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REVIEW

The STK38–XPO1 axis, a new actor in physiology and cancer

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Abstract
The Hippo signal transduction pathway is an essential regulator of organ size during developmental growth by controlling multiple cellular processes such as cell proliferation, cell death, differentiation, and stemness. Dysfunctional Hippo signaling pathway leads to dramatic tissue overgrowth. Here, we will briefly introduce the Hippo tumor suppressor pathway before focusing on one of its members and the unexpected twists that followed our quest of its functions in its multifarious actions beside the Hippo pathway: the STK38 kinase. In this review, we will precisely discuss the newly identified role of STK38 on regulating the nuclear export machinery by phosphorylating and activating, the major nuclear export receptor XPO1. Finally, we will phrase STK38′s role on regulating the subcellular distribution of crucial cellular regulators such as Beclin1 and YAP1 with its implication in cancer.

Keywords STK38 · Hippo · XPO1 · YAP1 · Cancer

The Hippo transduction pathway and its final contributor: YAP1

The Hippo pathway is a highly conserved signal transduction cascade that was discovered more than two decades ago in *Drosophila melanogaster* functioning as a key coordinator of tissue growth control and homeostasis [1]. Genetic screens in fly identified the core components of the Hippo pathway: Hippo (Hpo), Warts (Wys), Salvador (Sav), and Mob (Mats) [2, 3], named after Hpo mutations led to oversized organs, resembling like a hippopotamus [4]. The discovery of the transcriptional co-activator Yorkie (Yki) allowed to pave the way for the establishment for the current model of the Hippo signaling pathway [5] (Table 1).

From a restrained point of view, the core cassette of the mammalian Hippo pathway comprises the Ste20-like serine/threonine protein kinases MST1 and MST2 (mammalian Ste20-like kinases, also known, respectively, as STK4 and STK3), the AGC serine/threonine kinases LATS1 and LATS2 (for large tumor suppressor kinase), the SAV1 (aka WW45) and MOB1 (for Mps one binder 1) scaffold proteins, and finally the transcriptional co-activators YAP1 (Yes-associated protein 1) and TAZ (transcriptional co-activator with PDZ-binding motif), functioning as major effectors of the Hippo pathway [6, 7] (Table 1). As shown in Fig. 1, when the Hippo pathway is turned "on", by several cellular mechanisms that will be detailed thereafter, MST1/2 binds to SAV1, resulting in the phosphorylation of SAV1, MOB1, and LATS1/2. Activated LATS1/2 phosphorylate YAP/TAZ on multiple serine/threonine residues, inducing YAP/TAZ cytoplasmic retention and 14-3-3-mediated proteasomal degradation [8]. On the other hand, a turned "off" Hippo pathway results in the nuclear accumulation of active tyrosine-phosphorylated YAP/TAZ and the transcription of target genes via association with TEAD1-4 (TEA domain transcription factor 1-4) transcription factors [9, 10].

The mechanisms by which the Hippo pathway can be regulated have been extensively reviewed in the last decades

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Table 1 Mammals and fly orthologs of the core-cassette of the Hippo transduction pathway

Mammals	Fly
MST1/2 (also termed STK4/3)	Hippo (Hpo)
SAV1 (also termed WW45)	Salvador (Sav)
MOB1	Mob (Mats)
MAP4K1-7	Happyhour (Hppy) / Misshapen (Msn)
LATS1/2	Warts (Wts)
STK38/STK38L (also termed NDR1/2)	Tricornered (Trc)
YAP/TAZ	Yorkie (Yki)
TEAD1-4	Scaloped (Sd)

[1–4, 8]. Briefly, it has been reported that the Hippo pathway can be regulated by mechanotransduction. YAP/TAZ have been characterized as crucial sensors of mechanotransduction, where the stiffness of the extracellular matrix as well as the cell shape or the tensions of cells directly controls the activity status of YAP/TAZ [4]. In addition, it has also been reported that the Hippo pathway can be regulated by cell polarity and cell adhesion [1]. Some publications reported that the tight junction-associated scaffold protein Angiomotin (Amot) is a critical regulator of the Hippo pathway by directly interacting with YAP/TAZ [11]. More, a major component of adherens junctions has been also linked to the Hippo pathway: α-Catenin functions as a tumor suppressor by negatively regulating YAP1 activity during epidermal stem cell proliferation and tissue expansion [12]. Evidences have also been found about the implication of the Rho GTPases signaling pathway on the Hippo signaling pathway [13, 14]. The Hippo pathway can also be regulated by ligand-mediated activation (hormones, growth factors, etc.) of G protein-coupled receptors and the subsequent transduction pathways activation. The resulting YAP/TAZ activity status has been shown to depend on the types of coupled heterotrimeric G protein coupled to the transmembrane receptor [15]. Finally, cellular stress has a direct impact on the Hippo pathway: Energy sensing, osmotic stress, endoplasmic reticulum stress, and hypoxia have been shown to mediate the Hippo pathway activation status [4].

Observations of overgrowth upon Hippo pathway dysregulation have led to the investigation of its role in cancer. It has been reported that hyperactivation of YAP/TAZ or TEAD, found in many human cancers, confers proliferative advantage, promotes cell migration, and enhances cell metastasis as well as drug resistance [16]. Recent studies highlighted the role of the Hippo pathway in several aspects of altered metabolisms pathways in cancer cells. For example, YAP1 increases the glucose uptake in cancer cells by enhancing the transcription of the GLUT3 transporter [17]. More, the mevalonate pathway of the cholesterol synthesis pathway activates YAP/TAZ via Rho GTPases, while inhibition of this pathway suppresses YAP1 nuclear localization and YAP1-driven tumor growth [18]. Finally, YAP1 activation by LATS1/2 deletion in cancer cells triggers an antitumor immune response via activation of the TLR–MYD88/TRIF pathway by secreting nucleic acid-rich extracellular vesicles [19].

This linear signaling model served well for the initial studies of the Hippo pathway, but recent studies linked additional kinases as novel members of the Hippo signaling such as the AGC serine/threonine STK38 and STK38L (also known as NDR1 and NDR2, respectively) and members of the Ste20-like MAP4K family (Fig. 1). In detail, members of the MAP4K kinase family can phosphorylate STK38 [20] and LATS1/2, resulting in YAP/TAZ transcription activity inhibition [21]. Finally, a recent study, using a combination of biochemical, cell biological, and genetic approaches, has established STK38/STK38L as additional YAP1 kinases [22].

Characteristics of STK38/STK38L

The AGC (for protein kinase A (PKA)/PKG/PKC-like) class of protein kinases is the third largest represented group of kinases in the human cell by containing 70 proteins classed in 14 groups [23]. All members of this class of protein kinases require phosphorylation on a conserved motif for their activation. Based on the sequence of their catalytic domain, the STK38 and STK38L (aka NDR1 and NDR2, respectively, for nuclear Dbf2-related 1/2) serine/threonine kinases define a subgroup of the AGC group of protein kinases. For reading simplicity, we will refer as the STK38 family to define the two STK38/STK38L isoforms. The STK38 family is evolutionarily conserved from yeast to human: Members can be found in *Drosophila melanogaster* (Trc, tricornered), *Caenorhabditis elegans* (sensory axon guidance-1 (SAX-1)), *Saccharomyces cerevisiae* (Dbf2p and Dbf20p), *Schizosaccharomyces pombe* (Sid2p), and some other fungi and plants [24].

The primary structure of STK38 kinases family is well conserved from yeast to human [24] and is composed of three main domains. First, a N-terminal regulatory domain (NTR) located at its N-terminus contains a high number of hydrophobic amino acids and is known to be essential for the binding of the regulatory MOB1A protein to STK38 (Fig. 2) [25], a mechanism required for STK38 activation. Interestingly, a phosphorylation site (Thr74) is located within this NTR only in humans and is required for full kinase activity [26, 27]. Because of this, the NTR domain is also known as the S100B/hMOB1 association (SMA) domain. The second domain (highlighted in yellow in Fig. 2), specific of the STK38/STK38L subgroup within the AGC group

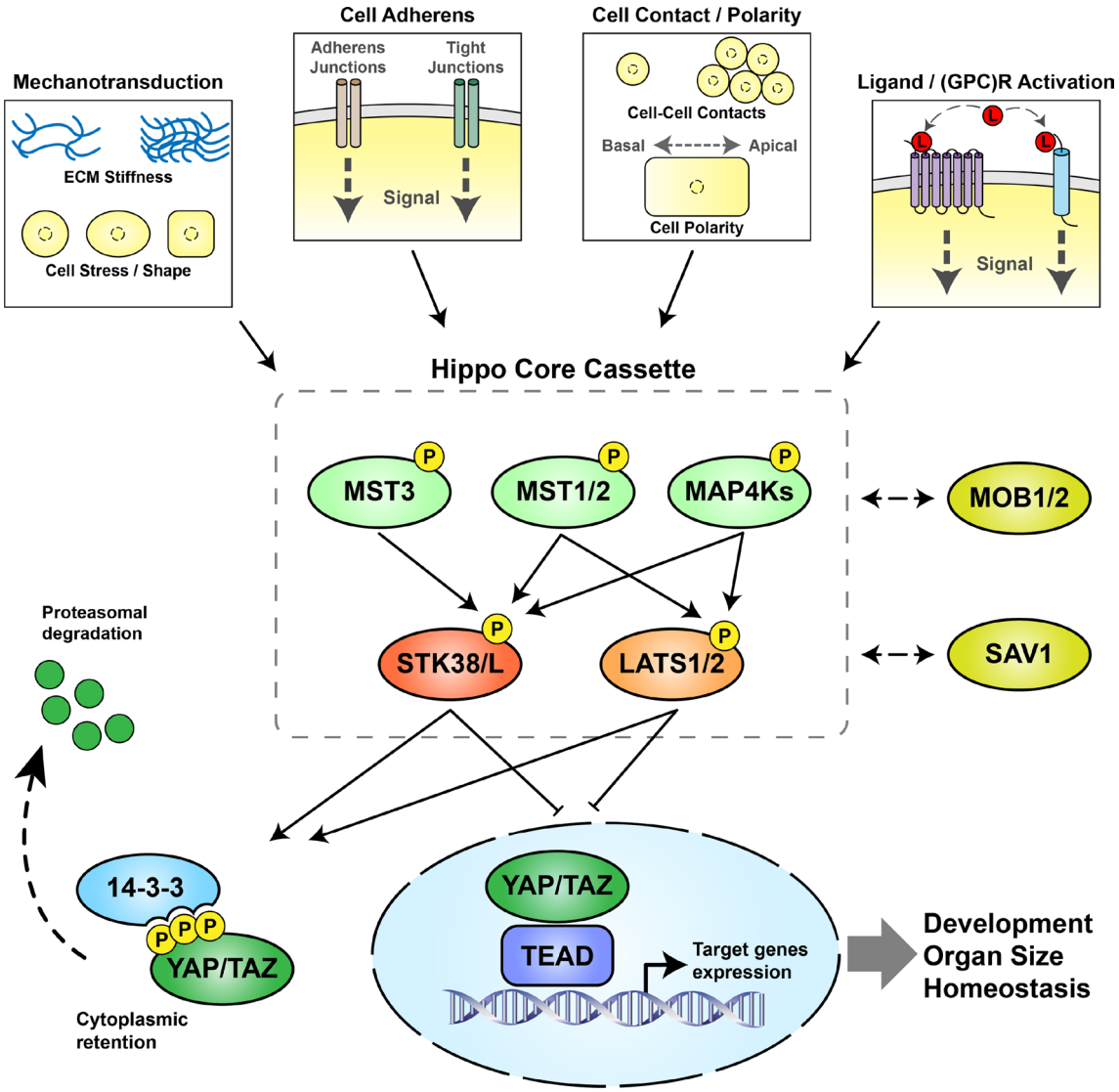

Fig. 1 Overview of the Hippo pathway. The Hippo pathway can be turned "on" by several cellular mechanisms such as mechanotransduction, extracellular matrix stiffness, cell polarity and adhesion, ligand-mediated activation of receptors, and crosstalk with other signaling pathways. Components of the Hippo core cassette comprise the MST1/2/3 and MAP4Ks kinases that phosphorylate and thus activate, STK38, STK38L, and LATS1/2 proteins. The binding/scaffolding proteins MOB1/2 and SAV1 participate in the phosphorylation/activation of the Hippo kinases. Important: MST3 seems not to participate in LATS1/2 phosphorylation and activation. Activated STK38/STK38L and/or LATS1/2 inhibit YAP/TAZ by multiple phosphorylations, leading to YAP/TAZ cytosolic sequestration and 14-3-3-mediated proteasomal degradation. While turned "off", YAP/TAZ accumulate in the nucleus, associating with TEAD1-4 transcription factors, and activating the transcription of target genes implicated in processes such as development, organ size control, and homeostasis

of protein kinases, is the catalytic/kinase domain that can be divided into 12 subdomains. The activity domain that is located in subdomain VIII contains a second phosphorylation site at Ser281 [24]. This site, whose phosphorylation is required for STK38 kinase activity, has been defined as an auto-phosphorylation site, thus phosphorylated by STK38 itself [26–28]. As mentioned above, this activity segment is present in all STK38-family proteins and is essential for the catalytic activity of the STK38 kinases, indicating here a highly conserved activation mechanism. Finally, the last domain, located at the C-terminus of STK38, has been characterized as a hydrophobic motif and contains the last phosphorylation site (Thr444), phosphorylation of which is required for the kinase activity (Fig. 2) [29].

It had to wait until 2018 to have to first reported tridimensional structure of STK38. There is only one report for a tridimensional structure of STK38 [30]. In this publication, the authors performed X-ray crystallographic analysis of the kinase domain of human STK38 (highlighted in yellow in Fig. 2) and revealed an entirely defined elongated activation

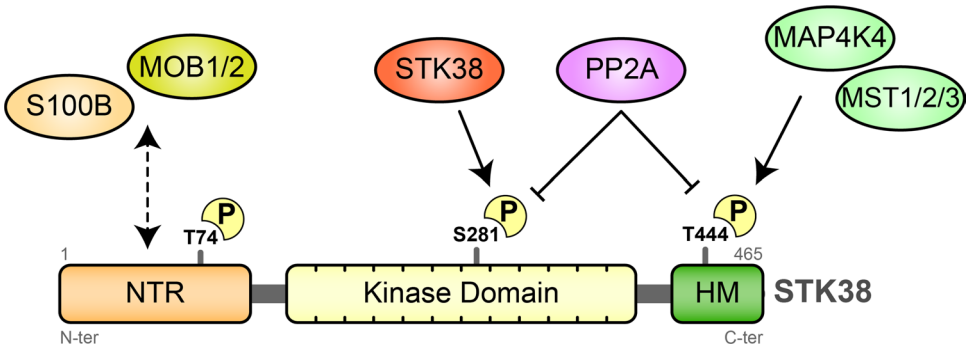

Fig. 2 STK38 characteristics. The primary structure of human STK38 is composed of three major domains. The N-terminal regulatory domain (NTR) highlighted in orange contains the binding site(s) for both S100B and MOB1/2 scaffold/regulatory proteins and the Thr74 phosphorylation site. The kinase domain (in yellow) encompasses the Ser281 (auto-)phosphorylation site and the hydrophobic motif (HM) in green carry the Thr444 that can be phosphorylated by MST1/2/3 and/or MAP4K4 kinases. Both Ser281 and Thr444 can be dephosphorylated by PP2A, participating in STK38 activity regulation

segment that blocks substrate binding in STK38 inactive state. More, mutations of this helix αC activation segment dramatically enhanced STK38 kinase activity when deletion of this segment caused an increase in binding with upstream Hippo components, demonstrating that this loop can be characterized as an auto-inhibitory segment [30].

Regulation of STK38

Extensive biochemical analyzes have been carried out in mammalian cells in order to understand the molecular mechanisms regulating STK38 in the past years. In this section, we will resume how the human STK38 kinase is regulated by post-translational modifications such as phosphorylation and by association with regulators.

Phosphorylations

In a simplistic view, STK38 is activated by phosphorylation and inactivated by dephosphorylation on multiple sites. STK38 contains three main regulatory phosphorylation sites required for its kinase activity: one in the NTR domain at Thr74, one in the activation segment at Ser281, and one in the hydrophobic motif at Thr444 (Fig. 2) [31]. It is established that binding of MOB1A/B to the NTR domain of STK38 dramatically increases the auto-phosphorylation of STK38 on Ser281 in the activation segment and thus its kinase activity [25, 27]. Phosphorylation of Thr444, located in the HM of STK38, is performed independently of STK38 kinase activity [26] by upstream kinases. It is well established that MST1, MST2, and MST3 phosphorylate STK38 on Thr444, inducing the activation of the kinase [27, 29, 32–35] (Fig. 2). Additionally, MAP4K-type kinases, which are also members of the Ste20-like kinases family, can regulate STK38 through phosphorylation on the HM [21]. In this context, our team recently reported that RalA and MAP4K4 activate STK38 upon stress response and apoptotic signaling. In detail, our laboratory reported that the Ste20-like kinase MAP4K4, an effector of RalA via the exocyst complex [36, 37], directly phosphorylates STK38 on its Thr444 under osmotic and oxidative stress [20]. Moreover, the team found that TNF-α (for tumor necrosis factor α) triggered apoptosis induction signals through this RalA–MAP4K4–STK38 pathway.

Very little is known on the contribution of Thr74 phosphorylation to STK38 kinase activation. It seems that Thr74 is only involved in the binding of S100B to the NTR of STK38, mechanism crucial for STK38 activity [26] (Fig. 2). In conclusion, both Ser281 and Thr444 must be phosphorylated for the full activation of the STK38 kinase [24, 31, 32, 38]. Mutating either Ser281 in the activation segment or Thr444 in the HM to Ala almost completely abolished the kinase activity of STK38 [26–29, 39–42]. Interestingly, mutations of the above-mentioned residues into phosphomimetics alterations (S281D/E and T444D/E) cannot trigger the activation of STK38 [32]. Both Ser281 and Thr444 can be dephosphorylated by PP2A (protein phosphatase type 2A) [24] (Fig. 2). Treatment of cells with okadaic acid (OA), a potent inhibitor of PP2A, results in an important increase in STK38 phosphorylation on both Ser281 and Thr444 and its subsequent kinase activity [26, 28, 43]. Purified PP2A is able to completely inactivate STK38, indicating that STK38 is controlled by this general phosphorylation/dephosphorylation cycle [28]. In addition to OA treatment, in vitro artificial activation of STK38 can be accomplished through the above-mentioned mutations into either the activation segment or the HM [44] and also by targeting STK38 to the plasma membrane [45]. Numerous post-translational modifications, such as other phosphorylation sites, ISGylation, and acetylation, have been detected for STK38 and can be found on the Cell Signaling PhosphositePlus database (www.phosp

hosite.org). Nevertheless, neither of their molecular or physiological relevance has been determined yet.

MOB proteins

Another layer of complexity can be added on the STK38 activation processes: the MOB family adaptor proteins. In the Hippo core signaling, MOB1 can acts as a central adaptor by directly interacting with MST1/2, LATS1/2, and STK38/STK38L kinases [46]. It has been reported that MOB1A/B and MOB2 bind to the positively charged NTR of STK38 by a negatively charged area on its surface [25, 45, 47, 48]. Current evidences suggest that MOB1 phosphorylation on Thr12 and Thr35 by MST1/2 can regulate MOB1 binding to the NTR of STK38 where some studies showed that MOB1 binding to STK38 can have multiple functions. First, this binding can stimulate STK38 autophosphorylation on the serine residue located in the T-loop (S281) [38]. More, it has been reported that MOB1 binding to STK38/LATS kinases is required for their HM phosphorylation on T444 by MST1/2 in human cells [33]. It has also been reported that the MOB1/STK38 complex formation seems to be essential for STK38 activation by STK38 auto-phosphorylation on Ser281 and HM phosphorylation at Thr444 by MST1 [44] (Fig. 2).

Interestingly, a competition for MOB isoforms binding to STK38 has been reported in several publications. While binding of MOB1 to STK38 increases STK38 activation [33], the binding of MOB2 to STK38 results in the inhibition of STK38 activation [49], highlighting a divergent effect of MOB isoforms binding to STK38, and a novel layer of regulation. Importantly, a recent publication reported that MOB1 binding to STK38 induced the NTR domain to interact with the HM [50], suggesting that a conformational change, in addition to post-translational modifications, is crucial for STK38 activity.

Scaffolding proteins and subcellular localization

To ensure that the system works with rapid exposure and to minimize the diluting effect of free diffusion in the cellular soluble space, a group of scaffolding proteins (identified in yeast, *C. elegans*, *D. melanogaster*, and humans) is mobilized to optimize the responsiveness of this "alarm system" [51]. In detail, in yeast that Tao3p and Mob2p interact genetically and biochemically with the Cbk1p and Orb6p kinases (homologues of human STK38), respectively, interaction important for kinases activation. In *C. elegans* and *D. melanogaster*, SAX-2 and Fry (for Furry) also exhibit a strong genetic interaction with SAX-1 and Trc, homologues of human STK38 [24], respectively. It has also been reported that STK38 kinase activity is required for chromosome alignment during cytokinesis, kinase activity being under the dependency of Fry and MST2 [52]. These results suggest that MST2, Fry, and MOB2 are crucial for STK38 activation. Finally, it has been shown that targeting MOB proteins to the plasma membrane was sufficient to activate both STK38 and STK38L [29].

STK38 is regulated by a wide spectrum of mechanisms at various levels. Phosphorylation by Ste20-like kinases (MST1/2/3, MAP4K4), dephosphorylation by PP2A, MOB/S100B binding to the N-terminus, association with scaffolding proteins, and cellular localization seems all to regulate STK38 activity and functions. These multiple regulations mechanisms reflect the requirement for stringently controlled spatial and temporal activation systems.

Biological functions of STK38

As a general model, it has been reported that mammalian STK38 is not essential for development because STK38 deficient mice are viable [53]: Loss of STK38 seems to be compensated by up-regulation of STK38L protein level [54, 55]. Here, we will provide an overview of the cellular functions of STK38 both in physiology and if not in cancers at least in oncological features of cancer cells.

Centrosome duplication

The first function in mammals attributed to both STK38 and STK38L is their role in centrosome duplication [33]. As a first insight, STK38 kinases have been detected on centrosomal structures throughout the entire cell cycle [56]. More, overexpression of STK38/STK38L resulted in centrosome overduplication in a kinase-dependent manner, while expression of kinase-dead STK38/STK38L or depletion of STK38/STK38L by small interfering RNA (siRNA) negatively affected centrosome duplication [57]. It has also been reported that STK38/STK38L kinase activity regulates centriole duplication directly on the centrosome in a Cdk2-dependent manner. As a final layer on STK38/STK38L impact on centrosome duplication, further work demonstrated that STK38/STK38L function on centrosome duplication relies on their interaction with MOB1A/B and the regulation of their HM phosphorylation by MST1 [24].

Cell cycle progression

STK38 has also been linked to the regulation of G1/S cell cycle progression through the regulation of MYC and p21/Cip1 protein level. It does so, downstream of the Hippo kinase MST3, by mobilizing MYC and preventing the accumulation of p21 [58]. Interestingly, p21 was the first direct in vivo substrate of mammalian STK38/STK38L kinases, getting phosphorylated on its Ser146, which leads to its

degradation. In the absence of STK38 kinases, unphosphorylated p21 accumulates in the cell, resulting in G1-arrest and impaired cell proliferation, while overexpression of STK38/STK38L resulted in p21 degradation. In addition, it has been shown that Cyclin D1 promotes cell cycle progression by enhancing STK38/STK38L kinase activity [59]. Even more, Cyclin D1 directly interacts with STK38/STK38L, increasing their kinase activity required for the G1/S transition.

Additionally, it has been reported that both STK38 and STK38L directly bind to MYC, independently of their kinase activity, and that this interaction requires the phosphorylation of their HM domain [35]. MYC is a transcription factor regulating cell proliferation, growth, apoptosis, and differentiation with protein levels tightly regulated by both transcriptional and post-transcriptional mechanisms, while defects in controlling MYC levels result in tumor development [60]. MYC directly interacts with the NTR (residues 1 to 82) of STK38 for its stabilization, interaction being modulated by STK38 HM phosphorylation status. STK38 overexpression increases the endogenous MYC level, a phenomenon phenocopied by MST3 overexpression and the consequent STK38′s HM domain phosphorylation. This relationship has been functionally tested in MYC-addicted lymphoma: STK38 silencing resulted in c-myc protein level decrease and the apoptosis of cancer cells [61]. The effect shows a tumor suppressive role for STK38 by the intermediate of its action on MYC abundance, in addition to its disarming action on YAP in the different cellular context [22]. Finally, we recently established that STK38L could phosphorylate the RhoB GDP-GTP exchange factor GEF-H1, leading to its inhibition and down-regulation of RhoB, inducing cytokinesis defects, since we reported that proper chromosome segregation was STK38L- and RhoB-dependent, upon RASSF1A loss, and subsequent hyperactivation of YAP1 [62].

DNA damage response

It has been reported that STK38 can interact with and participates in the activation of XPA (xeroderma pigmentosum A protein), which triggers the nucleotide excision repair (NER) pathway [63, 64]. STK38 increases XPA nuclear localization after UV irradiation, while STK38 silencing delayed the DNA repair response after UV irradiation in both normal and cancer cells. In line with its contribution to DNA repair, HeLa cells presented an increased sensitivity to ionizing radiation upon STK38 silencing in a HSP90-mediated way [65]. STK38 is involved in DNA damage repair in more than one way via more than one partner: STK38 regulates also the DNA damage-induced G2/M checkpoint by directly phosphorylating CDC25A (for cell division cycle 25 homologue A) at Ser76, leading to CDC25A degradation [66]. This indicates that phosphorylation of CDC25A by STK38 and its subsequent degradation contributes to promote DNA damage-induced G2/M checkpoint activation.

Immune response and immunology

STK38/STK38L double knockout in mice revealed that STK38/STK38L function downstream of MST1 in thymocytes and are required for thymocyte exit and migration [65, 67]. In addition to adaptive immunity, STK38 plays also an important role in the innate immune response by reducing cytokine secretion and limiting inflammation, in a kinase-independent way [68]. Relationship to immunity is even broader: Both STK38 and STK38L are incorporated in HIV-1 particles and are cleaved by the HIV-1 protease, inhibiting their activity [69, 70]. To end this collection of data, STK38 enhances anti-viral immune response by positively regulating type I and type II IFN pathways [71]. Controversy to its tumor suppressive role in some solid tumors, the deregulation of STK38 expression level in acute lymphoblastic leukemia cells has suggested a supportive role for STK38 in the development of leukemias [72].

Autophagy

At odd with the above-mentioned roles of STK38 related to DNA metabolism regulation, STK38 was revealed as a positive regulator of starvation-induced autophagy, acting very early in the process of autophagy induction. These observations followed the original finding that STK38 was a novel binding partner of Beclin1, a key regulator of autophagy [73]. This showed that STK38 promotes autophagosome formation in human cells and in fly in a kinase-dependent manner. Moreover, in this process STK38 supports the interaction of the exocyst component Exo84 with Beclin1 and RalB and that STK38 activity is stimulated in a MOB1- and exocyst-dependent manner. In contrast, RalB depletion triggers hyperactivation of STK38, resulting in STK38-dependent apoptosis under prolonged autophagy conditions [74]. STK38 lies at the heart of an intricated network of signaling pathways and, together with the RalB GTPase, assists the coordination between autophagic and apoptotic events upon autophagy.

Mitochondrial quality control and anoïkis resistance

Eukaryotes employ elaborated mitochondrial quality control (called mitophagy) in order to maintain the function of this power-generating organelle where Parkinson's disease-associated PINK1 and Parkin proteins are involved in. In flies, PINK1 induces STK38 (Trc) relocalization to the mitochondria, resulting in STK38 phosphorylation and activation [75]. Reciprocally, knockdown of STK38 in HeLa cells, but not STK38L, led to altered mitochondrial distribution,

compromised recruitment of Parkin by PINK1 to the mitochondria and therefore delayed clearance of damaged mitochondria. Importantly, they showed that STK38 silencing significantly attenuated Parkin phosphorylation, consistent with Parkin acting downstream of STK38.

Consistently with this model, STK38 is permissive for anoïkis survival in Ras-driven cancer cells [76]. The consequence impacts also key oncological feature: STK38 knockdown impaired anoïkis resistance, anchorage-independent soft agar growth, and in vivo xenograft growth of Ras-transformed human cells. Thus, STK38 supports Ras-driven transformation through promoting detachment-induced autophagy and that STK38 is required to sustain the removal of damaged mitochondria by mitophagy. Moreover, knockdown of PINK1 or Parkin, two positive regulators of mitophagy, also impaired anoïkis resistance and anchorage-independent growth of Ras-transformed human cells. These results shed light on the supporting oncogenic role of STK38 in Ras-dependent cancer cells. Upon extracellular matrix detachment, PINK1, Parkin, and STK38 work in concert for mitochondrial clearance and allow the anoïkis-induced apoptosis, this avoidance being an oncogenic transformation landmark.

Apoptosis and osmotic stress

Several publications shed light on STK38′s role in stress and apoptosis management. The first one, published in 2008 and establishing STK38/STK38L as novel pro-apoptotic kinases, reported that Fas receptor stimulation induced STK38/STK38L phosphorylation and activation, by MST1, acting downstream of RASSF1A, in a MOB1-dependent way [34]. More, the authors found that knockdown of STK38 significantly reduced cell death, while overexpression of the kinase potentiated apoptosis. Two years later, Cornils and colleagues found that STK38 was activated by a variety of pro-apoptotic stimuli in mice [55]. In addition, they found that tumor development in mice and humans was accompanied by a decrease in the overall amounts of NDR proteins in T cell lymphoma samples, suggesting that a reduction of STK38/STK38L protein level results in deficient apoptosis, thereby facilitating the development of tumors [55].

Some publications from the Camonis Lab also pinpointed the apoptotic role of STK38 in stress management: TNF-α cytokine treatment or overexpression of RASSF1A, a rather upstream regulator of the Hippo pathway, induced apoptosis through a RalA-MAP4K4-STK38 pathway and that MAP4K4 phosphorylates STK38 on Thr444 under several oxidative stresses [20]. It has also been reported that RalB depletion triggers hyperactivation of STK38, resulting in STK38-dependent apoptosis under prolonged starvation conditions, suggesting that STK38 and RalB assist the coordination between autophagic and apoptotic events upon autophagy induction [73, 74].

Since the Hippo/YAP pathway can be interpreted as a stress management pathway, the above-presented data point toward a complex network of regulation with RalB limiting STK38 activation upon starvation, slowing the path to cell death. On the other hand, under a different stress (TNF-α) RalA, similar to RalB and sharing almost all RalB partners, is required for STK38 proper activation and cell death. Finally, upon a third stress (anoïkis), death is avoided upon STK38 activation, so STK38 can be seen as a two-edged sword, leading to or voiding cell death. This "schizophrenic" kinase warrants more investigations to get the truth of its total function. With all these uncertainties, it remains elusive whether STK38 inhibition would be beneficial or detrimental to cancer patients.

Nuclear export and XPO1

Our team recently reported a new role for STK38, regulating the nuclear export of proteins. Faithfull in our mission to establish protein interaction maps that would build up signaling pathways and taking advantage of the APEX2-based proximity labeling [77], we found that STK38 shuttles between the nucleus and the cytoplasm in a kinase and XPO1-dependent manners, depending on the context: suspension growth and nutrient starvation-induced autophagy, respectively [43]. At the end of the day, we documented a model where STK38 phosphorylates XPO1 on Ser1055 within an auto-inhibitory domain; this action relieves the auto-inhibition and consequently activated the XPO1-mediated nucleo/cytoplasmic shuttling. What follows is the nuclear export of XPO1 cargoes, including STK38 itself. Among those cargoes, we found that the subcellular distribution of Beclin1, a key regulator of autophagy, YAP, and to a lesser extent, Centrin, a crucial mediator of centrosome duplication, was regulated by XPO1_S1055 phosphorylation by STK38 [43] (Fig. 3).

In addition to describe a new crucial role for STK38, we identified the first activator of the nuclear export receptor XPO1. Not only the first but also the ultimate one: without STK38 kinase activity, XPO1 remains stuck in an inactive form and cannot fulfill its physiological nuclear export duties like: 1) bringing Beclin1 into the cytoplasm upon starvation for the autophagy activation and 2) delivering YAP out of the nucleus upon cell confluence, limiting the risk of overgrowth.

STK38 and YAP1

The first insight in the regulatory role of STK38 on the transcriptional co-activator YAP1 came out in 2015 when Zhang and colleagues discovered that mammalian STK38/

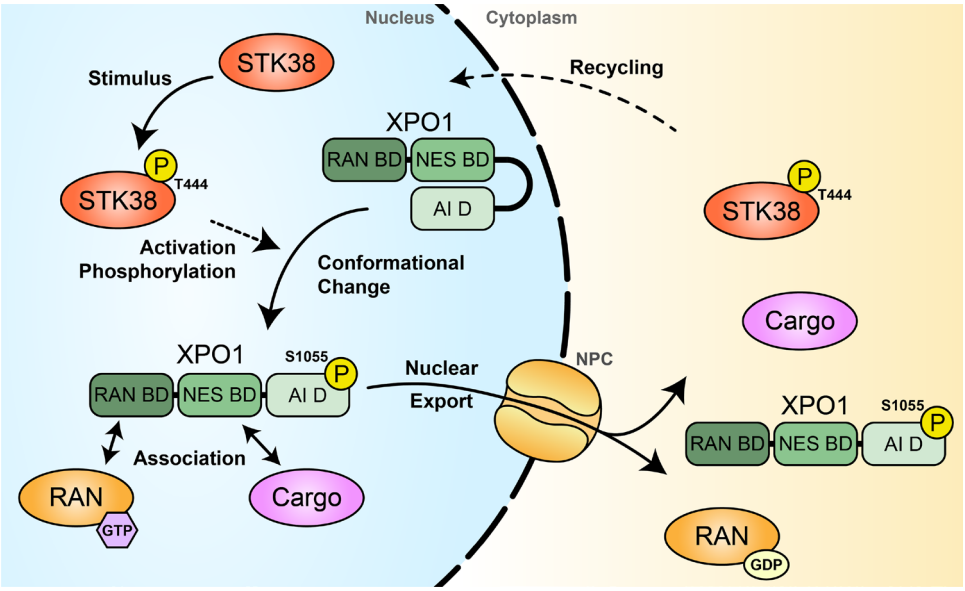

Fig. 3 STK38, XPO1, and nuclear export. Activated STK38 (phosphorylated at least on Thr444) phosphorylates XPO1 on the Ser1055 embedded in XPO1′s auto-inhibitory domain (AI D). This phosphorylation induces a conformational change that reveals XPO1′s cargo binding site. This results in the binding of the cargo to XPO1′s nuclear export sequence binding domain (NES BD) and to the binding of RanGTP to XPO1′s Ran-binding domain (RAN BD). This newly quaternary STK38–XPO1–Cargo–RanGTP complex is then exported in the cytoplasm by GTP hydrolysis through the nuclear pore complex (NPC). The exported components are then recycled into the nucleus

STK38L function as YAP kinases both in vitro and in vivo [22]. First, the authors established STK38/STK38L as upstream YAP kinases in vitro by finding that YAP was phosphorylated on multiple sites (S61, S109, S127, and S164) by STK38/STK38L [22] similarly to what LATS1/2 do. Importantly, they found that YAP_S127 phosphorylation by STK38/STK38L generates YAP cytoplasmic retention and its resulting inactivation [22], a phenomenon already well established for LATS1/2 [38, 78, 79]. Then, the authors investigated the in vivo impact of STK38 on YAP phosphorylation, and thus, activation status. They found that murine intestinal epithelium knocked-out for STK38/STK38L, but without any alterations for LATS1/2, displayed a reduced Ser127 phosphorylation accompanied by an elevated total YAP protein, a nuclear accumulation pf YAP, and an elevated YAP target genes expression [22].

As already reported above in the nuclear export function of STK38, our team recently reported that STK38 modulates the subcellular localization of YAP1 by phosphorylating, and thus activating, the major nuclear export receptor XPO1 on Ser1055 (Fig. 3) [43]. In detail, we found that YAP_S127 phosphorylation is not dependent on STK38, while its nuclear exit is. These results suggest that STK38, but not STK38L, and LATS1/2 act collectively for the efficient nuclear export, and thus inactivation, of YAP: STK38 is needed to activate XPO1 for YAP1 nuclear export per se and LATS1/2 creates an effective 14-3-3 binding site that will sequester YAP1 in the cytoplasm [43].

Connections with other transduction pathways

A link between STK38 and the NFκB (for nuclear factor kappa B) signaling pathway has emerged since few years. The first hint in this relationship started in 2012 when STK38 has been shown to potentiate NFκB activation by its kinase activity [80]. The authors showed that overexpression of STK38 potentiates NFκB activation induced by TNFα, whereas knockdown of STK38 inhibits NFκB activation. They also revealed direct interaction of STK38 with multiple components of the NFκB signaling pathway. More, siRNA against STK38 and its replacement with kd mutants resulted in defect of NFκB activation by TRAF2 (a NFκB activator). Another publication reinforced the nascent role of STK38 on the NFκB signaling pathway. The authors showed that SOCS2 (a pleiotropic E3 ligase) interacts with STK38 and promotes its degradation through K48-linked ubiquitination [81]. In addition, SOCS2 overexpression counteracts STK38-induced NF-κB activity after TNFα-stimulation. More, this study is the first report of an identified E3 ligase for STK38 and strengthens the role of STK38 on the NF-κB signaling pathway.

In addition, STK38 has been linked to the TGFβ (transforming growth factor-beta) transduction pathway. It has

been first reported in 2013 that STK38 can associate with SnoN, a key component of the TGFβ signaling pathway. STK38 represses TGFβ-induced transcription of target genes and the cell cycle arrest [82]. In detail, the authors found that STK38 kinase activity is required for suppressing the ability of TGFβ to induce the phosphorylation of Smad2, a crucial process for the TGFβ-induced transcription and cellular response. Interestingly, the authors also found that STK38 is reciprocally regulated by TGFβ [82]. Independently, the connections between the Hippo and the TGFβ signaling pathways have been firmly established via the interaction of STK38 with Ski, a transforming protein of the avian Sloan–Kettering retrovirus, an inhibitor of the TGFβ signaling pathway, resulting in the inhibition of TAZ transcriptional functions through multiple mechanisms [83].

Finally, a link between STK38 and mTORC2 (mechanistic target of rapamycin 2) has been established in Drosophila: (1) TORC2 components interact with Trc, the fly counterpart of mammalian STK38/STK38L, and that mTORC2 is essential for the phosphorylation of Trc and its resulting activation in vitro and in vivo [84], and (2) Trc is phosphorylated in a TORC2-dependent and TORC2-independent ways, inducing the relocalization of Trc to the mitochondria in response to PINK1 in order to regulate the mitochondrial quality control [75], emphasizing the observations of STK38 role in mitochondrial quality control and anoïkis survival in Ras-driven cancer cells [76].

STK38 and Cancer

It appears that the human STK38 kinase can have opposing roles in tumorigenesis by functioning as a tumor suppressor or an oncogene, depending on the context. On one side, the STK38 mRNA levels have been reported as up-regulated in breast [85], ovarian [86, 87], and lung [88, 89] cancers (Fig. 4) and STK38 protein levels have been detected increased in some melanomas [53]. By positively regulating the centrosome duplication and cell proliferation, STK38 could provide oncogenic properties at the cellular level: It has already been reported that STK38 overexpression leads to centrosome overduplication [53], leading to chromosomal instability. More, it has been reported that overexpression of STK38 leads to overexpression of the proto-oncogene MYC [61].

In addition, there are more indirect ways to support oncogenesis: By supporting the survival of Ras-transformed cells, especially for anoïkis survival, and by maintaining the removal of damaged mitochondria upon cell detachment [76], STK38 helps cells to dodge death, unveiling here its oncogenic properties. More, as mentioned previously, STK38 has been implicated in regulating the nuclear export, and thus the subcellular distribution, of crucial

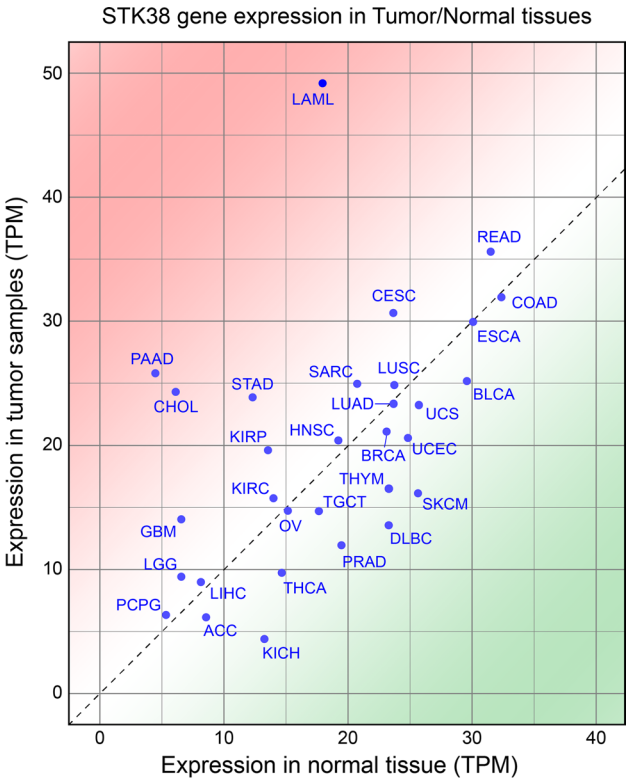

Fig. 4 STK38 expression levels in tumor and normal tissues. STK38 expression level (transcripts per million, averaged) in tumor samples vs normal tissue (adjacent to tumor) generated using the GAPIA web service [102] on TCGA data. *LAML* acute myeloid leukemia, *ACC* adrenocortical carcinoma, *BLCA* bladder urothelial carcinoma, *LGG* brain lower grade glioma, *BRCA* breast invasive carcinoma, *CESC* cervical squamous cell carcinoma and endocervical adenocarcinoma, *CHOL* cholangiocarcinoma, *COAD* colon adenocarcinoma, *ESCA* esophageal carcinoma, *GBM* glioblastoma multiforme, *HNSC* head and neck squamous cell carcinoma, *KICH* kidney chromophobe, *KIRC* kidney renal clear cell carcinoma, *KIRP* kidney renal papillary cell carcinoma, *LIHC* liver hepatocellular carcinoma, *LUAD* lung adenocarcinoma, *LUSC* lung squamous cell carcinoma, *DLBC* lymphoid neoplasm diffuse large B-cell lymphoma, *OV* ovarian serous cystadenocarcinoma, *PAAD* pancreatic adenocarcinoma, *PCPG* pheochromocytoma and paraganglioma, *PRAD* prostate adenocarcinoma, *READ* rectum adenocarcinoma, *SARC* sarcoma, *SKCM* skin cutaneous melanoma, *STAD* stomach adenocarcinoma, *TGCT* testicular germ cell tumors, *THYM* thymoma, *THCA* thyroid carcinoma, *UCS* uterine carcinosarcoma, *UCEC* uterine corpus endometrial carcinoma

cellular regulators such as Beclin1 and YAP [43]. Protein mislocalization, generated by the deregulation of the nuclear export machinery, has been found to be associated with various diseases [90, 91], many tumor suppressor transcription factors displaying cytoplasmic retention, being thus ineffective [92].

On the other hand, STK38 exhibits some tumor suppressor features. First, STK38 mRNA level is down-regulated in prostate [93–95], lymphoblastic [72], skin [96], and gastric [97] cancers (Fig. 4). Second, by controlling MYC protein stability, STK38 represses MYC-induced tumorigenesis

[61], hence acting as a tumor suppressor. In addition, STK38 exerts tumor suppressive functions by phosphorylating YAP, inducing its cytoplasmic retention and subsequent degradation [22]. Whether STK38 supports oncogenesis or is a tumor suppressor, it does not act in a kinase autonomous manner but last certainly in interaction with other pathways, expression of which would depend on the tissue of origin, the cell of origin, and maybe on epigenetic events.

Discussion

Many pathways converge on STK38 (many, in numbers but also for their functional diversity). For several of them, if not all, only one emerges from STK38 to convey a heterogeneity of signals and hits XPO1, which has instructive capabilities for several of these functions. Example given is: autophagy. Nutrient starvation-induced autophagy accomplishment requires Beclin1 to get out of the nucleus [43, 98] and reach its compartment of action: the cytoplasm. STK38 and XPO1 are in charge of achieving such relocalization. However, constitutively active XPO1 will eject Beclin1 from the nucleus even in nutrient-rich conditions, thus triggering autophagy [43]. In this case, the STK38–XPO1 axis is both permissive and instructive for autophagy.

An unrelated example is the co-transcription factor YAP1. At cell confluence, YAP1 exits the nucleus, a migration that depends on the STK38–XPO1 axis [43]. Constitutively, active XPO1 expels YAP1 from the nucleus, even when cells have not reached confluence. Since the deactivation mechanism of YAP1 is likely mobilized in the main cellular function of the Hippo pathway (organ size control), the STK38–XPO1 can be seen as required for the regulation of organ size. This latter implication has been largely eluded. Would this conclusion be experimentally validated, XPO1 becomes a developmental gene required for "body plan homeostasis".

From the previous statements, a trivial question strikes: Is XPO1 the effector of STK38 functions for all multifarious functions of STK38? Many functions, one effector? We have shown that the answer is positive at least for one other function: centrosome duplication [58, 59], making STK38 a cell-cycle gene. Another issue is once XPO1 gets by STK38 within the frame of a specific pathway (e.g., nutrient starvation-induced autophagy), does it ensue a "cargo storm" where many, if not all, cargoes shuttle concomitantly into the cytoplasm? If such cargoes storm, what is the specific biochemical syntax allowing these cargoes to get discriminated? Should each cargo be in an "active" state (e.g. exposure of its nuclear export signal by post-translational modification) in order to be exported by XPO1?

The STK38–XPO1 axis is permissive for some oncogenic functions like anoïkis resistance [99, 100] and in vivo tumor formation in nude mice [76]. Although this has not been warranted for all oncogenic hallmarks, the question might be also reversed: Is the STK38–XPO1 axis not only permissive but also instructive for oncogenesis? Mechanistically, would the forceful nuclear exit of some cargoes be sufficient to trigger oncogenesis in immortalized cells? As an initial response, several members of the inhibitor of apoptosis protein (IAP) family have been identified as XPO1 cargoes [101], making them alluring candidate for this hypothesis. The contribution of inhibiting this axis for cancer treatment should be carefully evaluated: Sequestering tumor suppressors such as p53 in the nucleus can be seen beneficial for the outcome of patients where retaining (proto-)oncogenes in this same cellular compartment such as YAP1 can have the opposite role.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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