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Review

The LATS1 and LATS2 tumor suppressors: beyond the Hippo pathway

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Proper cellular functionality and homeostasis are maintained by the convergent integration of various signaling cascades, which enable cells to respond to internal and external changes. The Dbf2-related kinases LATS1 and LATS2 (LATS) have emerged as central regulators of cell fate, by modulating the functions of numerous oncogenic or tumor suppressive effectors, including the canonical Hippo effectors YAP/TAZ, the Aurora mitotic kinase family, estrogen signaling and the tumor suppressive transcription factor p53. While the basic functions of the LATS kinase module are strongly conserved over evolution, the genomic duplication event leading to the emergence of two closely related kinases in higher organisms has increased the complexity of this signaling network. Here, we review the LATS1 and LATS2 intrinsic features as well as their reported cellular activities, emphasizing unique characteristics of each kinase. While differential activities between the two paralogous kinases have been reported, many converge to similar pathways and outcomes. Interestingly, the regulatory networks controlling the mRNA expression pattern of *LATS1* and *LATS2* differ strongly, and may contribute to the differences in protein binding partners of each kinase and in the subcellular locations in which each kinase exerts its functions.
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Facts

- LATS1 and LATS2 proteins show extensive sequence similarity and share similar modes of post-translational modifications.
- The *LATS* genes are differentially regulated at the transcriptional level.
- LATS kinases engage divergent binding partners, although these effectors often converge on similar cellular processes.
- Whole-body deletion, as well as tissue-specific deletion, of either *Lats1* or *Lats2*, reveals critical differences in the *in vivo* functions of the two kinases.

Open Questions

- Additional signaling pathways: what other functions do LATS kinases have beyond restricting YAP/TAZ activity?
- Redundant *versus* divergent function: what is the contribution of each kinase to distinct biological processes?
- Phosphorylation substrates of LATS: how is LATS kinase target recognition determined beyond simple amino-acid sequence motifs?
- Pro- *versus* anti-tumor effects: how does cellular context direct LATS toward apparently opposing functional outcomes?

In recent years, the LATS1 and LATS2 kinases have become the focus of intense research interest. They are gaining prominence due to their broad range of biological activities in cell cycle regulation, differentiation and motility, as well as the diverse pathological outcomes of their deregulation. LATS kinases are critical for organism fitness, genome integrity and cancer prevention. The core kinase module is evolutionarily conserved from yeast through flies to humans, although effectors and biological impact have expanded over the course of evolution.

The yeast ortholog of LATS, Dbf2 is localized to the spindle pole body (yeast centrosome) and regulates mitotic exit.[1] Cdc15 (homolog of MST) is required for Dbf2 activation,[2,3] and together they constitute a kinase module of the mitotic exit network.[1,3] This module has been conserved in humans, manifested by LATS phosphorylation and activation by MST1/2 (MST) kinases.[4] During evolution, this module recruited numerous different effectors, most notably the transcriptional coactivators YAP and TAZ, and extended its repertoire of biological functions. The *Caenorhabditis elegans* LATS, Ce-Wts-1, is associated with development, lifespan and body length control.[5] Interestingly, nematodes lack YAP/TAZ,[6] and Ce-Wts-1 exerts its function via effectors of the TGF-beta signaling pathway.[5]

Deletion of the *Drosophila* Warts *(Wts,* the fly ortholog of *LATS)* causes dramatic tissue overgrowth and abnormalities in cellular polarity.[7,8] The fly Warts-Hippo (*Hpo*, MST ortholog) module exerts some of its functions via phosphorylation and inhibition of Yorkie (*Yki*, YAP and TAZ ortholog),[9] while maintaining ancestral Yki-independent functions.[10] The strong evolutionary conservation of the MST/LATS/YAP cascade (the Hippo pathway) is exemplified by the fact that human LATS

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proteins are able to rescue the loss of Wts functions in *Drosophila*.[11,12]

As in other developmental pathways, complexity tends to increase over evolution. This is evidenced by the existence of additional components impacting the Hippo pathway, a diversity that might have been facilitated by duplication of the single ancestral *LATS* gene into two paralogs (coinciding with the duplication of other Hippo components, i.e., *MST*, *TEAD* and *YAP*) during deuterostome evolution.[6] Genetic studies in mice have underscored the functional differences between the duplicated LATS kinases. Loss of *Lats2* is embryonic lethal on or before embryonic day E12.5, and this lethality is postulated to result from aberrant proliferation, mitotic defects and accumulated genomic instability.[13,14] In contrast, *Lats1*-null mice are viable. However, they suffer from developmental defects such as infertility, growth retardation, pituitary dysfunction and lack of ductal structures in the mammary gland. In addition, *Lats1−/−* mice are prone to spontaneous and oncogene-induced sarcomas.[15]

In this review, we examine the features of LATS1 and LATS2, some of which are redundant (presumably representing a common primordial LATS function), and others distinct (presumably acquired in the course of evolutionary diversification). The common ability of both LATS kinases to repress YAP/TAZ has been studied extensively (reviewed recently in Zanconato *et al.*[16] and Meng *et al.*[17]). Therefore we will focus mainly on LATS utilization of effectors other than YAP/TAZ, and the impact of those interactions on cell fate.

Protein Structure and Post-Translational Modifications of LATS Kinases

Human LATS1 and LATS2 are Ser/Thr kinases of the AGC subfamily, most closely related to the nuclear Dbf2-related kinases (NDR1/2).[18] While LATS1 and LATS2 share extensive sequence similarity within their kinase domain (85% similarity) located at the C terminus of the proteins, the N terminus portion displays significantly lower conservation (Figure 1 and detailed in Table 1).[19,20] Immediately carboxyterminal to the catalytic domain of both kinases is a hydrophobic motif; this pattern is akin to other AGC kinases such as AKT, S6K1 and PKC.[18] Within the lowly conserved amino (N) terminus, there are two stretches of conserved sequences (LCD1 and 2) that are required for proper LATS regulation and function.[21,22] Also within the N terminus, both LATS1 and LATS2 harbor evolutionarily conserved ubiquitin-associated domains. Such domains are known to bind ubiquitinated proteins and may function in LATS activation.[23] Interestingly, each of the kinases possesses unique features, which may facilitate different protein–protein interactions; the N terminus of LATS1 contains a proline-rich domain,[24] while a unique PAPA repeat is found in LATS2.[20] Furthermore, *LATS2* encodes one, and *LATS1* encodes two, PPxY motifs; these are essential for interaction with the WW hydrophobic pockets of YAP, TAZ and other Hippo pathway components.[25]

Superimposed on the amino-acid sequence is a combinatorial 'code' of post-translational modifications governing LATS activity (Figure 1; Table 1). Upstream signals such as cell cycle progression, cytoskeleton alterations and growth signals shape this code, defining different cellular outcomes.

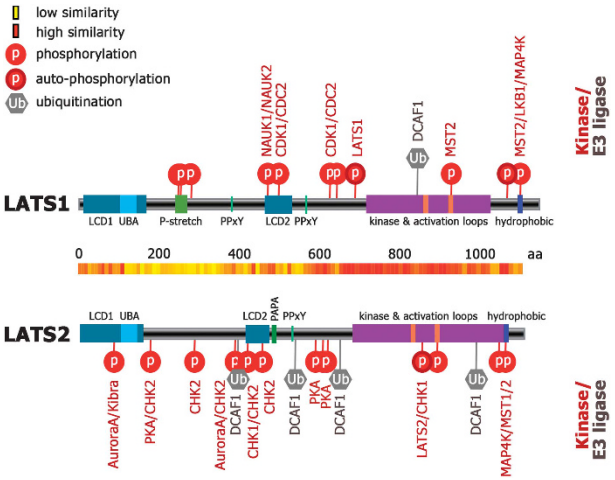

Figure 1 Schematic comparison of human LATS1 and LATS2 protein structures. Structural motifs, as defined by UniProtKB database, are represented as solid boxes on gray background. Reported phosphorylation sites are designated as red lollipops, with the phosphorylating kinase indicated above in dark red. Ubiquitination sites are gray denoted by hexagons, with the reported E3 ligase indicated above in dark gray. The heatmap between the LATS1 and LATS2 protein schemes represents the similarity of the aligned sequences, where dark orange represents high and yellow represents low amino-acid similarity. Similarity was calculated using the Waterman–Eggert local alignment application (EMBOSS explorer), comparing LATS1 (O95835-1) and LATS2 (Q9NRM7). Numbers above heatmap represent amino-acid position

LATS1 and LATS2 share dual phosphorylation–autophosphorylation mechanisms that are commonly employed by a subset of AGC kinases (including the aforementioned).[26] MST-dependent phosphorylations of LATS (S909/T1079 on LATS1 and T1041 on LATS2) increase its kinase activity.[4,27] Subsequently, MOB1 binding to the LATS hydrophobic domain relieves LATS autoinhibition and facilitates activating autophosphorylation (LATS1 residues S674 and S1049; LATS2 residue S835).[28] In humans and flies, recruitment of LATS to the plasma membrane promotes MST-dependent phosphorylation and activation.[29] PP2A-mediated dephosphorylation of these sites may counter MST-mediated phosphorylation to quench LATS1 activation.[28,30] The effect of PP2A on LATS2 phosphorylation status has not been examined.

Importantly, MST are neither obligatory nor the sole LATS activators. For instance, deletion of *Mst* in mouse liver results in YAP hyperactivity without reduction in LATS phosphorylation status.[31] In line with this, MAP4Ks phosphorylate both LATS1 and LATS2 hydrophobic motifs resulting in their activation and YAP inhibition.[32] Similarly, phosphorylation of LATS2 by PKA bypasses MST to augment LATS2 kinase activity toward YAP.[33] Other MST-independent phosphorylation of LATS may also result in cellular activities that are not related to YAP/TAZ regulation. For example, CHK1/2 phosphorylation of LATS2 S408 is associated with DNA damage-induced apoptosis.[34] Likewise, LATS2 is activated by CHK1 and ATR in response to oncogenic H-RAS.[35,36]

Additional phosphorylation events of LATS1 and LATS2 relate to mitotic progression. A subset of molecules of both LATS1 and LATS2 is located at the centrosome,[13,24] an organelle known for its crucial role in cell division.[37] In mitosis,

Table 1 Summary of reported LATS1/2 protein motifs and post-translational modifications

LATS1					LATS2				
Amino acid	**Motif/modification type**	**Catalyzed by**	**Associated with**	**Ref**	**Amino acid**	**Motif/modification type**	**Catalyzed by**	**Associated with**	**Ref**
13–167	LCD1			21,22	1–160	LCD1			21,22
103–143	UBA domain				101–141	UBA domain			
1075–1080	Hydrophobic motif				1037–1042	Hydrophobic motif			
236–266	Proline-rich domain (P-stretch)			24	403–463	LCD2			21,22
373–376	PPxY motif				467–480	Proline–alanine (PAPA) repeat			20
458–523	LCD2			21,22	515–518	PPxY motif			
556–559	PPxY motif				666–1046	S-TKc (catalytic domain)			19,20
705–1010	S-TKc (catalytic domain)			19,20	668–973	S-TKc (catalytic domain)			19,20
845–857; 905–915	Activation loop				808–820; 868–878	Activation loop			
S244	Phos		Nuclear phosphoproteins	194	S83	Phos	Aurora A, KIBRA	Mitosis	38,40,195
T246	Phos		Cancer; mitosis	196–198	S172	Phos	PKA, CHK2	YAP regulation	33,34
S278	Phos		Mitosis	198	T279	Phos	CHK2	UV radiation	198
S462	Phos			199,200	S380	Phos	Aurora A, CHK2	Mitosis	34,39,197
S464	Phos	NuaK1, NuaK2	Protein stability	41,198	S408	Phos	CHK1, CHK2	UV radiation	34
T490	Phos	CDK1/CDC2	Mitosis	197,201	S446	Phos	CHK2		34
S613	Phos	CDK1/CDC2	Cancer; mitosis	4,197,201	S576	Phos		Cancer	197,198
S633	Phos			4	S592	Phos	PKA	YAP regulation	33
S674	Phos		Autophosphorylation	4,121	S598	Phos	PKA	YAP regulation	33
S909	Phos	MST2	Activation	4	S835	Phos	Trans-auto-phosphorylation, CHK1	Apoptosis	153
S1049	Phos		Autophosphorylation	4	S872	Phos		Activation	27
T1079	Phos	MST2, LKB1, MAP4K	Activation	4,30,32,118,119,202–204	T1024	Phos		Mitosis	198
S1111	Phos			199	T1026	Phos		Mitosis	198
K830	Ub	DCAF1	Protein stability	51	T1041	Phos	MST1, MST2, MAP4K	Activation	4,27,30,32,118,119,203,204
Unknown	Ub	Itch	Protein stability	48,49	K383	Ub	DCAF1	Kinase inactivation	51
Unknown	Ub	WWP1	Protein stability	50	K527	Ub	DCAF1	Kinase inactivation	51
					K633	Ub	DCAF1	Kinase inactivation	51
					K968	Ub	DCAF1	Kinase inactivation	51
					Unknown	Ub	SIAH2	Protein stability	52

LATS1 (but not LATS2) is phosphorylated on T490 and S613 by CDK1/CDC2,[12] whereas LATS2 (but not LATS1) is phosphorylated on S83 and S380 by Aurora A kinase.[38–40] This may reflect a general divergent and complementary phosphorylation pattern, whose functional consequences remain to be explored.

Differential phosphorylation of LATS1 and LATS2 also affects their stability. Thus, LATS1 phosphorylation on S464 by NUAK1 reduces its protein levels,[41] whereas KIBRA stabilizes LATS2 by augmenting its phosphorylation and inhibiting its ubiquitination.[42] Additionally, LATS protein stability and kinase activity can be bolstered by binding to heat-shock proteins. For instance, both LATS kinases are clients of the molecular chaperone HSP90.[43] Interestingly, MOB1 binding rescues LATS destabilization caused by HSP90 inhibition,[43] suggesting that MOB1 also functions to stabilize the LATS proteins. On the other hand, destabilizers of LATS include the LIM domain-containing proteins Ajuba, Dachsous and Zyxin,[44,45] which facilitate cell proliferation by reducing LATS protein levels and inhibition of LATS activity.[45]

LATS protein stability is regulated also through ubiquitination by a number of E3 ligases. Thus, NEDD4 ubiquitinates and promotes the degradation of both kinases,[46,47] whereas additional E3 ligases with WW domains, such as ITCH and WWP1, specifically bind and destabilize LATS1.[48–50] The WW–PPxY interaction between these E3 ligases and LATS1 might serve a dual purpose, by both decreasing LATS1 levels and displacing YAP/TAZ from its PPxY-binding site. Interestingly, CRL4-DCAF1 performs inhibitory ubiquitination of both kinases.[51] However, whereas LATS1 is polyubiquitinated and directed to proteasomal degradation, LATS2 is oligoubiquitinated at multiple sites, resulting in kinase inactivation without enhanced degradation. This might reflect a cellular mechanism to free YAP/TAZ from LATS2 inhibition while retaining LATS2 kinase-independent functions. Yet, LATS2 is targeted for degradation by a distinct E3 ligase, SIAH2.[52] Intriguingly, SIAH2 activity is associated with hypoxic response,[53] and a decrease in LATS protein levels is critical for ROS-induced senescence.[54]

Regulation of *LATS* Gene Expression

Classically, tumor suppressors may undergo loss of function due to genomic deletions or mutations, or through epigenetic silencing. Loss of heterozygosity of *LATS1* was reported in ovarian,[55,56] cervical[57] and breast[58–60] cancer. Likewise, frequent copy number loss of *LATS2* also occurs in breast,[61] ovarian,[62] hepatocellular[63,64] and lung[65] cancer, as well as in chronic lymphocytic leukemia.[66]

On the other hand, mutations in the *LATS* genes are relatively rare. However, due to the growing popularity of large genomic sequencing projects, evidence of *LATS* mutations in cancer is gradually emerging.[67] In basal cell carcinoma of the skin, mutations occur specifically within the kinase domain of either LATS1 or LATS2 (16% or 12%, respectively), but rarely in both together.[68] Interestingly, in other tumor types only one of the kinases is significantly mutated. This is exemplified in esophageal and non-small-cell lung cancer, where tumor-specific mutations were found in *LATS2* but not *LATS1*.[65,69] This further suggests that LATS1 and LATS2 may play distinct, non-redundant roles in some tumors. Nevertheless, the low rates of mutations in *LATS* genes emphasize that other mechanisms are dominant in reducing LATS activity, and it remains to be shown whether these mutations are driver rather than passenger mutations during tumorigenesis.

Promoter hypermethylation is another mechanism by which tumor suppressors are often inactivated.[70] Such mode of inactivation has been documented for *LATS1*,[71–73] *LATS2*,[74,75] and in some cases for both, in various types of tumors.[76–82] Importantly, downregulation of *LATS* expression has been associated with more aggressive cancer phenotypes.[74,76–78,83] Promoter silencing can be mediated also by long non-coding RNAs (lncRNAs), which recruit the epigenetic machinery. Recently, it has been reported that the oncogenic lncRNAs PVT1, AGAP2-AS1 and LINC00673, whose elevated expression correlates with bad prognosis in non-small-cell lung and gastric cancers, tether polycomb repressive complexes to the *LATS2*, but not *LATS1*, promoter.[84–86] Depletion of lncRNA reinstates *LATS2* expression and causes p53-dependent cell death.

More broadly, *LATS2* mRNA levels are exquisitely sensitive to tumor suppressive signaling, and are tightly regulated both transcriptionally and post-transcriptionally (Figure 2 and detailed in Table 2), while this seems to be less pertinent to *LATS1* expression. Induction of *LATS2* contributes to p53 tumor suppressive functions through a positive feedback mechanism, wherein the LATS2 protein promotes p53 stabilization by binding and inactivating the major p53 inhibitor MDM2, while p53 directly positively regulates the transcription of the *LATS2* gene.[87–89] In addition to regulating basal levels of *LATS2*, binding of p53 to the *LATS2* promoter augments transcription in response to genotoxic, developmental and metabolic stresses.[35,87,89–91]

Like p53, FOXP3 also interacts directly with the *LATS2* promoter to induce *LATS2* expression.[92] Interestingly, the levels of FOXP3 are positively regulated by MST,[93] representing an additional mechanism by which MST promotes LATS2 activity. Intriguingly, also within the Hippo pathway, YAP/TAZ and their canonical partner transcription factor TEAD directly transactivate *LATS2* (but not *LATS1*) gene expression.[94,95] Hence, YAP/TAZ positively regulates the expression of one of their key negative regulators. Similarly, in fly wing disks, *Wts* expression is upregulated upon expression of activated Yki, and this depends on the fly ortholog of TEAD, Scalloped.[94] It has been proposed that this negative feedback loop between *LATS2* and YAP/TAZ serves to dampen the duration of YAP activity,[95] maintain homeostasis[96] and render the Hippo pathway more robust, in order to resist the oncogenic effects of excessive YAP.[94]

Nevertheless, positive regulation of *LATS* transcription does not always have a tumor suppressive outcome. For example, the *LATS1* promoter can be transactivated by CUX1, a transcription factor associated with acceleration of S-phase and tumorigenesis.[97,98] *LATS2* overexpression in nasopharyngeal carcinomas was found to be associated with poor prognosis,[99] and in metastatic human breast cancer cells high levels of LATS2 are associated with invasive and migratory capacities.[100] Furthermore, according to publicly available TCGA data, *LATS2* expression levels are elevated in glioblastoma, and the expression of both *LATS1* and *LATS2*

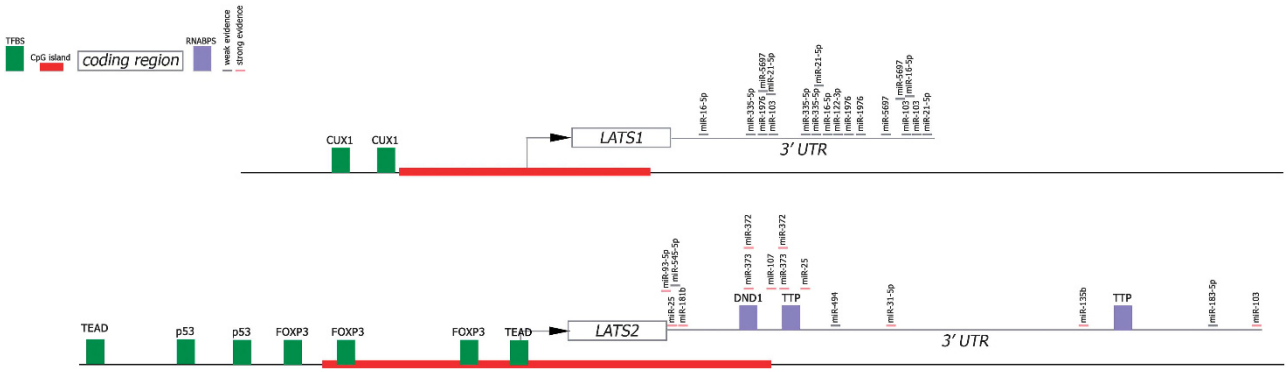

Figure 2 Scheme of human *LATS1* and *LATS2* genomic and mRNA structure. DNA is represented as a single black line. CpG islands (GC content >50%), as defined by UCSC Genome Browser (GRCh37/hg19), are indicated by thick red lines, the length of which corresponds to the relative length of the *LATS1* and *LATS2* CpG stretch. Transcription factor binding sites (TFBS) are represented schematically as dark green boxes, whereas RNA-binding protein sites (RNABPS) are mauve colored. The coding regions of LATS1 and LATS2 are not drawn to scale, but the 3′UTR is drawn in the same scale as the CpG island designation. miR binding sites with strong experimental documentation are indicated by an orange underline, whereas putative miR binding sites, documented in broader screens with less conclusive direct evidence (miRTArBase[193]), are indicated by light gray lines

is significantly augmented in stomach cancer.[101] This suggests that, contrary to the common assignment of LATS1 and LATS2 as tumor suppressors, retention of high LATS expression may actually sometimes be beneficial to the tumor, at least in some settings.

Post-Transcriptional Regulation of *LATS* mRNA

Several RNA-binding proteins have been shown to affect *LATS2* mRNA stability. Both Piwi-like 2 (PiwiL2), a protein which usually mediates gene silencing, and Deadend 1 (DND1) stabilize the *LATS2* transcript.[102,103] DND1 binds to the 3′UTR to protect *LATS2* mRNA from microRNA (miR)-mediated repression.[104,105] On the other hand, TTP, an AU-rich domain RNA-binding protein, promotes the degradation of *LATS2* mRNA by binding to its 3′UTR.[106] Interestingly, the DND1-binding site overlaps not only with miR target regions but also with one TTP binding site, consistent with the notion that multiple layers of RNA-binding proteins and miRs are in place to safeguard and modulate *LATS2* mRNA levels.

Strong evidence exists that at least four miRs directly bind the *LATS2* mRNA 3′UTR to repress LATS2 expression (Figure 2 and detailed in Table 2). One miR, miR-135b, targets the mRNA of *LATS2*,[107] as well as of additional components within the Hippo pathway (for instance *MOB1* and *NDR2*[108]), making it a 'Hippo-centric miR'. In contrast miR-31, an oncogenic miR overexpressed in numerous cancers,[109] specifically targets *LATS2* mRNA.[110] Additionally, miR-372 and miR-373 have been shown to inhibit *LATS2* mRNA, causing reduction of LATS2 expression and protein levels in testicular germ cell tumors,[111] and in cell lines derived from gastric cancer[112] and esophageal cancer.[113]

In contrast to *LATS2*, strong evidence of direct targeting of the *LATS1* mRNA 3′UTR by miRs is lacking. This may, in part, be due to the difference in length of the 3′UTRs (*LATS1* 814 nucleotides *versus LATS2* 1838 nucleotides, Figure 2), which might render the *LATS2* mRNA more vulnerable to miR-mediated inhibition. This supports the notion that, subsequent to the diversification of the ancestral *LATS* into two genes, evolution has shaped each of these genes to receive inputs from different signaling modules, thereby expanding substantially the connectivity of the Hippo pathway and providing it with a broader portfolio of 'networking' opportunities. Indeed, consistent with such conjecture, although both *LATS1* and *LATS2* 3′UTRs are each highly conserved across different species, there is a very low similarity between them (only 3% similarity between the 3′UTRs of human *LATS1* and *LATS2*, according to the BLAST algorithm).

Interestingly, some miRs can have an indirect positive impact on *LATS1* expression. For instance, miR-106b targets *ITCH* mRNA, encoding an E3 ligase that promotes LATS1 degradation, and in this way positively modulates LATS1 protein levels.[114] Likewise, miR-9 and miR-137 suppress the translation of *CUL4A*, a negative regulator of LATS1.[115] Notably, miR-9-3p (processed from the complementary strand of miR-9) targets *TAZ* mRNA;[116] thus, both strands of miR-9 function to reinforce the tumor suppressive potential of the Hippo pathway and quench the output of its oncogenic effectors.

LATS Protein Interactions and Cellular Localization

Pathway analysis of fly Warts binding partners (data from Kwon *et al.*[117]) revealed an enrichment of metabolic and DNA repair pathways. Some of these functions may be conserved in mammals, as energy stress and DNA damage have been shown to activate LATS.[118–121] Two studies have provided comprehensive pictures of the mammalian Hippo signaling interactome (refs 122,123 and Figure 3). As expected, proteins binding to both LATS1 and LATS2 are enriched for 'Hippo signaling'. However, proteins binding exclusively to LATS1 or LATS2 are quite different in their pathway enrichment. Thus, proteins associated with LATS1, but not LATS2, are related to Estrogen signaling, whereas LATS2 has Evolved a divergent interactome related to cell cycle, metabolism and p53. Of note, in both of these studies, the number of unique LATS2 interacting proteins was higher than of unique LATS1 interactors. Although this might have arisen from technical

Table 2 Summary of reported regulators of LATS1/2 mRNA levels

LATS1

Transcription factor	Binding position relative to TSS (approx.)	Ref
CUX1	– 400 bp – 600 bp	98

LATS2

Transcription factor	Binding position relative to TSS (approx.)	Ref
p53	– 4700 bp – 3000 bp – 2500 bp – 2000 bp – 800 bp – 600 bp	89
FOXP3	– 400 bp	92
YAP-TEAD	–10 000 bp 0 bp	94,95

LATS1

miRNA	3′UTR location	F function	Validation method	Refs
hsa-miR-103a-3p	717, 745, 301		NGS	205
hsa-miR-16-5p	94, 480, 718		NGS	205
hsa-miR-4279	NA		NGS	208
hsa-miR-1976	277, 538, 570		NGS	208
hsa-miR-6747-3p	NA		NGS	208
hsa-miR-6727-3p	NA		NGS	208
hsa-miR-4722-3p	NA		NGS	208
hsa-miR-3691-3p	NA		NGS	208
hsa-miR-5697	292, 660, 720		NGS	208
hsa-miR-335-5p	231, 413, 428	Suppresses lung and bone metastasis of breast cancer cells	Microarray	210
hsa-miR-122-3p	491		NGS	208
hsa-miR-21-5p	441, 300, 775	Promotes tumor invasion	Microarray	212,213
hsa-miR-5581-5p	NA		NGS	208
hsa-miR-4297	NA		NGS	208
hsa-miR-3614-3p	NA		NGS	208
hsa-miR-5697	292, 660, 720		NGS	208
hsa-miR-3653-5p	NA		NGS	208

LATS2

miRNA	3′UTR location	Function	Validation method	Ref
hsa-miR-103	1833	Promotes invasion and proliferation of colorectal cancer cells	qPCR, luciferase assay, western blot	206
hsa-miR-6773-3p	NA		NGS	207
hsa-miR-3153	NA		NGS	207
hsa-miR-25-3p	408 or 1	Proliferation and invasion of the gastric cancer cells	Reporter assay, western blot, qPCR	209
hsa-miR-545-5p	14		NGS	207
hsa-miR-4668-5p	NA		NGS	207
hsa-miR-4257	NA		NGS	207
hsa-miR-494-3p	507		NGS	207
hsa-miR-6847-5p	NA		NGS	207
hsa-miR-183-5p	1673		NGS	207
hsa-miR-135b-3p	1271	Lung cancer metastasis; MAPK/ERK signaling and proliferation	Microarray, qPCR	107,108,211
hsa-miR-1182	NA		NGS	207
hsa-miR-93-5p	2	Enhances tumor cells survival	Reporter assay, western blot, qPCR	214
hsa-miR-1178-5p	NA		NGS	207
hsa-miR-574-5p	NA		NGS	207
hsa-miR-562	NA		NGS	207
hsa-miR-4789-5p	NA		NGS	207
hsa-miR-570-5p	NA		NGS	207
hsa-miR-6867-5p	NA	NA	NGS	215
hsa-miR-548ba	NA	NA	NGS	207
hsa-miR-223-5p	NA	NA	NGS	215
hsa-miR-548ai	NA	NA	NGS	207
hsa-miR-223-3p	NA	NA	NGS	207
hsa-miR-548ag	NA		NGS	207
hsa-miR-6801-5p	NA		NGS	207
hsa-miR-548 m	NA		NGS	207
hsa-miR-4697-3p	NA		NGS	207

Table 2 *(Continued)*

LATS1					LATS2				
miRNA	**3′UTR location**	**F function**	**Validation method**	**Refs**	**miRNA**	**3′UTR location**	**Function**	**Validation method**	**Ref**
									207
					hsa-miR-510-3p	NA		NGS	
					hsa-miR-373-3p	249, 346	Bypass of p53-dependent senescence	Reporter assay, western blot, qPCR, microarray	111,113,216
								NGS	207
					hsa-miR-1256	NA		NGS	207
					hsa-miR-6739-5p	NA		Reporter assay, western blot, qPCR	217
					hsa-miR-181b-5p	2	Promotes proliferation and invasion		
					hsa-miR-372-3p	247, 347	Bypass of p53-dependent senescence	Reporter assay, western blot, qPCR, microarray	104,111,216
								NGS	207
					hsa-miR-202-3p	NA		NGS	207
					hsa-miR-215-3p	NA		NGS	207
					hsa-miR-6733-5p	NA		Reporter assay, western blot, qPCR	209
					hsa-miR-107	307	Proliferation and invasion of gastric cancer cells		
					hsa-miR-31-5p	678	Promotes lung cancer	Reporter assay, qPCR	109

reasons, it also suggests inherent differences between the kinases. Hence, as is also the case for regulation by miRs, evolution following the gene duplication event may have resulted in a broader spectrum of LATS2-binding partners, in order to increase its networking capabilities.

Among other things, choice of binding partners both is affected by, and affects, protein subcellular localization. Both LATS kinases have been detected on centrosomes,[13,24] which are presumably associated with their role in regulation of mitosis. Both can also be tethered to the plasma membrane[29,124] or localize to the cytoplasm.[21,125] It is commonly assumed that LATS kinases phosphorylate YAP/TAZ in the cytoplasm. Yet, phosphorylation-dependent activation of LATS has been observed in the nucleus,[51,126] while dephosphorylation of LATS1 and subsequent activation of YAP/TAZ can occur both in the nucleus and cytoplasm.[127] Furthermore, LATS1 was recently shown to localize to either the nucleus or the cytoplasm of mammary epithelial cells, depending on cell lineage.[128]

Many of the functions unique to LATS2 have been attributed to its nuclear localization[20] and its interaction with nuclear proteins. Upon mitotic or oncogenic stress, nuclear LATS2 potentiates the activity of the tumor suppressor p53.[35,36,89] In addition, nuclear LATS2 regulates chromatin dynamics by binding to polycomb repressive complex 2 (PRC2).[129] Nuclear LATS2 was shown to restrict oncogenic β-catenin signaling by disrupting the chromatin-bound β-catenin–BCL9 complex.[130] Accordingly, cardiac muscle-specific conditional knockout of *Lats2* generates an elevated Wnt signature,[131] and LATS2 expression is inversely correlated with the levels of Wnt target genes in human colorectal cancer.[130] In contrast, in similar experiments LATS1 was not shown to bind chromatin or restrict β-catenin-induced transcription.[130]

Also within the nucleus, LATS2 restrains steroid rector transcriptional activity. In the prostate, LATS2 inhibits androgen receptor chromatin binding and transcriptional activity,[132] while in breast tissue it modulates estrogen receptor (ER) activity.[133] More recently, LATS kinases have been shown to restrict the activity of ER by binding and promoting its degradation.[128] These studies implicate a nuclear function of LATS kinases in cell lineage commitment and in preventing the malignant progression of breast and prostate cancers.[128,132]

Together, a spectrum of subcellular localizations enables LATS kinases to impact a variety of physiological functions.[134]

Cell cycle Regulation and Apoptosis

Both LATS1 and LATS2 are involved in processes related to different stages of the cell cycle. Inhibition of CycE/CDK2 activity by LATS1 and LATS2 limits G1/S transition, under basal[21] as well as potentially genotoxic conditions.[120,121] In addition, LATS2 phosphorylation of DYRK1A promotes the assembly of the DREAM complex, which represses the expression of S-phase E2F target genes to promote senescence.[135]

Multiple studies have linked LATS kinases to mitosis. Both LATS1 and LATS2 can bind to CDC25B[136] and phosphorylate CDC26,[137] master regulators of mitotic exit. Other studies suggest distinct modes of action for LATS1 and LATS2 during mitotic transition.[138–140] In this scenario, LATS2 is

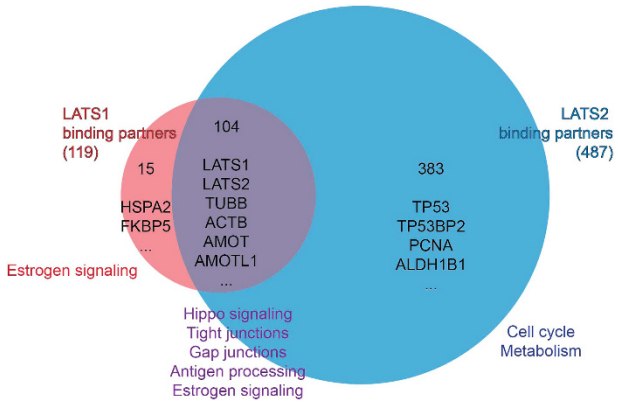

Figure 3 The protein interactome of LATS kinases. The Venn diagram depicts the overlap between putative LATS1 (119, light red circle) and LATS2 (487, light blue circle) binding partners in mammalian cells, as reported by Couzens *et al.*[123] and Wang *et al.*[122] The numbers of common or exclusive binding partners and specific notable examples are indicated. Key-enriched biological processes (KEGG pathway database) are shown below the diagram

phosphorylated by Aurora A, and phospho-LATS2 translocates to the spindle along with LATS1, which phosphorylates Aurora B to ensure proper cytokinesis.[39] The above-described mitotic function of LATS kinases in mammalian cells is reminiscent of the role of yeast Dbf2,[3] and may therefore represent an ancient dedication of the pathway to governing mitotic exit, which has been preserved in all metazoans.[6]

Since one of the functions of the mitotic exit pathway is to ensure that cytokinesis does not occur before proper partitioning of the genetic material, it may not be surprising that LATS1 and LATS2 are crucial in sensing mitotic stress that occurs in response to microtubule poisons such as nocodazole or during hyperproliferation owing to oncogene activation.[35,89,141] These functions are strongly associated with the ability of LATS2 to promote activation of p53-dependent checkpoints, which may lead to either G1/S arrest or apoptosis.[35,89] Indeed, extra chromosomes resulting from cytokinesis failure are sufficient to activate the Hippo pathway via the LATS2-p53 axis.[142] Together with its ability to be transactivated by p53, this constitutes a LATS2-p53 tumor-suppressive positive feedback loop. In line with this, nuclear LATS2 can associate with p53 on the *p21* promoter to inhibit proliferation under stress conditions.[143] In this context, it is interesting to note that overexpression of kinase-dead LATS1 suppresses the ability of cells to induce p53 in response to mitotic stress.[144] Although this suggests that p53 is also sensitive to LATS1, it remains plausible that the effects of kinase-dead LATS1 might be due to dominant-negative inhibition of endogenous LATS2.

Alleviation of the MDM2-dependent inhibition of p53 can eliminate potentially transformed cells from the replicative pool.[145] Sustained K-RAS signaling promotes LATS1/MDM2/p53-dependent apoptosis.[146] Likewise, expression of oncogenic H-RAS facilitates LATS2-dependent phosphorylation of the pro-apoptotic protein ASPP1, and drives p53-dependent apoptosis.[36] Furthermore, ASPP1 can bind and inhibit LATS1-mediated phosphorylation of YAP, resulting in increased YAP activity.[147] This molecular wiring might exemplify another mechanism by which LATS2 indirectly modulates LATS1 activity.

Additional means by which LATS1 can impact apoptosis have been suggested. LATS1 is activated by death receptors downstream of RASSF1A and MST2.[148] In turn, LATS1 increases the expression of the pro-apoptotic protein BAX.[140] Furthermore, LATS1 binds and enhances the protease activity of Omi/HtrA2,[149] a mitochondrial protein that is released into the cytoplasm during apoptosis.[150] LATS1 also feedbacks to inhibit MST2 pro-apoptotic activities by phosphorylating RAF1 on Ser259.[151] This phosphorylation promotes the inhibitory binding of RAF1 to MST2 and restricts RAF1 binding and activation of MEK signaling. Thus, by phosphorylating RAF1, LATS1 restricts both ERK-dependent cellular proliferation and MST2-dependent apoptosis.[151]

LATS2 can downregulate the expression of the anti-apoptotic proteins BCL-xL and BCL2 by a mechanism that requires its kinase activity.[152] Interestingly, the LATS2-p53 functional axis can regulate apoptosis not only through the downstream activation of p53 transcriptional target genes, but also by non-transcriptional mechanisms. In particular, following UV irradiation, LATS2 phosphorylates the p21 protein, encoded by a major p53 transcriptional target gene, to induce its degradation.[153] In this way, cells bypass cell cycle arrest and are directed to die. Of note, the p53 family member p73 can act as potent inducer of apoptosis when bound to YAP.[154,155] Interestingly, in leukemic cells, LATS2 promotes the pro-apoptotic activity of the p73–YAP complex.[156]

Surprisingly, inhibition of the p73–YAP complex by the LATS kinases can also have an anti-apoptotic affect.[157] LATS2 can also inhibit DNA damage-induced apoptosis through inhibitory phosphorylation of c-Abl.[158] The tyrosine kinase c-Abl is a strong inducer of the YAP-p73 pro-apoptotic axis in response to DNA damage.[159,160] Specifically, phosphorylation of YAP Tyr357 by c-Abl potentiates the binding to p73 and induction of pro-apoptotic genes.[159] Since, c-Abl and YAP can contribute or inhibit apoptosis,[159,161–163] their inhibition by LATS kinases results in opposing outcomes. Overall, this highlights an interplay between LATS, YAP, p73 and c-Abl, whose eventual impact on apoptosis is highly cell context-dependent.

In sum, LATS kinases govern cell fate by manipulating both cell cycle and apoptosis. This becomes particularly important when cells are faced with replicative or oncogenic stress and must be removed from the proliferative pool in a cost-effective manner and with the least harm to the organism as a whole.

Migration and EMT

Epithelial to mesenchymal transition (EMT) and migration, two important features in development and oncogenic transformation, are both regulated by LATS kinases. Mechanistically, human LATS1 and *Drosophila* Warts can bind to actin and inhibit actin polymerization.[164,165] In mammals, reduced LATS expression promotes cell migration by altering the functional state of p53[101] and by increasing the activity of the YAP/TAZ transcriptional module.[166] It is noteworthy that YAP/TAZ sensitivity to cytoskeleton and cell motility dynamics is critical to their role in mechanosensing, some of which is LATS-independent.[167] Overall, the inhibitory effects of LATS kinases

on cell migration are in line with their assignment as tumor suppressors.

Surprisingly, LATS2 can also potentiate the activity of tumor-promoting factors and augment EMT. In fact, LATS2 was reported to increase the cell invasive capacities of metastatic breast cancer cell lines harboring mutant p53.[100] In that case, the underlying mechanism was proposed to be the phosphorylation of SNAIL1 by LATS2, leading to increased SNAIL1 stability, nuclear localization and transcriptional activity.[100]

Embryogenesis and Stem Cells

The LATS-YAP/TAZ axis plays a key role in patterning of mammalian embryos and determining cell lineage and differentiation, as exemplified in mouse studies.[168–170] In support of this, inhibition of *Lats1* and *Lats2* expression in early embryos results in irreversible lineage misspecification and aberrant polarization of the inner cell mass.[170] Specifically, LATS2 seems to play a critical role in early embryogenesis. The pluripotent transcription factors OCT4 and NANOG bind a region near the *Lats2* (but not *Lats1*) gene, and repress *Lats2* expression.[171] Accordingly, deletion of *Lats2* (but not *Lats1*) is embryonic lethal.[13] Mouse embryonic stem cells (mESCs) lacking *Lats2* display an altered chromatin landscape that retains H3K4me3/H3K27me3 bivalent histone marks;[91] this may be related to the ability of LATS2 to associate with PRC2 to promote H3K27 tri-methylation.[129] In line with this, mESCs lacking *Lats2* are deficient in both sustaining pluripotency and responding to differentiation signals,[91] suggesting a cellular mechanism for the embryonic lethality phenotype of *Lats2−/−* mice. Importantly, inhibition of Yap/Taz activity fails to rescue the transcriptional defect of *Lats2−/−* mESCs; rather, the ability of LATS2 to maintain mESC homeostasis is mediated by the LATS2-p53 functional axis.[91]

Members of the miR-290 family of microRNAs (mouse orthologues of human miR-372/373) are highly expressed in undifferentiated mESCs, and can promote their proliferation by potentiating G1 to S transition. Downregulation of *Lats2* by these miRs contributes to pluripotency by interfering with the ability of LATS2 to promote G1 arrest.[172] Intriguingly, on the other hand, reprogramming to induced pluripotent stem cells has been shown to be inhibited by LATS2 via a p53-independent mechanism that does not accelerate cell proliferation.[173]

In more advanced stages of development, such as lineage-specific differentiation, LATS2 was shown to contribute to the differentiation process. For example, LATS2 inhibits preadipocyte proliferation and promotes adipocyte differentiation by inducing a PPARγ pro-adipogenic transcriptional program.[174,175] Although this was shown to be mediated by cytoplasmic retention of TAZ, it still remains to be investigated whether this function is shared also with LATS1. Altogether, LATS2 plays a unique role in embryonic stem cells and in differentiation.

Tissue-Specific Roles of LATS Kinases

YAP/TAZ are key regulators of liver size and, when hyperactivated, can drive liver tumorigenesis.[163,176] Thus, it is not surprising that inactivation of both LATS kinases in liver cells leads to failure of proper differentiation and augments proliferation.[177,178] Embryonic deletion of both kinases in the mouse liver results in neonate lethality.[177] In adult livers, acute deletion of *Lats1/2* results in dedifferentiation of hepatocytes into immature biliary epithelial cells, fibrosis and lethal liver impairment.[178] LATS2 also has additional hepatic functions, which are not mediated by YAP/TAZ activity and are not shared with LATS1. For example LATS2, but not LATS1, inhibits hepatic cholesterol accumulation by binding and quenching the transcriptional activity of SREBP1 and SREBP2, transcription factors that are master regulators of lipid and cholesterol homeostasis.[90] Consequently, mice lacking *Lats2* in the liver have deregulated cholesterol metabolism and are prone to fatty liver disease, suggesting that LATS2 plays a role in metabolic homeostasis.[85]

As in the liver, *Lats1* and *Lats2* are essential also in the kidney ureteric bud lineage: deletion of both *Lats* genes results in severe defects in branching morphogenesis, deregulated cell polarity and hyperactivation of YAP and TAZ.[179]

In the heart, inactivation of both LATS kinases reflects a role for LATS in restricting cardiomyocyte renewal and regeneration.[180] Interestingly, the individual functions of each kinase in cardiomyocytes may not be fully redundant, since inactivation of *Lats2* is sufficient to cause myocardial expansion[131] and *Lats2* overexpression negatively regulates ventricular mass in the heart.[181] Furthermore, the kinase activity of LATS2 is required for YAP's ability to regulate coronary vascular formation.[182] In line with these observations, expression of *Lats2*, but not *Lats1*, promotes apoptosis in cultured cardiomyocytes.[181]

Both LATS kinases are expressed ubiquitously throughout different human tissues,[134] except the spleen in which neither kinase is detected (Human Protein Atlas available at: www.proteinatlas.org).[183] Protein levels differ, with very few tissues showing similar trends of expression between LATS1 and LATS2. While LATS1 protein is detected in high levels throughout most tissues, LATS2 protein levels seem to vary, with highest expression in the gastrointestinal tract and the brain.[183] The functional impact of each kinase in different tissues remains to be further examined.

Conclusion

The great interest in the Hippo pathway components has generated a wealth of new information. Yet, many of the studies have focused exclusively on the pathway downstream effectors YAP and TAZ, and LATS kinases function, if addressed at all, has been examined merely in the light of their effect on YAP/TAZ. Furthermore, most studies employ only one *LATS* gene or protein, making it difficult to identify true differences between LATS1 and LATS2. In this review, we have tried to tease out and analyze discrete characteristics of LATS1 and LATS2, as recorded in the literature to date. We show that although, as expected, there does exist substantial functional overlap between these two paralogs, many of their features are nevertheless distinct.

The *LATS* duplication event set the stage for evolution to 'teach' us about LATS function. Gene duplication establishes a platform for exploring genetic novelty, while augmenting

genomic robustness by buffering paralogs.[184] Actually, evolution pushes the duplicated genes toward diversification, as total redundancy among duplicates is both genetically unfavorable and potentially disruptive to biochemical pathways due to dosage sensitivity.[185] Together, this suggests that the second copy is liberated from selective pressure and can evolve novel functions, as long as any ensuing functional losses can be complemented by the other copy.[186] Interestingly, alterations in gene expression often precede functional changes in paralog evolution.[187]

LATS1 and LATS2 embody this evolutionary format. The most striking differences between LATS1 and LATS2 occur on the transcript level. The difference in transcription factors regulating *LATS1 versus LATS2* may represent the necessity to keep tight reigns on the 'brakes' and 'gas' of proliferation signals by maintaining proficient levels of LATS in both conditions. Further indication of tight regulation on the transcriptional level is evident in their 3′UTRs: *LATS2* contains a long, highly regulated 3′UTR, whereas the shorter *LATS1* UTR may evade, at least to some extent, negative (miR) or positive (RNA-binding proteins) regulation. Interestingly, lengthening of 3′UTRs has been associated with increased morphological complexity over evolution[188] and might be linked to observations that regulatory motifs in UTRs are often conserved in genes within similar functional pathways.[189] It will be interesting to examine the possibility that *LATS2* has evolved functions that enable it to be co-regulated within the context of a larger functional gene family; this concept is illustrated by the observation that miR-372/3 commonly targets *LATS2* as well as other factors that are critical in stem cell differentiation.[190]

The divergent expression patterns of *LATS1* and *LATS2* might contribute to their likelihood of encountering distinct binding partners that, in turn, might tether the two LATS proteins to different cellular localizations and facilitate their distinct functions. This is illustrated by the specialized connection of LATS1 to estrogen signaling, and of LATS2 to stem cell differentiation and to the p53 network. It is important to note, however, that even in these 'dedicated' interactions, there is substantial redundancy between LATS1 and LATS2, which probably underpins their ability to serve as partial backups for each other. Thus, LATS2-specific interacting partners are not enriched in estrogen signaling,[122,123] yet both LATS1 and LATS2 have been shown to regulate the stability of the ER.[128] Likewise, p53 exclusively binds LATS2 but not LATS1[122] and transcriptionally activates the *LATS2* but not *LATS1* promoter,[89] but LATS1 can nevertheless modulate p53-dependent apoptosis.[146] Similarly, OCT4 and NANOG repress *Lats2* but not *Lats1* expression,[171] which is essential for proper embryonic development, but *Lats1* is also important for embryogenesis, since re-expression can rescue *Lats* depletion phenotype in early embryogenesis.[170]

In fact, a considerable proportion of LATS functions intersect on different elements of the same pathway. For instance, LATS2 is phosphorylated by Aurora A and LATS1 phosphorylates Aurora B.[39] Both Aurora kinases impact mitotic progression, however Aurora A associates with the spindle poles to regulate entry into mitosis and spindle assembly, whereas Aurora B regulates chromosome cohesion and cytokinesis.[191] Therefore, although the LATS1/2-specific mechanisms may have diverged, in most cases the broader physiological 'agenda' of the LATS kinases has been retained. Probably for these reasons, both LATS genes undergo selective silencing in cancer.

The LATS kinases restrict the 'canonical' Hippo effectors YAP and TAZ, and also control 'non-canonical' novel signaling pathways to integrate critical cellular processes. However, the distinction between 'canonical' and emergent LATS functions quickly becomes blurry. Some novel activities of LATS indirectly impinge on YAP/TAZ functions.[36,90,147] Additionally, due to YAP-LATS2 feedback, hyperactivation of YAP is expected to also inherently affect LATS2 non-canonical functions. Furthermore, LATS2 has been shown to act upstream to LATS1 and enhance its kinase activity toward non-canonical effectors.[39] Many non-canonical LATS kinase-regulated events are not associated with the HXRXXS/T consensus LATS phosphorylation motif,[192] suggesting that in these cases LATS substrate selection is shaped by factors other than just amino-acid sequence. Thus, complicated and multi-directional mechanisms are in place, even within the Hippo module itself.

Consequently, LATS-dependent cell fate decisions are the sum total of innumerous signaling inputs and outputs, the weight of each signal being determined (among many other factors) by cell density, cell type, developmental stage, neighboring cells and whether the cells are normal or transformed. Together, these complex signals lead to a vast and sometimes contradictory spectrum of LATS functions and activities. Some of the most striking examples are illustrated by the ability of LATS1 and LATS2 to both promote and inhibit apoptosis,[139,152,153,157,158] and the ability of LATS2 to both augment and inhibit differentiation[91,129] or cellular migration.[100,101]

Many open questions still remain to be answered. More meticulous studies need to be performed to accurately define LATS1 and LATS2 shared *versus* distinct functions. Advances in understanding LATS signaling may aid to resolve basic scientific enigmas such as how kinases choose phosphorylation substrates, how signaling pathways balance cell division, differentiation and proliferation, and how these pathways are skewed during cancerous transformation. Moreover, deciphering the details of LATS-mediated tumor suppression will hopefully elucidate opportunities for improved early detection, prognostication and treatment of cancer.

Conflict of Interest

The authors declare no conflict of interest.

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