Regulation of Myocardial Cell Growth and Death by the Hippo Pathway

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Stress in the heart causes loss of cardiomyocytes (CMs), the accumulation of which leads to heart failure, a major cause of clinical mortality. The improvement of CM survival and facilitation of CM regeneration are major goals in treatment for heart failure. The Hippo pathway is an evolutionarily conserved signaling mechanism that regulates organ size by controlling both apoptosis and cell proliferation. The main components of the Hippo pathway, including Mst1/2, Lats1/2 and Yes-associated protein (Yap), are present in the mammalian heart and play an important role in regulating the growth and death of CMs. Recent research in the cardiac field has demonstrated that Yap, a key downstream transcriptional cofactor in the Hippo signaling pathway, plays a crucial role in regulating survival and proliferation/hypertrophy of CMs. Increasing lines of evidence suggest that Yap promotes regeneration of the heart after myocardial infarction. In this review, we summarize the current knowledge regarding the roles and functions of the Hippo pathway in the heart, with a particular emphasis on the role of Yap in regulating growth and death of CMs. (*Circ J* 2016; **80**: 1511–1519)

Key Words: Apoptosis; Cardiac hypertrophy; Hippo signaling; Signal transduction; Yap

Hearth failure (HF) is a critical risk factor for cardiac death, which is a major cause of human mortality in developed countries.^{1,2} Cardiac stress, including myocardial ischemia-reperfusion (IR) and high blood pressure, promotes the death of cardiomyocytes (CMs), resulting in decreases in the total number of CMs and cardiac dysfunction. Among the signaling mechanisms regulating the death of CMs, the Hippo signaling pathway plays an important role in the progression of HF by regulating growth and death of CMs.^{3–5} This pathway, originally identified in *Drosophila*, is evolutionarily conserved from *Drosophila* to mammals,⁶ and generally serves as a key regulator of organ size, a function that is mediated through regulation of both apoptosis and cell proliferation.

A major function of the Hippo pathway is mediated through the Yes-associated protein (Yap), a transcription cofactor. Activation of the Hippo pathway promotes phosphorylation and consequent inactivation of Yap, thereby leading to cell apoptosis. In contrast, Yap activation leads to suppression of cell apoptosis and enhances cell survival and proliferation. Recent studies demonstrate that Yap plays a critical role not only in cardiac development but also in the control of cardiac function in the postnatal/adult heart.^{4,7–10} The fact that the presence of endogenous Yap is critical also in the adult heart⁴ is interesting because Yap induces cell proliferation in other cell types, whereas adult CMs do not proliferate efficiently. This review provides an overview of current findings about the role and the function of the Hippo-Yap pathway in the heart, with a particular emphasis on the role of Yap in medi-

ating survival and growth of CMs in the postnatal heart and the underlying signaling mechanisms mediating the function of Yap.

Hippo Pathway Overview

Components of the Hippo pathway were identified in *Drosophila* by genetic screens in 1995. Two studies demonstrated that genetic deletion of Warts (wts) leads to a phenotype of tissue overgrowth in *Drosophila*.^{11,12} Subsequently, many studies have revealed that core components of the Hippo pathway are highly conserved in mammals (**Table**). **Figure 1** shows a schematic representation of the Hippo pathway. Main components of the mammalian Hippo pathway include mammalian sterile 20-like kinase 1 and 2 (Mst1/2), large tumor suppressor 1 and 2 (Lats1/2), the scaffold protein Salvador (Sav, also known as WW domain-containing adaptor 45, or WW45), Mps one binder 1A and B (Mob1A/B), and Yap 1 (Yap)/transcriptional coactivator with PDZ-binding motif (Taz), which are the mammalian orthologs of *Drosophila* hpo, wts, sav, mats, and yki, respectively.

Mst1/2 physically interacts with Sav1 and phosphorylates and activates Lats1/2. Recent evidence suggests that MAP4K family kinases act in parallel to Mst1/2 in HEK293A cells.¹³ However, the relative importance in CMs of MAP4Ks over Mst1/2 for activation of Lats1/2 and suppression of Yap/Taz remains unknown. Lats1/2 phosphorylate and inactivate the transcriptional cofactor Yap by inducing its cytoplasmic translocation through 14-3-3 proteins and degradation through the

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Table. Components of the Hippo Pathway in Mammals and <i>Drosophila</i>			
Mammalian		<i>Drosophila</i>	
MST 1/2	Mammalian sterile 20-like kinase 1/2	Hpo	Hippo
LATS 1/2	Large tumor suppressor kinase 1/2	Wts	Warts
MOB 1A/1B	Mps one binder kinase activator-like 1A/1B	Mats	Mob as tumor suppressor
WW45/SAV 1	Salvador homolog	Sav	Salvador
Yap	Yes-associated protein	Yki	Yorkie
Taz	Transcriptional coactivator with PDZ-binding motif		
TEAD 1–4	TEA domain family member 1–4	Sd	Scalloped

ubiquitin proteasome system.¹⁴ When the Hippo pathway is inactivated, Yap translocates to the nucleus and interacts with multiple transcription factors, including the TEAD/TEF family transcription factors.^{15–18} The activity of Yap as a transcription cofactor is determined primarily by the level of Yap in the nucleus. In addition, vestigial-like family member 4 (VGLL4), a mammalian ortholog of Tondu-domain-containing growth inhibitor (Tgi), competes with Yap for TEAD binding,^{19,20} thereby serving as an endogenous inhibitor of Yap. TEAD regulates expression of genes involved in cell survival, proliferation, and metabolism, including connective tissue growth factor, cysteine-rich angio-

genic inducer 61 (CYR61), axl receptor tyrosine kinase (AXL), amphiregulin (AREG), Myc, survivin (BIRC5) and angiomin-like protein 2 (AMOTL2).^{21–25} The Yap-TEAD complex also recruits the NuRD transcriptional corepressor complex, thereby repressing target genes, including tumor-suppressor genes, such as DNA-damage-inducible transcript 4 (DDIT4) and TNF-related apoptosis-inducing ligand (Trail).²⁶ Yap also interacts with myocardin-related transcription factor A (MRTA), a transcription cofactor, in response to sphingosine-1-phosphate, thereby positively regulating transcription of CYR61 through cooperative actions between the Yap-TEAD pathway and the MRTA-serum response factor pathway.²⁷

Yap also interacts with other transcription factors, including TBX5,^{28,29} Smads,^{30–35} p63,^{36,37} p73,^{38–40} ErbB4,⁴¹ FoxO1,⁴² FOXM1,⁴³ Runx1/2,^{44–49} HIF1 α/β ,^{50,51} KLF5,^{52,53} Fos,⁵⁴ EGR1,^{55,56} C/EBP α ,⁵⁷ CREB,⁵⁸ OCT4,⁵⁹ GLI,⁶⁰ TTF-1,⁶¹ Pax3,⁶² Pax8,⁶³ PPAR γ ⁴⁵ and MyoD,⁶⁴ thereby regulating a wide variety of genes (Figure 2).

In the adult heart, weak basal Mst1/2 and Lats1/2 activity allows only modest nuclear accumulation of Yap at baseline conditions.⁸ This poses the question of when and how Yap is activated in the adult heart. Because Mst1/2 and Lats1/2 are further activated by stress, it is important to know when these upstream kinases are inactivated in the heart. How the activity of Yap is regulated in CMs is poorly understood. Importantly, Yap can be regulated by upstream signaling mechanisms not traditionally included in the Hippo pathway. For example, mechanical forces, stiffness of extracellular matrixes, cell-cell contact, and cell adhesion regulate Yap through cellular tension, RhoA, and actin dynamics.^{65–68} Agonists for G protein-coupled receptors also regulate Yap through similar mechanisms.⁶⁹ In addition, it has recently been shown α -catenin negatively regulates Yap,⁷⁰ while S1P positively regulates Yap in CMs.⁴

There are many structural similarities between Yap and Taz (Figure 3). Although Yap cardiac-specific knockout (cKO) mice exhibit a significant cardiac phenotype,⁴ Taz cKO mice⁷¹ exhibit a normal cardiac phenotype and their survival curve appears identical to that of wild-type mice. Thus, it is possible that Yap can compensate for the loss of Taz but that Taz may not compensate for the loss of Yap. However, double cKO of Yap and Taz worsens the survival rate compared with Taz cKO and Yap cKO, suggesting that Yap and Taz also have non-overlapping functions.⁷¹ Alternatively, suppression of either Yap or Taz alone may not be sufficient to completely block their common downstream targets in the heart.

Hippo Pathway in Heart Development

The mammalian heart is the first organ formed during development. The heart-forming process from mesodermal tissues is precisely programmed and consists of forming a heart tube and heart loop architecture, which then progresses to 4-chamber components and an outflow tract. The molecular mechanisms regulating mammalian heart development remain to be

fully elucidated. However, it is known that the Hippo pathway plays a crucial role in regulating cardiac development. Mouse models of embryonic deletion of Sav1, Mst1/2 or Lats2 exhibit similar hyperplastic phenotypes with thickened ventricular walls. These mice die at early postnatal stages, with obvious heart enlargement.⁷² Interestingly, the Hippo pathway restrains CM proliferation and heart size by inhibiting Yap/Taz and the Wnt pathway during the development of the heart (Figure 4). Yap/Taz interacts with Tbx5, a key transcriptional factor regulating embryonic heart development.²⁸ Yap inactivation during development leads to cardiac hypoplasia, causing lethality.⁷ Gain-of-function of Yap during development stimulates CM

proliferation and enhances ventricular hypertrabeculation. Several genes containing the TEAD-binding MCAT motif are regulated by Yap.⁸ The MCAT motifs are located in the promoter-enhancer regions of muscle-specific genes, such as cardiac troponin T, β -myosin heavy chain, smooth muscle α -actin, and skeletal α -actin. TEADs play a crucial role in the regulation of these genes during development.⁷³ TEAD1 disruption leads to heart defects and embryonic lethality in mice.⁷⁴ On the other hand, TEAD1 overexpression in the postnatal mouse heart upregulates the fetal-type gene program and induces age-dependent dysfunction.⁷⁵ These findings suggest that Yap-TEAD interaction is necessary for embryonic heart growth

and that the appropriate control of Yap is necessary for the well-organized development of the heart. Interestingly, the heart size is normal in β -MHC-YapS112A transgenic mice, in which the transgene is expressed from E9, with decreases in CM size accompanied by increases in cell numbers.⁷ Taken together, the data suggest that Yap has several roles at each stage of heart development. These findings demonstrate the critical role of the Hippo pathway during cardiogenesis and suggest that appropriate levels of Yap activity are required for proper heart development.

Myocardial Infarction/Ischemia-Reperfusion

Loss of CMs is an important mechanism facilitating the development of HF.⁷⁶ Mst1 is activated by pro-apoptotic stimuli and contributes to programmed cell death in cancer cell lines.^{77–81} Mst1 is one of the most strongly activated protein kinases, detected by in-gel myelin basic protein kinase assays, when CMs die by apoptosis.³ Cardiac-specific overexpression of Mst1 in transgenic mice induces elevated caspase activation and CM apoptosis, leading to dilated cardiomyopathy and premature death.³ Cardiac-specific overexpression of DN-Mst1 in mice protects the heart against IR injury and post-myocardial infarction (MI) cardiac remodeling.³

The Hippo pathway is highly compartmentalized in CMs. For example, IR activates Mst1 through a K-Ras-Rassf1A-dependent mechanism in mitochondria, where Mst1 stimulates the mitochondrial mechanism of apoptosis by phosphorylating Bcl-xL.⁸² Mst1 activated through currently unknown mechanisms also phosphorylates Beclin 1 in the endoplasmic reticulum, thereby inhibiting autophagy.⁸³ Because neither induction of apoptosis nor suppression of autophagy by these pathways requires either Lats2 or Yap, we have designated these as “non-canonical Hippo pathways”. Cardiac stress also activates Mst1 and Lats2 through an NF2-dependent mechanism in the nucleus, where Lats2 induces nuclear exit of Yap (Matsuda et al, unpublished data). This pathway utilizes many components of the Hippo pathway, from NF2 to Yap, and, thus, it is designated as the “canonical Hippo pathway”. Activation of the canonical Hippo pathway leads to stimulation of cell death and inhibition of compensatory hypertrophy by inhibiting Yap.^{4,10,42} Thus, depending upon the type of stress, Mst1 is activated in different subcellular spaces and mediates CM apoptosis through different mechanisms. Because the Hippo pathway in each subcellular compartment is activated by distinct mechanisms and targets distinct substrates, it is important to further clarify the specific molecular targets (cellular functions) regulated by the Hippo pathway in each subcellular compartment. Therapeutically, suppression of Mst1 may allow inhibition of Mst1 in multiple cellular compartments, thereby inhibiting the pro-apoptotic effects of Mst1 altogether.

Activation of the canonical Hippo pathway causes nuclear exit and downregulation of Yap.⁸⁴ Deletion of Yap in the heart with *tnnt-Cre*, which allows downregulation of Yap during the fetal stage, causes lethal cardiac hypoplasia with low proliferative ability. In this model, the mice did not show significant differences in CM apoptosis.⁸ Interestingly, primarily postnatal deletion of Yap with α MHC-Cre induces robust increases in CM apoptosis, thereby inducing cardiomyopathy with premature death.⁴ Furthermore, a study using cardiac-specific Yap heterozygous KO mice generated with α MHC-Cre demonstrated significant increases in apoptosis after MI in adult mice.⁴ These findings suggest that endogenous Yap (manifested by loss-of-function studies) may have distinct roles in the heart before and after birth, namely, that it primarily

affects cell proliferation during the fetal stage, but cell survival in the postnatal stage. Transgenic expression of activated Yap exhibited cardioprotective effects after MI.⁹ Similar findings were observed in *Sav1* cKO mice, in which endogenous Yap is activated, after MI.⁸⁵ In these models, increased proliferation of CMs was also observed in the heart. The relative importance of the pro-survival effect and cell-proliferative effects of overexpressed Yap in mediating cardioprotection in the post-MI heart remains to be clarified.

What is the downstream molecular mechanism mediating the pro-survival effects of Yap in the postnatal heart? At least 3 mechanisms are involved. First, Yap binds to FoxOs in the nucleus and promotes transcription of antioxidant genes, including catalase and manganese superoxide dismutase (MnSOD).⁴² Second, Yap promotes expression of miR-206 through stimulation of E-box binding transcription factors. miR-206 in turn suppresses forkhead box P1 (FoxP1), a transcription factor that promotes death of CMs.¹⁰ Third, Yap promotes activation of Akt, a serine/threonine kinase that promotes cell survival, through unknown mechanisms stimulating PI3K.⁴⁹ The importance of each mechanism may differ depending upon the type of stress.

Hypertrophy

The Hippo pathway controls organ size by affecting both cell death and proliferation. An interesting question is whether activation and inactivation of the Hippo pathway affects the size of the adult mammalian heart, in which growth is regulated primarily by hypertrophy rather than proliferation.

Overexpression of Mst1 in the mouse heart induces chamber dilation and wall thinning of the left ventricle because of increased cell death. According to Laplace's law, dilation of the left ventricle with wall thinning increases wall stress,⁸⁶ which normally stimulates hypertrophy as a compensatory mechanism in order to normalize the wall stress. However, mice with cardiac overexpression of Mst1 (Tg-Mst1) generated on the C57BL/6 background do not show significant increases in left ventricular weight/tibial length ratio at 3 months of age, and the longitudinal length of CMs isolated from the left ventricle is even smaller in Tg-Mst1 mice than in control mice, suggesting that compensatory hypertrophy is attenuated.³ We speculate that this contributes to the progressive deterioration of cardiac function in Tg-Mst1 mice, because the elevated wall stress increases oxygen consumption and cell death. Transgenic mice with cardiac-specific overexpression of Lats2 also exhibit a dilated cardiomyopathy phenotype without cardiac hypertrophy that is similar to that of Tg-Mst1 mice.⁵ These results suggest that activation of the upstream kinases of the Hippo pathway negatively regulates cardiac hypertrophy. It would be interesting to test whether Mst1 and Lats2 also inhibit physiological hypertrophy, such as that induced by exercise.

Suppression of the upstream Hippo kinases alleviates Ser127 phosphorylation of Yap, thereby inducing nuclear accumulation of Yap. Overexpression of DN-Mst1 does not show any significant effect on cardiac function, chamber size or cardiac hypertrophy at baseline.³ However, α -MHC-specific Tg-DN-LATS2 mice show modest cardiac hypertrophy.⁵ In addition, human hypertrophic cardiomyopathy patients showed Yap activation in the heart.⁸⁷ These results are consistent with the notion that inhibition of the Hippo pathway and activation of Yap may induce cardiac hypertrophy.

Interestingly, however, in both inducible cardiac-specific *Lats1/2* KO mice and inducible cardiac-specific *sav1* KO

mice, the adult heart shows increases in CM proliferation but decreases in cardiac hypertrophy.⁸⁵ Similarly, miR-302/367 induces Yap activation through suppression of the core components of the Hippo pathways, thereby increasing cardiac proliferation in the adult heart. Importantly, these mice do not show cardiac hypertrophy.⁸⁸ Thus, how suppression of the Hippo pathway affects the growth of the adult heart appears to be context-dependent even though the different interventions commonly stimulate Yap. It is possible that the extent of Yap activation may differ among different interventions. Furthermore, Mst1, Lats1 and Lats2 may have additional targets besides Yap. As we discuss later, the different interventions may allow Yap to interact with distinct transcription factors, such as TEAD and E-box binding transcription factors. Interestingly, regardless of the mode of cell growth, namely hypertrophy or proliferation, the adult mouse heart does not show obvious organ enlargement in response to inhibition of the Hippo pathway, a property that is distinct from that observed in several organs in *Drosophila*, mammalian liver, and the fetal heart, possibly because CM proliferation is inefficient in the adult heart.

It should be noted that although heterozygous Yap cKO mice have no obvious phenotype at baseline, they develop more severe cardiac dysfunction and dilation after MI.⁴ Despite cardiac dysfunction and increases in the left ventricular wall stress caused by cardiac dilation, heterozygous Yap cKO mice do not exhibit enhancement of cardiac hypertrophy compared with wild-type mice, indicating that compensatory hypertrophy is suppressed when endogenous Yap is down-regulated.

Although the role of Yap in cardiac hypertrophy is complex, we propose the following hypothesis. A certain level of Yap is required for compensatory hypertrophy in the presence of stress. Thus, loss of Yap function causes insufficient cardiac hypertrophy in response to stress, which leads to exacerbation of cardiac dysfunction. Overactivation of Yap, however, induces CM proliferation rather than hypertrophy. What is the underlying mechanism of the apparently dose-dependent function of Yap? Yap may regulate either hypertrophy or proliferation depending upon how it couples to downstream signaling mechanisms. For example, miR-206 mediates Yap-induced cardiac hypertrophy by downregulating FoxP1.¹⁰ On the other hand, TEAD mediates proliferation rather than hypertrophy. In fact, overexpression of TEAD1 in the mouse heart rather inhibits hypertrophy.⁷⁴ It is also possible that cross-talk between Yap and other signaling pathways regulating cell growth, such as Wnt^{7,57,72,89–91} and mTOR,^{92–94} may determine how Yap affects hypertrophy and proliferation of CMs under given conditions.

Hippo Pathway in Heart Regeneration

A low level of CM turnover is observed in the adult mammalian heart because of proliferation of existing CMs.^{95,96} Regeneration of damaged hearts may take place also through CM differentiation of cardiac stem cells.^{97,98} However, the adult mammalian heart obviously has insufficient ability to regenerate following injury,⁹⁹ and the loss of CMs in response to stress leads to the development of HF.¹⁰⁰ The Hippo pathway is known to play an important role in the regulation of tissue repair and regeneration in some organs. In particular, Yap promotes the ability to self-renew and differentiate in embryonic stem cells,¹⁰¹ satellite muscle cells¹⁰² and liver cells.¹⁰³

Increased expression of Yap in the heart induces CM proliferation⁵ and protects against MI in mice.⁷¹ Activation of

endogenous Yap in the adult heart in Hippo-deficient mice, such as cardiac-specific Sav 1 KO and cardiac-specific Lats1/2 KO, also protects against MI.⁸⁵ Conversely, cardiac-specific deletion of Yap decreases CM proliferation after MI.⁸ In a mouse model of MI, Yap-positive CMs are observed in the peri-infarct area 3–5 days after initiation of MI. Because the Yap cKO mice had a larger scar area and developed more severe cardiac dysfunction, we speculate that Yap-positive CMs have salutary functions in the post-MI heart. Although the mechanism responsible for the greater infarct area in Yap cKO mice is currently unknown, endogenous Yap inhibits CM apoptosis and promotes CM proliferation in the peri-infarct area, thereby preventing expansion of MI.^{4,71} Thus, endogenous Yap appears necessary for the post-MI recovery process. The mechanism by which Yap is upregulated in CMs in the peri-infarct area is currently unknown. Likewise, whether Yap-positive CMs originate from resident CMs or progenitor cells remains to be clarified. Hippo deficiency also enhances cardiac regeneration after cardiac apex resection and MI at postnatal day 8.⁸⁵ Further investigation is required to clarify whether the cardiac regeneration and functional recovery caused by Yap really achieves long-term functional recovery in post-MI hearts.

Conclusions

Increasing lines of evidence suggest that the Hippo pathway plays a critical role in regulating growth and death of CMs at the cell level, and myocardial injury after IR and the progression of HF in the heart at the organ level. Although the functional involvement of the Hippo pathway in cardiac pathology has become increasingly clear, many unanswered questions remain. These include but are not limited to the following. First, how is the activity of Yap regulated during cardiac hypertrophy and HF and what are the upstream signaling mechanisms? Although nuclear accumulation of Yap is inhibited in CMs at baseline, it can be induced in response to stress despite the fact that the Hippo pathway is generally activated by stress and inhibits the nuclear localization of Yap. Elucidating both Hippo pathway-dependent and -independent mechanisms regulating the nuclear localization of Yap in CMs is important. Second, is stimulation of CM proliferation by Yap really beneficial? Although a gain of Yap function promotes myocardial regeneration in the post-MI heart,^{9,71,85,88} its long-term effects and its effects in response to other types of stress, such as pressure overload, remain to be shown. Third, activation of Yap is observed in human patients with hypertrophic cardiomyopathy.⁸⁷ In this condition, does inhibition of Yap ameliorate the progression of cardiomyopathy? Because Yap is involved in tumorigenesis, small molecule inhibitors of Yap are being developed.^{17,104–107} Whether inhibition of Yap alleviates cardiomyopathic growth remains to be tested. Fourth, Yap both positively and negatively regulates the activity of transcription factors. Thus, which transcription factor mediates the function of Yap in the heart during a given stress remains to be elucidated. Elucidating the detailed downstream signaling mechanisms of Yap may allow for the development of efficient treatments to protect the heart from stress. Fifth, the Hippo pathway may possess distinct functions in different cell types.^{69,108} The function of the Hippo pathway and Yap in the non-myocyte population in the heart remains to be elucidated. Finally, more study is needed to clarify both the overlapping and non-overlapping functions of Yap and Taz in the heart.

In summary, as prominent downstream effectors of the Hippo pathway, Yap/Taz appears to mediate many important

functions in the heart. We believe that Yap/Taz are promising targets for the treatment of heart disease. Further investigation is required, however, in order to apply our knowledge regarding this signaling pathway to the clinical setting and achieve effective treatment of patients.

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