morphological and structural changes known as physiological cardiac hypertrophy, in which the Hippo signaling pathway may contribute to cardiomyocyte hypertrophy, proliferation**,** and survivals. Several studies have reported the role of YAP and TAZ on cardiomyocytes in fetal, neonatal, and adult periods, however, the role of YAP and TAZ in aged cardiomyocytes has yet to be determined.

The aged heart might undergo pathological hypertrophy, but these changes may be reversible and potentially modified by regular exercise. The role of exercise in stimulating YAP and TAZ signaling might induce a beneficial or pathological response, but it still unclear whether YAP and TAZ is involved in physiological or pathological adaption in exercise. As different intensities of exercise might have different effects on cardiac hypertrophy, Hippo pathway might also be influenced differently. High intensity of exercise might induce cardiac hypertrophy accompanied by myofiber disarray and fibrosis.

We hope this review can trigger other researchers and practitioners to conduct studies on the tailor-made intensity, duration, and type of exercise for the elderly to determine the characteristic of such exercise that cause physiological or delayed pathological cardiac hypertrophy. So that people could find a better way to exercise to achieve a better quality of life during aging process.

LIST OF ABBREVIATIONS

ACE I/D	=	Angiotensin-converting enzyme I/D
αMHC	=	Alpha-Myosin Heavy Chain (MYH6)
Akt	=	Protein Kinase B
AMOT	=	Angiomotin protein families
AMOTL 1	=	Angiomotin like 1
AMOTL 2	=	Angiomotin like 2
AMP	=	Adenosine Monophosphate
AMPK	=	AMP-Activated Protein Kinase
ATG 5	=	Autophagy-Related Gene 5
ATP	=	Adenosine Triphosphate
ATPase	=	Adenosine Triphosphatase
Bag3	=	Bcl2-associated athanogene 3
cKO	=	Conditional Knockout
DNA	=	Deoxyribonucleic Acid
GDF 11	=	Growth Differentiation Factor 11
GPCR	=	G-Protein-Coupled Receptors
HPO	=	Hippo
IGF-1	=	Insulin-like Growth Factor-1
LATS 1/2	=	Large Tumor Suppressor 1 and 2
MAPK	=	Mitogen-Activated Protein Kinases
MAP4K 4/6/7	=	Mitogen-activated protein kinase kinase kinase kinase 4,6 and 7
Mats	=	Mob as a tumor suppressor
MOB1A/1B	=	Mps one binder kinase activator-like 1A/1B
miR-206	=	micro RNA 206
mRNA	=	messenger RNA
MST 1/2	=	Mammalian STE-20 kinase 1 and 2
mTOR	=	Mammalian Target of Rapamycin
PKC	=	*Protein Kinase C*
PKD	=	*Protein Kinase D*
RAS	=	*Reticular Activating System*
ROS	=	Reactive Oxygen Species
SAV	=	Salvador
SLC1A5	=	Solute carrier family 1A5
SWH	=	Salvador/ Warts/ Hippo
TAC	=	Transverse Aortic Constriction
TAZ	=	Transcriptional coactivator with PDZ-binding motif
TEAD	=	TEA Domain
TEF	=	Transcription Enhancer Factor
WW45	=	WW Domain-Containing Adaptor 45
YAP	=	Yes-Associated Protein

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

None.

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