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p53 shades of Hippo

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The three p53 family members, p53, p63 and p73, are structurally similar and share many biochemical activities. Yet, along with their common fundamental role in protecting genomic fidelity, each has acquired distinct functions related to diverse cell autonomous and non-autonomous processes. Similar to the p53 family, the Hippo signaling pathway impacts a multitude of cellular processes, spanning from cell cycle and metabolism to development and tumor suppression. The core Hippo module consists of the tumor-suppressive MST-LATS kinases and oncogenic transcriptional co-effectors YAP and TAZ. A wealth of accumulated data suggests a complex and delicate regulatory network connecting the p53 and Hippo pathways, in a highly context-specific manner. This generates multiple layers of interaction, ranging from interdependent and collaborative signaling to apparent antagonistic activity. Furthermore, genetic and epigenetic alterations can disrupt this homeostatic network, paving the way to genomic instability and cancer. This strengthens the need to better understand the nuances that control the molecular function of each component and the cross-talk between the different components. Here, we review interactions between the p53 and Hippo pathways within a subset of physiological contexts, focusing on normal stem cells and development, as well as regulation of apoptosis, senescence and metabolism in transformed cells.
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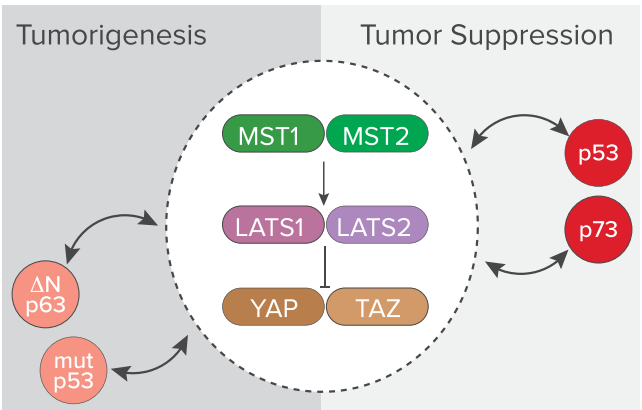

Graphical Abstract

p53 family members and the core components of the Hippo pathway interact on multiple levels. Together, they comprise a sensitive and context-dependent signaling network that exerts a profound and diverse impact on cell fate. Within the context of tumor development, the core components of the Hippo pathway cooperate with p53 and p73 to suppress tumorigenesis, whereas mutant forms of p53 and ΔNp63 can cooperate with the Hippo effectors YAP and TAZ to promote tumorigenesis.

Facts

- The balance between self-renewal and differentiation in embryonic and somatic stem cells involves multi-layered interactions between p53, p63, LATS2 and YAP.
- The tumor-suppressive functions of the Hippo pathway kinases and the pro-apoptotic functions of YAP are often mediated by p53 or p73.
- Oncogenic RAS signaling is a prominent activator of the Hippo-p53 signaling network.
- Maintaining metabolic homeostasis requires signaling between LATS2 and p53, whereas rewiring of cancer cell metabolism engages the oncogenic functions of both mutant p53 and YAP.

Open Questions

- What are the upstream cues that sway YAP function from promoting TEAD-dependent proliferation toward p73/p53-dependent apoptosis?
- How dynamic are the functional states of p53, and to what extent does the Hippo pathway modulate tumor-suppressive versus pro-survival functions of wild-type p53?
- What determines whether mutant p53 functionally interacts with YAP or TAZ, and how does this interaction change mutant p53-dependent phenotypes?

In approximately half of human cancers *TP53* is mutated; in many of the remaining half, the function of the retained wild-type (wt) p53 protein is compromised by deregulation of upstream or downstream regulators.[1] Functionally, p53 inhibits the proliferation of potentially tumorigenic cells, chiefly through transcriptionally instigating cell cycle arrest, differentiation, senescence or apoptosis.[2] Cancer-associated mutations in p53 may directly disrupt p53–DNA interactions or drive conformational changes in the p53 protein, in both cases leading to loss of transcriptional activity and tumor-suppressor capabilities.[3] Mutations in the *TP53* gene may also convey an additional selective advantage for tumors, as the mutant p53 (mutp53) protein may acquire cancer-promoting activities, augmenting cell migration, invasion and tumorigenesis.[3] This

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mutp53 gain-of-function (GOF) is executed often by 'piggy-backing' on other transcription factors or signaling pathways and enables the mutp53 to deregulate metabolic pathways, increase metastasis and enhance chemotherapy resistance.[4–8] Recently, pro-survival functions have been attributed also to wt p53, with some activities shared between the wt and mutant isoforms.[3,9–13] This may reflect a physiological role for p53 in maintaining homeostasis in the face of transient or fluctuating stress, and may confer context-dependent selective advantages also in those tumors that retain wt p53.[10]

The p53 family of transcription factors consists of three paralogs, p53, p63 and p73, which evolved from a common ancestor through two gene duplication events.[14] Interestingly, in organisms, which possess a single p53 family gene, for example, *C. Elegans* and *Drosophila*, this gene is more similar to an ancestral p63/p73 hybrid gene and less to p53 itself.[14] Duplication events enabled the family members to expand their function and engage in additional cellular processes and signaling pathways, while retaining some common activities.[14] Similar to p53, p63 and p73 are nuclear proteins that bind to canonical p53 DNA-binding sites and can transactivate p53-responsive promoters. Both are principally recognized for their role in development, with p63 necessary for skin development and p73 linked to the formation of the nervous system.[15–17] On top of their developmental roles, recent studies have determined that p63 and p73 are critical for the maintenance of genomic integrity and response to DNA damage in adult organisms.[18,19] Like *TP53*, also the p63 and p73 genes can be transcribed from two alternative promoters and are alternatively spliced,[20] giving rise to a profusion of isoforms.[21–23] Of relevance to this review, the p63 and p73 isoforms can be roughly categorized into two groups: transactivation (TA) domain isoforms, which structurally resemble full-length p53 and act as tumor suppressors, and the ΔN isoforms, which in some cases can bind to p53, TAp63 or TAp73 to inhibit their function and promote tumorigenesis.[24]

Differential upstream signaling distinctly impacts p53 family members' stability and activity. Upon DNA damage, p53 is phosphorylated by numerous kinases, whereas p73 is primarily phosphorylated by c-Abl.[25–27] Similarly, MDM2 is the primary E3 ubiquitin ligase for p53 but not p73,[28,29] whereas ITCH has been shown to control the stability of both p63 and p73 but does not promote the degradation of p53.[30,31] Another protein that differentially binds members of the p53 family is YAP. YAP binds p63, p73 and mutp53, but not wt p53.[32,33]

YAP was originally identified as a protein interacting with the c-Yes tyrosine kinase.[34] Subsequent studies demonstrated that YAP is a transcription cofactor without direct DNA-binding activity.[35] In addition to its interactions with p53 family members, YAP modulates transcription by binding to other transcription factors.[36,37] Importantly, TEAD family transcription factors, which bind directly to specific DNA sequences and anchor YAP to chromatin, mediate most of the cell proliferative and anti-apoptotic transcriptional output of YAP and its paralog TAZ.[38,39]

YAP and TAZ are phosphorylated and inactivated by the serine/threonine kinases LATS1 and LATS2 within the Hippo pathway.[40,41] In mammals, the core cascade of the canonical Hippo pathway involves the mammalian sterile 20-like kinases MST1/2 (MST), which can phosphorylate and activate the two large tumor suppressors, LATS1 and LATS2 (LATS) kinases.[42,43] This kinase module is bolstered by two adaptor proteins, WW45 and MOB1 (shown schematically in Figure 1). A plethora of upstream signals modulate this kinase module, facilitating diverse biological outcomes.[42] Although the core cascade is evolutionarily conserved,[44,45] the wide array of biological processes modulated by each component suggests that they elicit their biological impact also through additional pathways.[46–48] For instance, cytoskeleton dynamics and mechanical cues are prominent regulators of MST/LATS-independent[49] YAP/TAZ activity, which may liberate the kinases for interactions with the p53 pathway or other signaling pathways.

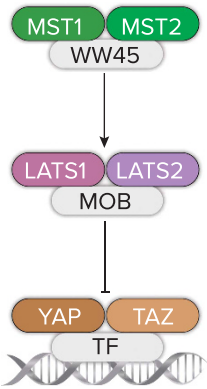

Figure 1 Simplified version of the key factors within the Hippo signaling pathway. The core of the Hippo pathway consists of MST1 and MST2, members of the Ste20 group of protein kinases; LATS1 and LATS2, members of the AGC kinase family, as well as their adaptor proteins Salvador (WW45) and MOB1, respectively. Activated LATS1/2 kinases phosphorylate the transcriptional co-factors YAP and TAZ on different sites, leading to their inactivation by cytoplasmic sequestering and proteasome-mediated degradation. TF, transcription factor

In this review, we examine the cross-talk between the Hippo and p53 pathways in an attempt to better understand mutual modulation and integration of function. The major interactions and biological outcomes are summarized in Table 1 and are detailed in the following sections. Although the specifics differ within different biological contexts, it is clear that the two pathways are strongly intertwined at multiple levels. Interestingly, in multiple cases, cross-talk between specific components may lead to different, sometimes contradicting, cellular outcomes. Similarly, deregulation of either pathway, as often occurs in cancer, has profound effects on the reciprocal pathway and, by extension, on cell fate.

Stem Cells and Development

A robust network of molecular regulation maintains embryonic stem cell (ESC) homeostasis. Signaling through Hippo and p53 pathways has important roles in dictating the fine balance of proliferation and differentiation of stem cells. For example, LATS kinases participate in maintaining the balance between pluripotency and differentiation, through both p53-dependent and -independent mechanisms. Inhibition of *Lats1* and *Lats2* expression in early mouse embryos results in irreversible

Table 1 Points of cross-talk between the Hippo and p53 pathways

Hippo component	p53		p63		p73	
	Biological process	**Reference**	**Biological process**	**Reference**	**Biological process**	**Reference**
RASSF1A	Induces p53 via inhibition of MDM2	107,108,113				
	p53 represses RASSF1A expression	114,115				
RASSF5	Activates both p53 and MST1-LATS1	104				
MST1/2	Dmp53 transactivates Hpo	93			ATM promotes MST2-LATS1-p73 apoptosis	108
	MST1 activates p53 via inhibition of SIRT1	97				
LATS1	Induces p53 in response to K-RAS activation	116				
LATS2	Activates p53 in response to mitotic stress	53,142–144,149				
	Activates p53 in response to oncogenic Ras	117,118				
	Activates p53 in response to excess cholesterol	156				
	Activates p53 during mESC differentiation	52				
YAP	Loss of YAP induces p53	145,147,148	YAP represses ΔNp63 to inhibit lung cancer squamous cells transdifferentiation.	182	YAP-p73 promotes apoptosis	106,108–110, 132–134, 136,183
	Yki inactivation induces Dmp53	119	p63 inhibits p73-YAP-dependent apoptosis	22,137	YAP-tyr357-p73 is a marker for well differentiated HCC	85
	Yki binds Dmp53 to promote apoptosis	131	YAP positively regulates p63 in epidermal stem cells	66		
	Locus is amplified in p53 null tumors	75–77,184,185	YAP positively regulates p63 in airway epithelium	71		
	p53 and YAP antagonistically regulate FOXM1	186–188	YAP-p63 block differentiation in HNSCC	86		
	p53 transactivates 14-3-3σ, which inhibits YAP/TAZ	124,125	Binds p63 and prevents its degradation	88,89		
	YAP and p53 cooperate in apoptosis and senescence	126–128				
	Hyperactivation of YAP/TAZ induces p53	152,154				
	YAP and mutp53 cooperate in transformation	33,82				
	Mutp53 induces miRs that target YAP output	159				
	Mutp53-SREBP induces YAP/TAZ activity	158				
TAZ	Loss of TAZ induces p53	146	p63 inhibits TAZ to maintain polarity in mammary stem cells	90		

The table summarizes studies showing functional interactions between Hippo core components and different p53 family members

lineage misspecification and aberrant polarization of the inner cell mass, because of aberrant cellular localization of YAP.[50] Furthermore, LATS2 is critical for blocking reprogramming of iPSCs by antagonizing the YAP paralog TAZ.[51] Although the ability of LATS2 to restrict reprogramming is p53 independent, the functional interaction between LATS2 and p53 is necessary to maintain ESC homeostasis.[52,53] Mouse ESCs (mESCs) lacking *Lats2* are deficient in both sustaining pluripotency and responding to differentiation signals;[52] hand-in-hand with this is an inability to fully activate p53 during differentiation. Similarly, during normal development, *Lats2* and p53 engage in a positive feedback loop to ensure terminal differentiation.[52]

Subsequent to their impact on ESC differentiation, the p53 and Hippo pathways also have critical roles during development, when embryos are threatened by genotoxic stress. BRCA2 and Aurora A engage the Hippo pathway during replication fork stalling and mitosis, respectively, to ensure high fidelity cell division.[54,55] Deletion of either gene in mice is embryonic lethal. Importantly, concurrent depletion of p53 accords partial rescue of lethality,[56,57] suggesting an epistatic relationship of these genomic integrity genes during

embryonic development. The core Hippo kinases and p53 act in parallel also in development to restrict organ size.[58–60] For instance, conditional embryonic ablation of *Yap* or overexpression of p53 in mouse kidneys similarly causes underdevelopment and small organ size.[61,62]

In adult organisms, stem cell maintenance is required to sustain long-term preservation of tissue homeostasis. The mammalian epidermis is a rapidly regenerating epithelial tissue whose maintenance depends on the self-renewing ability of epidermal stem cells residing in the basal layer.[63] Both p63 and YAP have essential roles in epidermal basal stem cell proliferation and epithelial stratification, and are considered epidermal stem cell markers.[64–68] Accordingly, activation of YAP increases the number of cells expressing p63 and expands the epidermal stem cell compartment.[66] One factor that may mediate YAP-p63 cross-talk is 14-3-3σ; downregulation of 14-3-3σ, which normally restrains YAP transcriptional activity by sequestration of phospho-Ser127 YAP in the cytoplasm,[41] results in the expansion and immortalization of primary keratinocytes expressing p63.[68,69] Interestingly, the ΔNp63 isoform can repress 14-3-3σ expression.[70] Together, these data suggest mechanisms by which YAP and p63 might augment each other's function.

In the lung, YAP and ΔNp63 functionally interact to regulate airway epithelial stem cell homeostasis.[71] YAP regulates differentiation of adult lung epithelium progenitors[72] by binding ΔNp63 to drive the expression of common target genes, including ΔNp63 itself.[71,72] Persistent YAP expression is required to restrain adult airway basal stem cell differentiation and following injury YAP is upregulated in the regenerative tissue.[73] Accordingly, loss of either YAP or p63 is associated with an excess of differentiated ciliated cells. p63 null mutants die at birth without basal progenitors in their airway epithelium.[74] Similarly, conditional deletion of *Yap* from fetal lung epithelial progenitors reduces p63-positive cells and disrupts branching morphogenesis, resulting in lung hypoplasia.[72]

Thus, proper regulation of YAP-p63 signaling maintains the steady-state stem cell pool through balanced rates of stem cell self-renewal and differentiation. Disparity of either of these processes can set the stage for tumorigenesis.

Cancer Stem Cells

Elevated expression of YAP may cooperate with loss of p53 to promote the emergence of cancers with an altered differentiation status, relative to their cell of origin. Thus, p53 deletion in mouse mammary gland luminal cells leads to clonal expansion without compromising luminal identity.[75] However, subsequent mammary tumors often undergo luminal-to-basal transition in conjunction with amplification of the *Yap* gene.[75] Additional studies also confirm that inactivation of p53, or combined loss of p53 and Rb, in mammary epithelium results in mammary carcinomas that bear recurrent *Yap* amplifications.[76,77] These carcinomas become 'addicted' to YAP overexpression[76] and harbor features of EMT and stem cell-like transcriptional signatures.[77] In line with this notion, amplification of the *Yap* genomic region is among the top ranked amplification events in mouse models of prostate cancer driven by p53/PTEN loss.[78]

Stem cell-like transcriptional signatures are often associated with the acquisition of stem-like properties, in that a subpopulation of transformed cells attains the ability to self-renew and generate the diverse types of cells that comprise the tumor.[79] Cancer stem cells (CSCs), or tumor-initiating cells (TICs), have been identified in a wide variety of solid tumors and, analogous to embryonic and adult stem cells, both p53 family members and the Hippo components have been implicated as central regulators. TAZ is required for self-renewal and tumor initiation capacities in breast CSCs.[80] Similarly, mutation of p53 is sufficient to instigate a CSC-like phenotype.[81] Recently, Escoll and colleagues[82] have demonstrated that mutp53 enhances YAP/TAZ stability by regulating the WASP-interacting protein, WIP, to promote CSC properties in breast cancer and glioblastoma. This study provides one mechanism to explain the functional link between mutp53 and YAP/TAZ during tumorigenesis.

Similarly, YAP inhibition restores hepatocyte differentiation in advanced hepatocellular carcinoma (HCC).[83] Interestingly, different post-translational modifications, which have been shown to govern YAP stability, may dictate the differentiation status of HCC.[84,85] Although hyperactivity of the YAP–TEAD functional axis predicts poor prognosis and stemness characteristics in HCC, tumors in which YAP is modified to interact with p73 (p-Y357) display more apoptotic markers and have better prognosis.[85] Thus, YAP can promote either tumor cell death or tumor-initiating properties, depending on its regulatory interactions with different members of the p53 family. In the next sections, we will review in more detail the YAP-p73 pro-apoptotic module and try to delineate the mechanisms that modulate the apparently opposing cellular functions of YAP.

p63 was also shown to engage with YAP to promote tumorigenesis. In head and neck squamous cell carcinoma (HNSCC), p63 collaborates with the chromatin-remodeling factor ACTL6A to block differentiation and drive regenerative proliferation in a YAP-dependent manner.[86] Mechanistically, p63 represses the *WWC1* (Kibra) promoter. As *WWC1* encodes a cytosolic phosphoprotein that activates LATS kinases,[87] p63-dependent silencing of *WWC1* activates YAP. In line with this, upregulation of YAP transcriptional targets is correlated with poor prognosis of HNSCC.[86] In addition to activation of YAP by p63, YAP binds ΔNp63, not only in developmental settings but also in a tumorigenic context.[88,89] Here, YAP binding leads to ΔNp63 stabilization by competition with the ITCH E3 ligase.[88] Furthermore, the co-protective YAP-ΔNp63 association promotes epidermal squamous cell carcinoma CSC survival and migratory phenotypes.[89] Interestingly, this interaction, like the YAP–mutp53 functional interaction,[82] is regulated by membrane-associated integrin signaling.[89]

In contrast to the oncogenic ΔNp63 isoform, which in some cases commandeers YAP to augment CSC properties, TAp63 and Hippo signaling seem to collaborate as tumor suppressors. In healthy tissue, TAp63 restricts mammary stem cell potential by inhibiting TAZ activity.[90] Mechanistically, *LKB1*, a transcriptional target of p63,[91] phosphorylates the microtubule affinity-regulating kinase family to safeguard LATS kinase activity.[92] In aggressive human mammary adenocarcinomas, loss of TAp63 depolarizes cells and activates TAZ (but not

YAP), which endows self-renewal capacity to breast cancer cells.[80]

In summary, oncogenic YAP/TAZ often exploit functional deficiencies in the p53 family of tumor suppressors to propel stem-like characteristics in cancers. Furthermore, tumors that harbor mutp53 or ΔNp63 rely on YAP/TAZ to reinforce the stem cell properties and elude death.

Regulation of Apoptosis

Cells bearing potentially transforming genomic aberrations must be eliminated to forestall tumorigenesis. The extent to which the Hippo tumor suppressors realize their anticancer function is often dependent on p53 or p73 activity.

Transcriptional control of MST-driven apoptosis is conserved from *Drosophila* to mammals, with p53 serving as a central mediator throughout evolution. In flies, *Hpo* (the MST ortholog) is activated by ionizing radiation in a *Drosophila melanogaster* p53 (Dmp53)-dependent manner (Figure 2). In fact, ectopic expression of Dmp53 is sufficient to activate *Hpo* and elicit cell death.[93] Induction of apoptosis by both Hpo and Dmp53 relies on inhibition of the *Drosophila* inhibitor of apoptosis protein, DIAP1. In response to radiation, Dmp53 transactivates the *Reaper* locus, which encodes DIAP1 inhibitors such as *Hid*, *grim* and *reaper* itself.[94] In addition, Hpo negatively regulates DIAP1 both by modulating the transactivation capacities of Yki (the fly YAP ortholog) and by directly phosphorylating and inducing the ubiquitin-dependent degradation of DIAP1.[95,96]

In mammals, the MST kinases facilitate apoptosis predominantly through transcription-independent mechanisms. MST1 augments apoptosis by phosphorylating and inhibiting the deacetylase SIRT1, thus enhancing p53 acetylation and function[97] (Figure 2). Interestingly, SIRT1 is regulated by multiple kinases, such as CK2,[98] cyclin B/Cdk1[99] and DYRK1A,[100] kinases regulated collectively by LATS kinases,[101–103] implicating a multi-pronged strategy by which Hippo kinases impact p53 activity.

In flies, as well as in mammals, p53 and MST share upstream regulatory factors. Overexpression of the Ras association domain family 5 (RASSF5) activates both the MST1-LATS1 and p53 axes.[104] Another RASSF member, RASSF1A, promotes p53 family and MST activation in response to genotoxic stress.[105–107] DNA damage-induced phosphorylation of RASFF1A by ATM promotes MST2-LATS1 activation and p73 stabilization.[108] Mechanistically, RASSF1A promotes MST2 activation by abrogating the RAF1–MST2 inhibitory interaction.[106] Subsequently, RASSF1A, together with the activated MST2-LATS1 complex, mediates apoptosis by inducing p73 transcription.[108–110] Although the RASSF1A-MST-WW45 (SAV1)[111] complex can regulate p73 activity, it has also been suggested that RASSF1-WW45 can regulate p73 independently of the MST-LATS module.[112] In addition to activating the MST and p73 pro-apoptotic arms, RASSF1A also stabilizes p53 by promoting MDM2 degradation.[107] Indeed, polymorphisms of RASSF1, in the region encoding the recognition site for ATM phosphorylation, convey resistance to DNA damage-inducing agents and are associated with decreased p53 stability and poor patient prognosis.[108,113] Surprisingly, wt p53 can bind and repress *RASFF1A* by facilitating its promoter hypermethylation[114,115] (Figure 2). Whether this represents an inherent negative feedback loop between p53 and RASFF1A, or a pro-survival function that is conferred upon wt p53 in the course of tumor progression, remains to be determined.

Upstream modulation by RASSF proteins suggest a general sensitivity of the Hippo and p53 tumor-suppressor pathways to RAS-related signals. Indeed, aberrant hyperproliferation of cells caused by RAS oncogenic activation is a robust trigger of the p53-Hippo functional axis. Mutant K-RAS-dependent activation of the MST2-LATS1 kinase cassette results in sequestration of MDM2 by LATS1 and subsequent stabilization and activation of p53[116] (Figure 2). Similarly, H-RAS triggers LATS2 nuclear translocation and an increase in LATS2 protein levels, which leads to p53 activation.[117] LATS2-p53-dependent apoptosis upon oncogenic stress is mediated by phosphorylation of the apoptosis-stimulating protein of P53 1 (ASPP1), which shunts p53 to the promoters of pro-apoptotic genes.[118] In transformed tissue, MST pro-apoptotic function is subverted by the ability of mutant

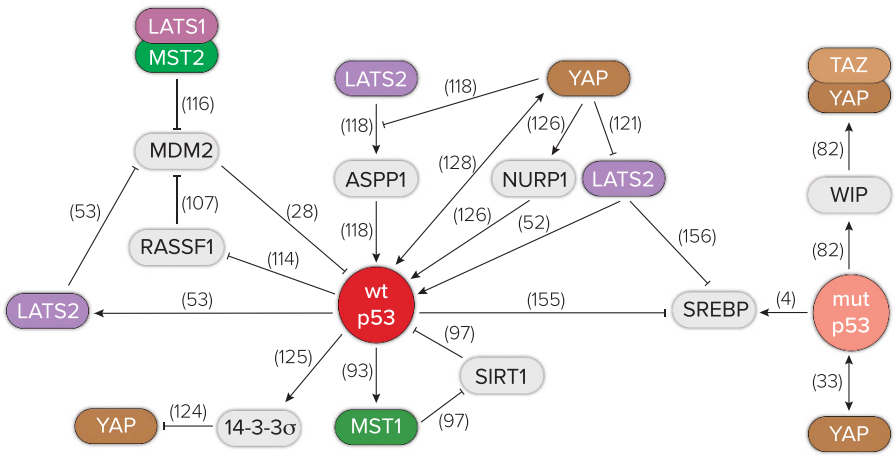

Figure 2 Scheme of reported cross-talk between core Hippo pathway components and wt (left) or mutant (right) p53. Both wt and mutp53 functionally interact with various components of the Hippo pathway (solid filled ovals) either directly or via additional factors (gray shaded ovals). Numbers above lines refer to publications describing the indicated regulatory vector

K-RAS to divert wt K-RAS signaling.[116] Similarly, H-RAS-driven transformation entails a reduction of LATS2 levels in order to overcome p53-dependent apoptosis and senescence.[117] Thus, during RAS-driven transformation there is a strong selective pressure to deregulate Hippo signaling in order to overcome p53-related tumor-suppressive functions.

Similar to oncogenic RAS, high YAP activity may disrupt the Hippo-p53 tumor-suppressive arm. In both flies and mammals, YAP expression overrides the ability of LATS and ASPP to drive p53-dependent transcription of pro-apoptotic genes. In *Drosophila*, Yki activation facilitates tissue growth by inhibiting p53 and ASPP, thereby repressing the expression of the pro-apoptotic gene *reaper* during tissue growth.[119] In mammals, binding of cytoplasmic ASPP1 to LATS1 releases YAP/TAZ from negative regulation.[120] Subsequently, the increased nuclear activity of YAP/TAZ inhibits apoptosis under low serum conditions and protects cells from anoikis. Over-expression of YAP can also inhibit apoptosis by disrupting the LATS2-ASPP1-p53 pro-apoptotic cascade[118] (Figure 2). Similarly, nuclear YAP can repress *LATS2* expression to inhibit replication stress-induced senescence mediated by p53-dependent induction of p21.[121] However, under different conditions, the YAP–TEAD complex can actually bind the *LATS2* promoter to augment its transcription,[122,123] suggesting that differential binding of YAP to various cofactors may differently modulate LATS2-p53 activity. Interestingly, this mode of regulation may be bidirectional, also enabling p53 to exert anti-YAP activities, as treatment with the YAP inhibitor Verteporfin causes sequestration of YAP in the cytoplasm, which is mediated by p53-dependent transcriptional induction of 14-3-3σ.[124,125]

In contrast to the above-described antagonistic roles of YAP and p53, there are apoptotic conditions in which YAP and p53 family members cooperate. In highly malignant tumor-repopulating cells, which are enriched by growing cancer cells on a soft matrix, the expression of nuclear protein 1 (NURP1) is compromised by reduced nuclear localization of YAP.[126] Reduction in NURP1 expression is followed by a reduction in p53 mRNA and protein levels, suggesting an anti-tumorigenic axis involving YAP-NUPR1-p53. Similarly, YAP increases the sensitivity of hepatocellular and renal carcinoma cells to chemotherapy by increasing p53 expression and activity.[127,128] Interestingly, p53 can also drive a positive feedback, to transcriptionally increase YAP expression; indeed, *YAP* was recently identified as a direct transcriptional target of p53 in a genome-wide characterization of putative p53 response elements[129] (Figure 2). Finally, YAP can facilitate p53-dependent cell death by promoting the stabilization of the pro-apoptotic factor ASPP2.[130]

In addition to modulation of p53 activity, YAP, as a transcriptional co-activator, can drive apoptosis by cooperating with p73. This functional interaction may be strongly conserved over evolution. In *Drosophila,* Yki interacts with the ancestral single p53 gene, Dmp53, to induce apoptosis.[131] As Dmp53 resembles a p63/p73 hybrid gene, this may be analogous to mammalian YAP binding to p73, protecting p73 from ITCH-dependent degradation and driving apoptosis.[132,133] YAP also enhances p73 transcriptional function by promoting p300-mediated p73 acetylation and recruitment to the promoters of apoptotic genes.[106,110,134] Of note, RASSF1 promotes binding of YAP to p73, in preference over other transcription factors such as TEAD and RUNX2.[135] Thus, under specific regulatory cues, YAP has a central role in the cellular response to DNA damage by augmenting p73 stability and driving pro-apoptotic transcription. In tumors retaining wt p53, curtailing of the tumor-suppressive YAP-p73 axis may be particularly crucial. Supporting this notion, re-expression of YAP in YAP-deficient multiple myeloma cells drives apoptosis by increasing p73 (not p53) levels and activity.[136] Interestingly, *YAP* and p73 are inhibited, transcriptionally and post-translationally, by ΔNp63,[22,137] delineating an additional layer of cross-regulation between the pathways.

Senescence and Ploidy

The role of apoptosis as a tumor-suppressive mechanism is intuitive: it irreversibly removes dangerously transformed cells from the replicative pool. However, in other instances, senescence is the cell's method of choice to prevent proliferation of pre-malignant cells.[138] One strong trigger for senescence is the genotoxic acquisition of aneuploidy,[139] which can occur when chromosomes fail to properly segregate during mitosis.[140] Numerical changes in whole chromosomes often precede transformation and are powerful inducers of p53.[140,141] In response to mitotic stress, LATS2 binds and inhibits MDM2, to enable p53 activation and induce G1/S arrest. In turn, activated p53 transcriptionally induces *LATS2* expression, creating a positive feedback loop to ensure that the cell maintains proper DNA content[53,142] (Figure 2). The ability of LATS2 to sense extra chromosomes has been attributed to changes in the actin cytoskeleton, specifically to the reduction of RHOA activity.[143] Indeed megakaryocytes, naturally occurring polyploid cells, in which polyploidization is needed for platelet formation, escape the p53-LATS axis by uncoupling RHOA activity from Hippo signaling.[144] Thus, induction of LATS2 in response to ploidy aberrations enables simultaneous activation of a protective p53-dependent growth arrest and inactivation of YAP/TAZ pro-proliferative signals.

LATS2 and p53 cooperate also in response to replication stress, to induce p21 expression and promote cellular senescence.[117,121] This p53-LATS homeostatic axis is targeted by oncogenes to overcome tumor-suppressive checkpoints and increase tolerance to polyploidy. For instance, silencing of *YAP*/*TAZ* in cancer or stem cell lines facilitates p53 activation and growth arrest.[145–148] Similarly, v-SRC, a viral mutant variant of the c-SRC cellular proto-oncogene, enables abnormal spindle formation and transformation by reducing p53 levels and promoting YAP nuclear localization by squelching LATS activity.[149] An analogous situation occurs during H-RAS transformation, in which silencing of *LATS2* permits proliferation of polyploid cells.[117]

On the other hand, perhaps akin to the above-mentioned p53-dependent oncogene-induced senescence,[150,151] hyper-activation of YAP/TAZ can also activate p53. Loss of WRN protein function, as seen in the premature aging Werner syndrome, results in cellular senescence.[152] In cancer models, depletion of WRN decreases tumor growth and increases chemotherapy sensitivity.[153] Mechanistically, the depletion of WRN induces ATM-dependent phosphorylation of YAP and p53, leading to YAP stabilization and p53-dependent

senescence.[152] Similarly, in the liver, YAP/TAZ hyperactivation leads to DNA damage and the generation of polyploid cells, which induces p53 and leads to hepatocyte senescence.[154]

Metabolic Homeostasis

The sterol regulatory element-binding protein (SREBP) transcription factors are master regulators of cholesterol and lipid homeostasis and are emerging as central factors in the cross-talk between p53 and the Hippo pathway. *SREBP1* expression is transcriptionally repressed by wt p53.[155] LATS2 acts in concert with p53 to inhibit SREBP function (Figure 2) by binding the ER-tethered precursors of SREBP1 and SREBP2, impeding their processing and quenching the subsequent transcriptional activity of the cleaved, nuclear SREBPs.[156] Expression of hepatic *Lats2* is required to avoid fatty liver disease and for induction of a p53 pro-apoptotic response when mice are challenged with excess dietary cholesterol.[156] Conversely, forced expression of SREBP1 in mouse liver leads to p53 activation.[157] Thus, together, p53 and LATS2 function to maintain appropriate levels of SREBP activity and cholesterol homeostasis within the liver.

Activation of the mevalonate–cholesterol pathway promotes YAP/TAZ nuclear localization and transcriptional activity by activation of RHO GTPases.[158] Contrary to wt p53 repression of SREBP, mutp53 cooperates with SREBP to promote the expression of sterol-related genes[4] and increases YAP/TAZ-dependent gene expression[158] (Figure 2). Accordingly, expression data from breast cancer patients show that both SREBP and YAP/TAZ-related genes are expressed at higher levels in mutp53 tumors compared with wt p53 tumors.[158] Of note, in this case the regulation of YAP/TAZ by SREBP activation is LATS independent.

In line with the epistatic regulation of YAP and mutp53, recently Di Agostino and colleagues[33] demonstrated a physical interaction between YAP (but not TAZ) and mutp53 in breast cancer cell lines (Figure 2). This interaction drives the expression of pro-proliferative genes such as cyclin A (CCNA), cyclin B (CCNB) and CDK1 to promote tumorigenesis. Mutp53 may also augment YAP/TAZ activity by deregulating upstream Hippo components. Indeed, the miRNA transcriptome associated with mutp53 substantially differs from that of wt p53, and is significantly enriched with miRNAs that putatively target Hippo pathway components.[159]

Tumors must coordinate the rewiring of cell hyperproliferation with the altered metabolic demands of oncogenesis. To unleash cells' pro-proliferative potential, mutp53 and YAP converge on additional facets of cell metabolism, beyond the aforementioned mevalonate pathway. For instance, tumor-associated mutp53 stimulates the Warburg effect through promoting GLUT1 translocation to the plasma membrane, which is mediated by activated RHOA and its downstream effector ROCK.[5] Not only is RHOA a well-documented upstream effector of the Hippo pathway,[49] but also augmented glycolysis has been shown to be crucial to sustain YAP/TAZ transcriptional activity and pro-tumorigenic functions.[160–163] Similarly, both YAP and mutp53 protein levels are dependent on nutrient availability. Intriguingly, glucose restriction selectively promotes both mutp53 and YAP degradation through autophagy.[164,165] Moreover, the recent discovery that the MST kinases sustain autophagosome formation by phosphorylating LC3[166] suggests that cross-talk between Hippo signaling, autophagy and mutp53 might function at multiple junctions.

Ultimately, homeostasis represents a balance between stemness and differentiation, cell death and proliferation, and anabolism and catabolism. Given the important functions of the Hippo and p53 pathways in these processes, it is no wonder that they are profoundly intertwined.

Conclusions

The complexity of signaling pathways tends to increase over evolution, facilitated at least partially by gene duplications events, as seen for both the p53 family members and Hippo pathway components.[14,44] Paralogs may provide a platform to increase and fine tune the integration of signaling pathways into a comprehensive and precise network that maintains homeostasis and fitness. In the case of the p53 and Hippo pathways, signaling integration is highly conserved, with multiple interaction nodes in organisms with no duplications of either *TP53* or Hippo genes (i.e., *Drosophila*). Interestingly, a significant portion of the cross-talk between the two pathways is dedicated to maintaining homeostasis between stemness and differentiation. This may be related to the primordial and conserved role of Hippo components and p53 family members in germline protection and organismal development.[14,167] Alterations in this balance may be hijacked by cancer cells to maintain stemness features and to increase their competitive advantage.

Coordination of the p53 and Hippo tumor-suppressive pathways occurs on multiple levels (simplified summary in Table 1). For example, LATS2 can bind directly to MDM2, the major negative regulator of p53, blocking the ability of MDM2 to target p53 for ubiquitin-dependent proteasomal degradation and resulting in p53 accumulation and activation.[53] Through this capacity, LATS2 mediates p53 activation in response to a number of diverse types of stress signals, including mitotic apparatus dysfunction, expression of oncogenic RAS and cholesterol overload,[53,117,118,156] and during ESC differentiation.[52] Similarly, both YAP and TAZ collaborate with different p63 isoforms to modulate adult and CSCs,[71,86,89,90] whereas MST and YAP cooperate to direct p73-dependent apoptosis.[106,168] mutp53 physically interacts with YAP to coordinately regulate the expression of cancer-related genes.[33] In turn, optimal activity of YAP and TAZ relies on products of the mevalonate pathway,[158] which is regulated positively by mutp53[4] and negatively by LATS2.[156] Importantly, downregulation of LATS alters the properties of wt p53. This is reflected by reduced phosphorylation, conformational changes and alteration of transcriptional targets, all of which contribute to a mutant-like phenotype of wt p53.[169]

These multiple points of regulatory interactions may also dictate selective forces during tumorigenesis that drive rewiring and alterations of the two pathways. Although the *TP53* gene is highly mutated in diverse cancer types, pan-cancer TCGA data[170] reveal that there are also tumor types with relatively low prevalence of such mutations, for example, kidney renal clear-cell carcinoma 3%; lymphoblastic acute myeloid leukemia (LAML) 8%; glioblastoma multiforme 29%, as opposed to cancers with frequent *TP53* mutations (ovarian

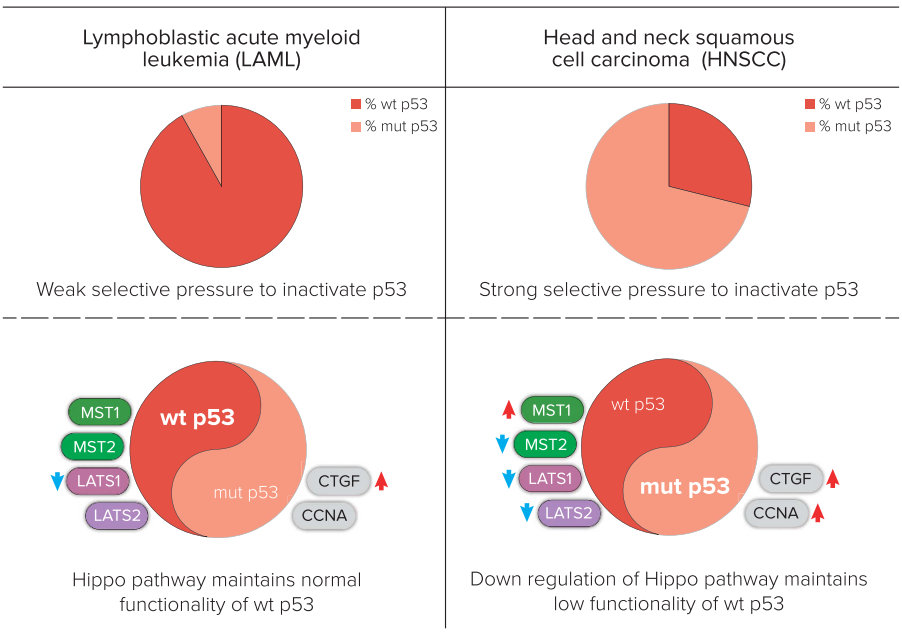

Figure 3 Different types of cancers have distinctive patterns of Hippo–p53 axis inactivation. The pressure to disable wt p53 (wt p53) function in human tumors is associated with deregulation of Hippo pathway components. LAML (left panel) represents a cancer type with a low percentage of *TP53* mutations, whereas HNSCC (right panel) represents a tumor type harboring a high percentage of *TP53* mutations. For both cancer types, the portion of wt and mutp53 cases are shown in the upper section (TCGA data). Within each cancer type, expression of core Hippo components (TCGA data) was compared between tumors with wt or mutp53. Statistically significant (FDR < 0.1) upregulation (red arrow) or downregulation (blue arrow) is indicated on the left or right of the yin-yang symbol, for cases with wt and mutp53, respectively

carcinoma 83%, lung squamous cell carcinoma 82%, HNSCC 71%). Comparing the expression levels of the core Hippo components in tumors with wt or mutp53 within each type of cancer reveals an interesting trend (Figure 3). In tumor types where the pressure to mutationally inactivate p53 is low (exemplified by LAML), the large proportion of tumors that retain wt p53 also preserve expression of the Hippo tumor-suppressive kinase module. Furthermore, in the relatively few tumors with p53 mutations, the YAP-mutp53 target CCNA is not upregulated. Interestingly in HNSCC in which there is a strong pressure to mutate *TP53*, tumors that retain wt p53 appear to compromise its function by downregulating the Hippo kinases. Furthermore, in this tumor type, CCNA is expressed at higher levels in mutp53 tumors, suggesting the existence of a transcriptionally active mutp53-YAP complex. Although only correlative, these observations may reflect the close-knit network of interactions between the two pathways, and its corruption in the course of different malignant contexts.

There is growing evidence supporting a scenario in which incoming physiological signals dynamically dictate a variety of functions and conformational states for different proteins. These conformational states might generate a functional spectrum ranging from wt to mutant-like behavior ('pseudo-mutant'), even in proteins that are wt by sequence. For instance, specific post-translational modifications trigger changes in the conformation of wt p53 that can mediate its ability to interact with binding partners and fortify its commitment to specific biological processes.[171] External and internal signaling events, such as growth factors, oxygen availability and differential binding to distinct DNA sequences or molecular chaperones also have an impact on the conformation of p53.[172–176]

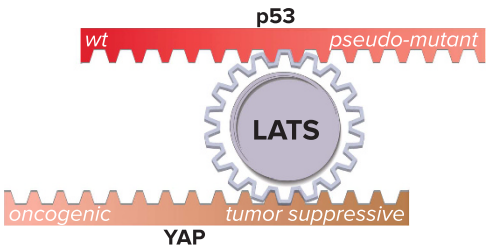

Figure 4 A LATS 'rheostat' may modulate p53 and YAP functionality. LATS1 and LATS2 (LATS) kinases are central modulators of both p53 and YAP activity. Although both p53 and YAP can facilitate both pro- and antitumorigenic activities, LATS kinases emerge as major regulators that maintain wt p53 activity and balance the tumor promoting functions of YAP

Similarly, differential binding of YAP to TEAD or p73 reflects the diametrically opposing roles of YAP. Whereas YAP association with TEAD leads to cell proliferation, epithelial-to-mesenchymal transition, inhibition of apoptosis and tumorigenesis,[177] YAP binding to p73 promotes apoptosis and differentiation.[106,110] Thus in different conditions, YAP can feature either as tumor suppressor or as oncogene.[36]

Both YAP and p53 might embody an inherent capacity to adopt pseudomutant status, which must be coordinated; perhaps by their common upstream regulator, LATS (Figure 4). Interaction of additional elements of the Hippo pathway beyond LATS,[169] might also modulate p53 conformation. In turn, pseudomutant wt p53 might mimic the impact of mutp53 on Hippo pathway function. In parallel, YAP itself might embody a spectrum of conformations that facilitate tumor-suppressive or oncogenic biological outcomes, depending on various signaling alterations including p53's functional state as suggested recently by Ferraiuolo and colleagues.[178]

Conceivably, YAP, which has been shown to bind mutp53, might bind wt p53 in conditions that induce pseudomutant conformation.

This dynamic situation is at odds with our binary categorization of genes into 'oncogenes' or 'tumor suppressors'. When proteins are thus labeled, our prediction of the range of their potential is restricted. For instance, we typically assume that tumor suppressors will inherently favor cell death. However, seemingly paradoxical observations made in tumor patients, as well as mouse models indicate that excessive apoptosis actually can aggravate tumorigenesis.[179,180] In contrast, through their ability to enable metabolic adaptation, p53 and Hippo components can support cell survival. These cell-protective functions help avoid damage and thereby prevent cancer development,[181] but these same functions may eventually by hijacked by cancer cells to assure their well-being and provide them with a competitive advantage in stressful conditions. Understanding the nuances that control context-dependent protein behavior and contrasting physiological fates is not merely a basic science puzzle, but will be essential for efficient therapeutic implementations.

Conflict of Interest

The authors declare no conflict of interest.

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