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The roles and regulation of Yes-associated protein 1 in stem cells

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Abstract: Yes-associated protein 1 (YAP1) is a downstream effector of the Hippo signaling pathway, and it is involved in tumorigenesis, tissue repair, growth, and development. In this review, the biological roles and the mechanisms of YAP1 in mediating stem cell fate decisions are discussed, including cell proliferation, differentiation, and apoptosis. In general, YAP1 promotes the proliferation and differentiation of stem cells, including embryonic stem cells and adult stem cells. It inhibits apoptosis by binding to the transcription factors, e.g., transcriptional enhanced associate domain (TEAD), Smad, runt-related transcription factor 1/2, p73, p63, and Erb84, to maintain tissue homeostasis. The translocalization of YAP1 in cellular nuclei and the phosphorylation in the cytoplasm work as important and unusual events for the activation of YAP1. Moreover, YAP1 serves as the crosstalk for the Hippo pathway and other signaling pathways, including the Wnt and Notch pathways. It is highlighted in this review that YAP1 is an essential regulator for stem cells that have significant applications in regenerative medicine and reproductive medicine.

Introduction

The *YAP1* gene, which encodes the Yes-associated protein 1, is located on the human chromosome 11q13, and it was first discovered in *Drosophila* in 1994. YAP1 lacks DNA-binding domains and is thus unable to bind to DNA directly, and it is a transcriptional coactivator. Notably, YAP1 is an important effector of the Hippo signaling pathway, which comprises a series of conserved kinase cascades, including mammalian sterile 20-like kinase1/2 (MST1/2), Salvador family WW domain containing 1 (SAV1), large tumor suppressor kinase 1/2 (LATS1/2), Mps one binder 1 (MOB1), and transcriptional coactivator with PDZ-binding motif (YAP1/TAZ). The Hippo signaling pathway can be activated by various factors, e.g., intercellular contact (Kim *et al.*, 2011; Schlegelmilch *et al.*, 2011; Varelas *et al.*, 2010), inflammatory cytokines (Deng *et al.*, 2018), cell polarity (Szymaniak *et al.*, 2015), and the stimulation of G protein-coupled receptor (Yu *et al.*, 2012). When the Hippo signaling pathway is activated, the interaction between MST1/2 and its adaptor protein SAV1 enhances the phosphorylation of MST1/2. The phosphorylated MST1/2 and SAV1 complex activate LATS1/2, which phosphorylates YAP1 in the cellular cytoplasm (Yu *et al.*, 2015). Interestingly, the phosphorylated YAP1 is retained in the cytoplasm and binds to the 14-3-3 proteins, resulting in the ubiquitination and degradation of YAP1 (Hong and Guan, 2012). Conversely, when the signal pathway is blocked by some factors, e.g., epidermal growth factor (EGF) (Fan *et al.*, 2013), YAP1 cannot be phosphorylated, and it thus enters into the nuclei to bind to transcriptional factors, e.g., TEAD, Smad, runt-related transcription factor 1/2 (RUNX1/2), p73, p63, and Erb84. The reduction of the phosphorylated YAP1 and the increase in YAP1 levels reflect the inhibition of the Hippo signaling pathway (Zhao *et al.*, 2011). In the nuclei, the combination of YAP1 with the target genes plays essential roles in tumorigenesis, tissue homeostasis, cardiac development (Chen *et al.*, 2020), and the fate decisions of stem cells, as we illustrated in Fig. 1.

Stem cells are a type of cells with self-renewal and differentiation potential. Significantly, stem cells can replace the dead cells, repair the injured cells, and regulate immunity (Li and Clevers, 2010; Shi *et al.*, 2012; Xiang *et al.*, 2018). As such, stem cells have important applications in regenerative and reproductive medicine because of their great plasticity and differentiation potential. Under normal conditions, stem cells remain in a dormant state, with a few

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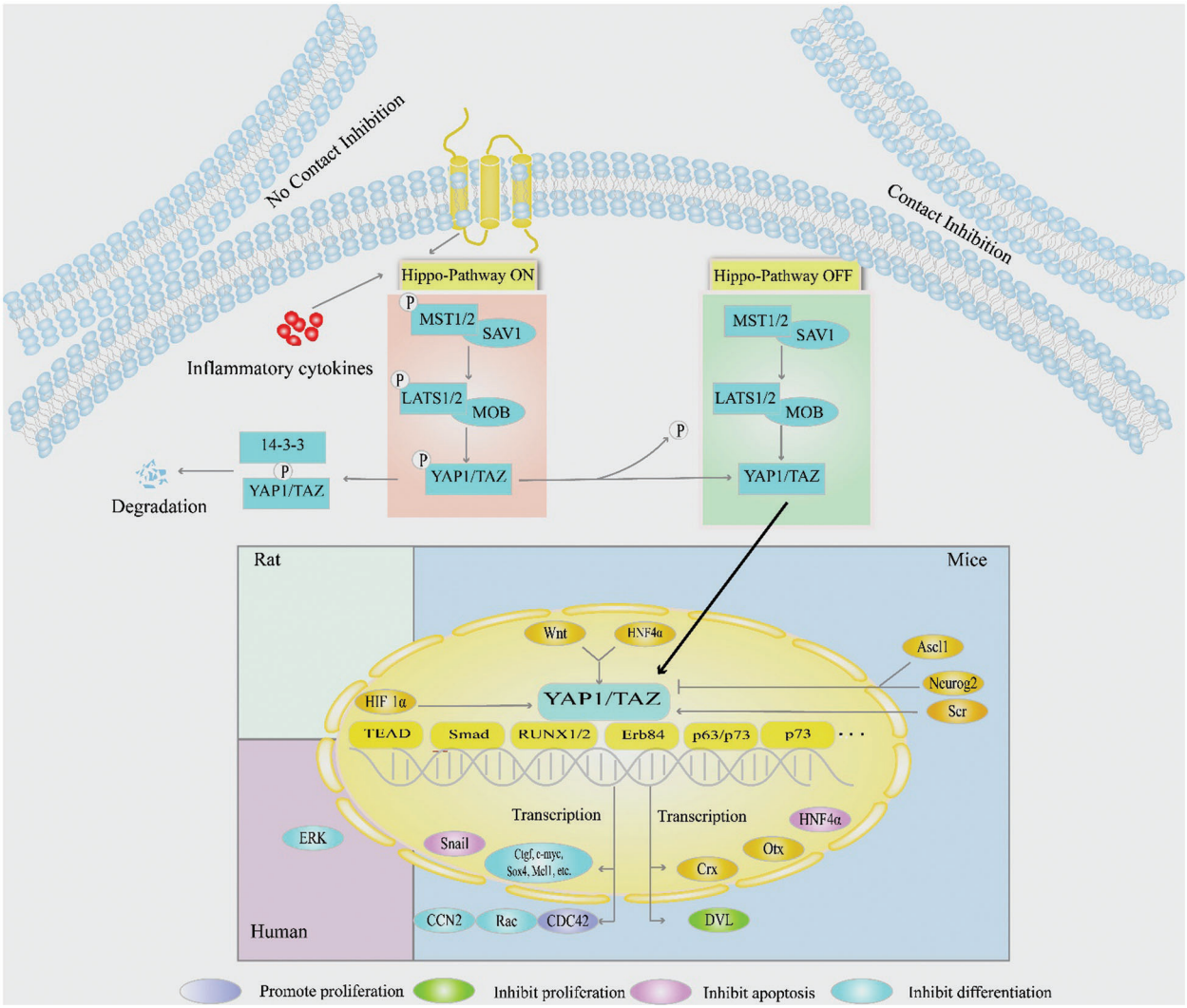

FIGURE 1. The role of YAP1 signaling pathways in regulating the fate decisions of stem cells. This schematic diagram shows the upstream and downstream regulators and signaling pathways of YAP1 in mediating the proliferation, differentiation, and apoptosis of various kinds of stem cells. YAP1 is phosphorylated in the cytoplasm of stem cells, whereas the dephosphorylated YAP1 localizes in the nuclei of these cells.

cells entering the proliferation cycle through asymmetric division (Li and Clevers, 2010). The stem cells undergo various fate decisions, including proliferation, differentiation, transdifferentiation, dedifferentiation, and apoptosis. The proliferation and differentiation maintain the dynamic balance of stem cells in the body. The microenvironment of stem cells, namely the niche, including extracellular and intracellular factors, is crucial for maintaining the fate determinations of stem cells (Vining and Mooney, 2017). As an intracellular transcriptional co-activator, YAP1 plays an important role in the regulation of stem cell fate determinations. For example, the deletion of *YAP1* leads to the loss of the static and symmetric self-renewal ability of hematopoietic stem cells (Althoff *et al.*, 2020). YAP1 controls the differentiation of mesenchymal stem cells (Guo *et al.*, 2018), while it promotes the transition of the differentiated mammary, neuronal, and pancreatic exocrine cells to stem/progenitor cells (Panciera *et al.*, 2016). In this review, we provide an overview of several types of stem cells which are regulated by YAP1. We focus on the functions and mechanisms of action of YAP1 in the fate determinations of stem cells, including the proliferation, differentiation, and apoptosis. This review will thus be helpful in providing insights into the molecular mechanisms of stem cell fate decisions, and significantly, it could offer important cells and targets for stem cell transplantation and gene therapy for a number of diseases.

Main Text

Yes-associated protein 1 regulates stem cell proliferation

Yes-associated protein 1 promotes the proliferation of stem cells

The canonical function of YAP1 promotes the proliferation of multiple types of stem cells. Hepatic stem cells regenerate themselves when the liver is injured. In most cases, YAP1 can promote the proliferation of hepatic stem cells. YAP1, together with TGFβ, stimulates hepatic stem cell proliferation to regenerate the damaged liver of mice undergoing partial hepatectomy (Oh *et al.*, 2018). Furthermore, mechanical destruction of the murine ovary inhibits the ovarian Hippo signaling pathway, resulting in the increase in nuclear YAP1, CRY61, and CCN2 content, which promotes follicle growth and the generation of mature oocytes (Kawamura *et al.*, 2013). The growth of

follicles might be due to the activation of female germline stem cells by YAP1. In addition, *Yap1*-deficient retinal progenitors displayed the decrease in S-phase cells and altered cell cycle progression, as evidenced by YAP1-mediated enhancement of the proliferation of retinal progenitors (Kim *et al.*, 2016). In porcine muscle stem cells, YAP1 promotes their proliferation at a high cell density (Liu *et al.*, 2021). Yap1/Taz signaling in mesenchymal progenitor indirectly regulates the proliferation of muscle stem cells (Kaneshige *et al.*, 2022). In the case of anemia, YAP1 stimulates the proliferation of erythroid progenitors by upregulating the expression of key enzymes involved in glutamine metabolism. This can be verified by the fact that erythroid progenitors fail to divide in the spleen for hematopoiesis when *YAP1* is mutated (Grimm *et al.*, 2019). Yap1 can also accelerate the proliferation of skin basal progenitor cells (Zhang *et al.*, 2011), and it plays an essential role in stimulating cell proliferation in the development of the nervous system. The activation of YAP1 and its analog TAZ increases transcriptional activities and upregulates the expression of many genes associated with neural progenitor growth and division (Lavado *et al.*, 2018). In neural stem cells of *Drosophila*, the loss of the Hippo signaling pathway leads to premature nuclear localization of Yorkie (equivalent to YAP1 in mammals), which increases the levels of microRNAs to trigger neural stem cell proliferation (Ding *et al.*, 2016). In the chicken spine, Yap1-Tead increases the number of neural stem cells by enhancing the level of cyclin D1 (Cao *et al.*, 2008). In mouse neural stem cells, YAP1 is an important downstream target of Notch, and it can rescue the inhibitory state of Notch signaling, thereby promoting cell proliferation (Li *et al.*, 2012). Additionally, YAP1 enhances the proliferation of human periodontal ligament stem cells (h-PDLSC) (Jia *et al.*, 2018). Collectively, these findings illustrate that YAP1 stimulates the division of numerous stem cells through the inhibition of the Hippo signaling pathway and regulation of the cell cycle and other factors.

Yes-associated protein 1 inhibits the division of stem cells

Interestingly, YAP1 assumes not only a powerful growth-inducing function for stem cells but also growth-suppressive biology. During the intestinal regeneration, YAP1 suppresses the Wnt signaling pathway by restricting the nuclear translocation of Dishevelled to inhibit the proliferation of intestinal stem cells and degenerate the intestinal crypts during regeneration. Additionally, deletion of Yap1 leads to Wnt hypersensitivity. This causes hyperplasia and expansion of intestinal stem cells and niche cells, which results in the formation of ectopic crypts and microadenomas (Barry *et al.*, 2013). Considered together, YAP1 promotes the proliferation of most types of stem cells or progenitors, whereas it inhibits the division of certain stem cells.

Yes-associated protein 1 mediates the differentiation of stem cells

Numerous studies have demonstrated that YAP1 plays a significant role in regulating stem cell differentiation in many tissues. The skin is a powerful regenerative tissue, and its regeneration relies on the homeostasis of keratinocytes and basal epidermal cells. In 2011, it was shown that YAP1 is highly expressed in the nuclei of the single-layered basal epidermal progenitors, whereas its level becomes lower in the differentiated and mature keratinocytes. Yap1 can inhibit the differentiation of primary mouse keratinocytes. In this case, YAP1 translocates to the cytoplasm of the differentiating cells (Zhang *et al.*, 2011) to be phosphorylated. Mechanistically, YAP1, together with TAZ, prevents the transformation of stem cells into progenitors through the interaction with TEAD, which inhibits the differentiation of keratinocytes and increases the lifespan of keratinocytes. YAP1 can be activated by cell stretching and low cell density, which further inhibits the downstream Notch signaling, thereby maintaining the stemness and undifferentiation of epidermal stem cells (Totaro *et al.*, 2017). Similarly, YAP1/TAZ is activated by Kindlin-2 signaling to promote the differentiation of BMSCs into osteogenesis and adipocytes (Guo *et al.*, 2018). YAP1 is essential for maintaining the differentiation of human epidermal stem cells (De Rosa *et al.*, 2019). YAP1 also participates in the recovery of the retinal, intestinal, and injured liver via mediating stem cell differentiation. When *Yap1* is ablated, retinal pigment epithelium transdifferentiates into retinal tissue (Kim *et al.*, 2016). Additionally, YAP1 regulates the differentiation of muscle tissue, including skeletal muscle, smooth muscle, and myocardium. In skeletal muscle, the role of YAP1 changes with the stage of differentiation of stem cells. In the early phase of myoblast stem cell differentiation, YAP1 increases the rate of mitochondrial division by activating the expression of mitochondrial motility-related proteins, which provides sufficient energy for cell differentiation. YAP1 suppression reduces the expression of mitochondrial motility-related proteins and thus inhibits myoblast differentiation. On the contrary, in the process of late differentiation, YAP1 inhibits the differentiation of skeletal muscle stem cells (Sun *et al.*, 2017). When MST1/2, the upstream of YAP1, is inhibited, YAP1 is phosphorylated to inhibit the differentiation of muscle satellite cells (Yang *et al.*, 2022). Meanwhile, YAP1 activation by doxycycline can promote the differentiation of pig muscle stem cells at a high cell density (Liu *et al.*, 2021). During osteogenesis, YAP1 is activated by tropomyosin-1 to maintain its nuclear localization and coaxes bone marrow mesenchymal stem cells (BMSCs) to differentiate into osteogenic cells (Brielle *et al.*, 2021). Similarly, YAP1/TAZ is activated by Kindlin-2 signaling to promote the differentiation of BMSCs into osteogenesis and adipocytes (Guo *et al.*, 2018). Meanwhile, YAP1 enhances the level of Snail and reduces hepatocyte nuclear factor 4 alpha (HNF4α) expression, which inhibits hepatic stem cell differentiation (Noce *et al.*, 2019). Ectopic activation of Yap1 triggers intestinal stem cell switch from symmetric to asymmetric structures, which allows Paneth cell differentiation (Serra *et al.*, 2019). Furthermore, YAP1 negatively regulates the differentiation of both absorptive and goblet cells in intestinal cells (Fallah and Beaulieu, 2020).

Notably, YAP1 assumes a dual role in regulating the differentiation of neural stem cells. On the one hand, YAP1 suppresses the differentiation of neural stem cells; on the other, Yap1-Tead reduces cyclin D1 expression to inhibit the differentiation of neural progenitor cells (Cao *et al.*, 2008). This can be confirmed by the observation that inhibiting YAP1 along with TAZ promotes the differentiation of neural

stem cells into mature functional neurons (Heng *et al*., 2020). It is consistent with the finding that inhibiting *Yap1/Tead* target genes in mouse embryonic neural stem cells contribute to the differentiation of premature neurons (Han *et al*., 2015). In pluripotent star stem cells, YAP1/TAZ is involved in maintaining cell differentiation and proliferation (Lorthongpanich *et al*., 2020). It is worth noting that YAP1, activated by tropomyosin-1 overexpression, maintains its nuclear localization and coaxes mesenchymal stem cell differentiation into osteogenic cells (Brielle *et al*., 2021).

In addition to the adult stem cells mentioned above, YAP1 silencing or depletion is required for the differentiation of pluripotent stem cells. YAP1 can be inactivated when embryonic stem cells (ESCs) differentiate, whereas the level of YAP1 expression increases when the induced pluripotent stem cells (iPSCs) are dividing. In mouse ESCs, Yap1 binds to the promoter of pluripotent genes, and it is essential for the pluripotency of mouse ESCs (Kaitsuka and Hakim, 2021). Knocking down *Yap1* in mouse ESCs leads to the loss of pluripotency markers, e.g., OCT4 and SOX2, which facilitates the differentiation of these stem cells (Kaitsuka and Hakim, 2021). *YAP1* deletion could further promote the differentiation of human ESCs into cardiomyocytes by inhibiting Wnt3 expression (Estaras *et al*., 2017), although the overexpression of YAP1 in human ESCs and iPSCs enhances the generation of naive PSCs (Qin *et al*., 2016). Therefore, the deficiency of YAP1 seems to be essential for the differentiation of pluripotent stem cells in humans and mice.

Yes-associated protein 1 controls the apoptosis of stem cells

Yes-associated protein 1 inhibits the apoptosis of stem cells

YAP1 is an inhibitor for apoptosis in many kinds of tissues. The mice with eye conditional knockout of *Yap1* show more cleaved caspase 3-positive cells in the retina or retinal pigment epithelium-derived multilayered epithelium (Kim *et al*., 2016; Lee *et al*., 2018). The loss of *Yap1* in the Nestin-expressing glial progenitors in mouse neonatal cerebellum enhances the apoptosis of later granule cell precursors (Yang and Joyner, 2019). Additionally, deficient YAP1 activity due to *Yap1* conditional knockout leads to the apoptosis of crypt stem cells (Guillermin *et al*., 2021).

In human periodontal membrane stem cells, the expression levels of B-cell lymphoma-2 (Bcl-2) family members, e.g., Bak, Bid, and caspase-3, are decreased when YAP1 is overexpressed (Jia *et al*., 2018), suggesting that YAP1 suppresses the apoptosis in h-PDLSC by affecting the Bcl-2 family. Similarly, other factors indirectly affect YAP1 expression and cell apoptosis. In bone BMSCs, when *Yap1* is activated, the mitochondrial apoptosis pathway promotes their apoptosis. In the hypoxia microenvironment, hypoxia-inducible factor 1-alpha (HIF1α) binds to the dephosphorylated Yap1 in the cell nuclei to form a complex, which transactivates the target genes responsible for the survival of BMSCs and thus inhibits the apoptosis (Wang *et al*., 2020). Likewise, the activation of YAP1 inhibits the apoptosis of h-PDLSC through extracellular signal-regulated kinase (ERK) and Bcl-2 signaling pathways (Jia *et al*., 2018).

Yes-associated protein 1 promotes apoptosis in stem cells

While in most cases, YAP1 inhibits the apoptosis of stem cells, it has a pro-apoptotic role in a specific environment, although it occurs less frequently in stem cells. Recurrent culture-acquired human pluripotent stem cells (hPSCs) display growth advantages over wild-type hPSCs (Price *et al*., 2021). YAP1 in the cytoplasm and f-actin redistribution promotes the apoptosis of wild-type hPSCs (Price *et al*., 2021). In neural progenitor cells, the high transcription of YAP1 inhibits differentiation and triggers replication stress and DNA damage, which results in cell apoptosis (Lavado *et al*., 2018). Together, these studies implicate the bi-directorial roles of YAP1 in either stimulation or suppression of apoptosis in stem cells under different conditions.

The upstream and downstream regulators of Yes-associated protein 1 in stem cells

YAP1 mediates decisions of stem cell fate through the upstream and downstream regulators. The expression of YAP1 is altered by multiple upstream cytoplasmic and nuclear factors. The cytoplasmic and nuclear factors include Ascl1, Neurog2 (Zhang *et al*., 2012), and Src family kinases (Guillermin *et al*., 2021), while the nuclear regulators include HNF4α (Noce *et al*., 2019), Wnt (Guillermin *et al*., 2021), and HIF1α (Wang *et al*., 2020). Downstream of YAP1, various factors are located in the nuclei or cytoplasm, e.g., HNF4α, Snail (Noce *et al*., 2019), Crx, and Otx, and various anti-apoptotic genes, including *c-myc*, *Sox4, Mcl1*, *CDC42* (Lee *et al*., 2018), *Rac*, *CCN2* (Miyamura *et al*., 2017), and *DVL* (Barry *et al*., 2013), that can be regulated by YAP1. Interestingly, YAP1 is bidirectionally regulated with Snail and HNF4α. YAP1 activation upregulates the *Snail* gene and downregulates the HNF4α gene, thereby inhibiting cell differentiation. Snail and HNF4α, in turn, affect YAP1 expression levels. Among the interaction, HNF4α has been shown to stably recruit at the YAP1 promoter and reduce its expression in liver cell lines and adult liver tissues (Noce *et al*., 2019). However, Snail inhibits the YAP1-dependent mesenchymal program to elevate YAP1 expression in hepatocytes (Noce *et al*., 2019). Thus, YAP1 and its upstream and downstream factors play essential roles in regulating the proliferation, differentiation, and apoptosis of certain types of stem cells; some of these factors and their functions and localization of the related factors are presented in Tables 1 and 2.

Conclusion and future perspectives

YAP1, as an important downstream effector of the Hippo signaling pathway, is involved in the regulation of stem cell fate determinations in various types of tissues, e.g., liver, cornea, skin, and intestine. In most cases, YAP1 promotes proliferation, inhibits apoptosis, and regulates the differentiation of stem cells. However, YAP1 mediates stem cell fate decisions with tissue specificity, which reflects the role of the Hippo-YAP1 signaling pathway in accurately regulating the size of organs and tissues. The precise regulatory mechanisms depend on the nuclear/cytoplasmic shuttling as well as the upstream and downstream factors of YAP1. The phosphorylation of YAP1 determines its location in the cytoplasm or the nuclei. Significantly, specific phosphorylation sites and post-transcriptional modifications, e.g., methylation, glycosylation, and ubiquitination, are important regulatory mechanisms that remain to be

TABLE 1

Upstream regulators and functions of YAP1 in stem cells

Factors	Regulation	Cell types	Species	Functions	References
Neurog2 Ascl1	Downregulation	Retinal progenitors	Mice	Reduces retinal progenitor proliferation and increases cell cycle exit and neuronal differentiation	(Zhang *et al.*, 2012)
Snail	Upregulation	Hepatic stem cells	Mice	Upregulates YAP1 at the protein level and induces its nuclear localization	(Noce *et al.*, 2019)
HNF4α	Downregulation	Hepatic stem cells	Mice	Inhibits YAP1-dependent mesenchymal program	(Noce *et al.*, 2019)
HIF1α	Upregulation	Bone marrow mesenchymal stem cells (BMSCs)	Rats	Promotes YAP1 dephosphorylation and activation and protects BMSCs against apoptosis	(Wang *et al.*, 2020)
Wnt Src	Upregulation	Small intestinal crypt stem cells	Mice	Drives YAP1 to the nuclei and activates YAP1-TEAD-mediated transcription	(Guillermin *et al.*, 2021)

Note: BMSC, bone marrow stem cells; TEAD, transcriptional enhanced associate domain; YAP1, Yes-associated protein 1.

TABLE 2

Downstream regulators and roles of YAP1 in stem cells

Factors	Regulation	Cell types	Species	Functions	References
CCN2	Upregulation	Primary female stem cells in the ovarian	Mice	Promotes follicle growth	(Kawamura *et al.*, 2013)
DVL	Downregulation	Intestinal stem cells	Mice	Inhibits cell proliferation and degenerates the intestinal crypts	(Barry *et al.*, 2013)
CDC42, Rac	Upregulation	Hepatic stem cells	Mice	Help the elimination of Yap1-activated hepatocytes	(Miyamura *et al.*, 2017)
Ccn2, c-myc, Sox4, and Mcl1	Upregulation	Retinal progenitors	Mice	Inhibits cell apoptosis	(Lee *et al.*, 2018)
Otx	Downregulation	Photoreceptor cells	Mice	Suppresses cell apoptosis	(Lee *et al.*, 2018)
Crx	Downregulation	Photoreceptor cells	Mice	Inhibits cell apoptosis	(Lee *et al.*, 2018)
ERK	Upregulation	Human periodontal membrane stem cells	Human	Suppresses cell apoptosis	(Jia *et al.*, 2018)
Snail	Upregulation	Hepatic stem cells	Mice	Inhibits cell differentiation	(Noce *et al.*, 2019)
HNF4α	Downregulation	Hepatic stem cells	Mice	Suppresses cell differentiation	(Noce *et al.*, 2019)

Note: BMSC, bone marrow stem cells; CCN2, cellular communication network factor 2; c-myc, cellular Myc protein; Crx, cone-rod homeobox; DVL, dishevelled 1; CDC42, cell division control protein 42; ERK, extracellular signal-regulated kinase; HNF4α, hepatocyte nuclear factor 4 alpha; Mcl1, myeloid cell leukemia-1; Otx, orthodenticle homeobox 2; SOX-4, SRY-box transcription factor 4; YAP1, Yes-associated protein 1.

explored. Second, several classical signaling pathways, including Notch and Wnt, are involved in the biological process of YAP1 to regulate the fate of stem cells. In this review, we summarized the upstream and downstream factors of YAP1, e.g., Snail, HIF1α, HIF4α, and CCN2, especially the bidirectional functions of Snail and HIF4α in the regulation of YAP1. It would be interesting to identify other factors of YAP1 activity and their epigenetic interactions, including miRNAs, lncRNAs, circRNAs, and piRNAs, in controlling the fate determinations of stem cells. These studies would offer novel molecular mechanisms underlying stem cells proliferation, differentiation, and apoptosis and provide sufficient types of stem cells for translational medicine.

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