The Interplay Between Centrosomes and the Hippo Tumor Suppressor Pathway

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Abstract

Centrosome amplification is a common feature of both solid and hematological human malignancies. Extra centrosomes are not merely innocent bystanders in cancer cells, but rather promote tumor progression by disrupting normal cellular architecture and generating chromosome instability. Consequently, centrosome amplification correlates with advanced tumor grade and overall poor clinical prognosis. By contrast, extra centrosomes are adversely tolerated in non-transformed cells and hinder cell proliferation. This suggests that in addition to acquiring extra centrosomes, cancer cells must also adapt to overcome the deleterious consequences associated with them. Here, we review evidence that implicates core components of the Hippo tumor suppressor pathway as having key roles in both the direct and indirect regulation of centrosome number. Intriguingly, functional inactivation of the Hippo pathway, which is common across broad spectrum of human cancers, likely represents one key adaptation that enables cancer cells to tolerate extra centrosomes.

Keywords

Introduction

The centrosome is the major microtubule nucleating structure in mammalian cells and plays a significant role in regulating diverse cellular functions, including cilia formation, cell signaling, cell migration, establishment of cell polarity, and mitosis (reviewed extensively in this issue and elsewhere) (Chavali et al., 2014, Doxsey et al., 2005, Godinho and Pellman, 2014, Nigg and Raff, 2009). Regulation of centrosome number is tightly controlled, as the presence of too many or too few centrosomes is known to significantly impair the proliferation and viability of non-transformed cells (Ganem et al., 2014, Ganem et al., 2009, Holland et al., 2012, Lambrus et al., 2015, Marthiens et al., 2013, Wong et al., 2015). However, somewhat paradoxically, centrosome amplification is prevalent in human tumors, suggesting that extra centrosomes may provide a fitness benefit to cancer cells (D'Assoro et al., 2002, Ganem et al., 2009, Ghadimi et al., 2000, Godinho and Pellman, 2014, Lingle et

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al., 2002, Sluder and Nordberg, 2004). Understanding the mechanisms that give rise to extra centrosomes, deciphering how cancer cells adapt to tolerate extra centrosomes, and determining the potential beneficial effects of extra centrosomes for cancer cells represent several key unresolved questions in cancer cell biology. Interestingly, several studies now implicate the Hippo tumor suppressor pathway, which is frequently inactivated in human tumors, as having key roles in both the direct and indirect regulation of centrosome number. Here, we provide a general overview of Hippo pathway signaling, introduce mechanisms that link centrosome amplification to activation of the Hippo pathway, and discuss the role of Hippo pathway core components in regulating centrosome number.

Causes and Consequences of Centrosome Amplification

Centrosome number, similar to chromosome number, is highly regulated within cells. Cells in G_0 or G_1 phase typically contain a single centrosome, comprised of two orthogonal centrioles surrounded by a cloud of pericentriolar material. Similar to DNA replication, centrosome duplication occurs only once during S-phase and generates two centrosomes for G_2/M (Firat-Karalar and Stearns, 2014, Nigg and Stearns, 2011, Sluder, 2014, Tsou and Stearns, 2006a, Tsou and Stearns, 2006b). The two centrosomes present during mitosis facilitate the formation of a bipolar mitotic spindle and thus promote high fidelity chromosome segregation during anaphase (Hinchcliffe, 2014). Following cell division, each daughter cell inherits a single centrosome and the replication cycle repeats.

While maintenance of centrosome number is highly regulated in non-transformed cells, errors do occasionally arise that lead to centrosome amplification. Extra centrosomes primarily arise via two distinct, yet non-mutually exclusive, mechanisms (Figure 1). Extra centrosomes can be generated by mitotic or cytokinetic failures, which produce tetraploid cells with twice the normal number of centrosomes (Davoli and de Lange, 2011, Ganem et al., 2007, Meraldi et al., 2002). Alternatively, extra centrosomes can arise from cellular and/or genetic defects that promote centriole overduplication (Firat-Karalar and Stearns, 2014, Nigg and Stearns, 2011, Sluder, 2014).

Regardless of the mechanisms underlying centrosome amplification, it is now well recognized that excess centrosomes are detrimental to the viability of non-transformed cells. Most notably, extra centrosomes have the capacity to greatly disrupt mitotic spindle formation and accurate chromosome segregation. Cells that enter mitosis with more than two centrosomes are predisposed to forming multipolar spindles (Brinkley, 2001, Nigg, 2002). Unless resolved prior to anaphase onset, multipolar spindles lead to catastrophic multipolar anaphase, the generation of grossly aneuploid daughter cells, and cell death (Ganem et al., 2009). This harmful effect of extra centrosomes can have profound consequences on organismal health. In mice, induced centrosome amplification in the brain promotes significant cell death through multipolar division, ultimately leading to microcephaly (Marthiens et al., 2013).

Extra centrosomes also appear to disrupt normal cell proliferation through mechanisms that are independent of abnormal mitosis and aneuploidy. Remarkably, it has been demonstrated that the presence of even a single extra centrosome in non-transformed cells is sufficient to

activate the p53 tumor suppressor pathway and impede further cell proliferation (Ganem et al., 2014, Holland et al., 2012). This holds true irrespective of whether extra centrosomes are generated by cytokinesis failure or centriole overduplication. Unsurprisingly, non-transformed cells with extra centrosomes are selected against in long-term culture experiments (Chiba et al., 2000, Ganem et al., 2009, Godinho et al., 2014).

Cancer Cells Adapt to Tolerate Extra Centrosomes

While centrosome number is strictly regulated in non-transformed cells, the opposite is true for many tumor cells. It is firmly established that centrosome amplification is a hallmark of human cancers (D'Assoro et al., 2002, Ganem et al., 2009, Ghadimi et al., 2000, Godinho and Pellman, 2014, Lingle et al., 2002, Sluder and Nordberg, 2004). This raises an obvious paradox: If extra centrosomes are so poorly tolerated by non-transformed cells, then why are they so common in human malignancies? One possibility is that there are positive selective pressures that promote the accumulation of extra centrosomes in cancer cells. For example, extra centrosomes are known to promote chromosome instability (reviewed below) (Ganem et al., 2009, Silkworth et al., 2009). Chromosome instability (CIN) is defined by the persistently elevated rate of whole chromosome missegregation during cell division (Lengauer et al., 1997). CIN generates significant genetic heterogeneity within tumors and can enable the outgrowth of cells that have acquired growth advantages (Davoli et al., 2013, Pavelka et al., 2010, Rancati et al., 2008, Selmecki et al., 2006, Sheltzer et al., 2011, Sotillo et al., 2010, Thompson and Compton, 2010). Thus, acquisition of a CIN phenotype may be a major positive selective pressure for cancer cells to accumulate extra centrosomes. Extra centrosomes have also been shown to disrupt cell polarity, promote asymmetric cell division, alter cellular signaling, and promote tumor cell invasiveness, any or all of which may promote tumor growth and progression (Basto et al., 2008, Godinho et al., 2014, Mahjoub and Stearns, 2012).

Another reason why extra centrosomes are more common in cancer cells could be that they are simply better tolerated. It is now obvious that cancer cells acquire several characteristics that make them more permissive of the negative effects imparted by extra centrosomes. One clear adaptation made by cancer cells to cope with extra centrosomes is to reduce the propensity of cells with extra centrosomes to undergo chaotic multipolar cell divisions. To accomplish this, most cancer cells cluster excess centrosomes into two spindle poles during mitosis, enabling a relatively normal bipolar anaphase (Basto et al., 2008, Kwon et al., 2008). While this mechanism saves cells from catastrophic mitosis and likely cell death, it is not without consequences. Cancer cells with extra centrosomes pass through a transient 'multipolar spindle intermediate' prior to centrosome clustering, during which merotelic kinetochore-microtubule attachment errors accumulate (Ganem et al., 2009, Silkworth et al., 2009). Merotelic attachments (defined as single kinetochores attached to two spindle poles) are known to promote chromosome missegregation (Cimini et al., 2001, Cimini et al., 2003, Compton, 2011, Salmon et al., 2005, Thompson and Compton, 2008, Thompson and Compton, 2011). Thus, extra centrosomes, even if clustered into two poles to preserve cell viability, continue to promote whole chromosome segregation errors with resultant CIN.

Additional adaptive mechanisms made by cancer cells to tolerate extra centrosomes remain less well defined. For example, although extra centrosomes are known to stimulate the p53 pathway and limit the proliferation of non-transformed cells, the mechanisms underlying this response are poorly understood. Recent studies demonstrate that centrosome amplification activates the Hippo tumor suppressor pathway, which indirectly stabilizes p53 (Ganem et al., 2014). This suggests that Hippo pathway inactivation, which is a widespread feature of human cancers, may represent one common adaptation that enables cancer cells to better tolerate extra centrosomes. Below, we describe canonical Hippo pathway signaling and speculate as to how extra centrosomes may trigger activation of this pathway.

The Hippo Tumor Suppressor Pathway

The Hippo tumor suppressor pathway is a conserved regulator of cellular proliferation, differentiation, and death. Canonically, the major function of the Hippo pathway is to restrain organ size (Pan, 2010, Yu and Guan, 2013), as loss of Hippo pathway activity is well known to promote tissue overgrowth and tumor development (Camargo et al., 2007, Dong et al., 2007, Lu et al., 2010, Song et al., 2010, Zhou et al., 2009a). However, recent studies have demonstrated that the Hippo pathway is also regulated by complex inputs that monitor cell-cell adhesion, cell-matrix adhesion, G-protein coupled receptor (GPCR) signaling, and contractile tension from the actin cytoskeleton (Aragona et al., 2013, Dupont et al., 2011, Ganem et al., 2014, Halder et al., 2012, Paramasivam et al., 2011, Wada et al., 2011, Yu et al., 2012, Zhao et al., 2012, Zhao et al., 2007). Indeed, several conditions known to induce cell cycle arrest, including contact inhibition, loss of cell attachment, and mitotic failure are now known to activate the Hippo pathway (Aragona et al., 2013, Aylon et al., 2006, Ganem et al., 2014, Zhao et al., 2012, Zhao et al., 2007).

The core components of the Hippo pathway, which are conserved in mammals, were first identified in genetic screens for tumor suppressors in *Drosophila melanogaster*. These include *Hippo* (Mammalian sterile 20-like kinases 1 and 2 (*MST1 and MST2*) orthologs in mammals) (Harvey et al., 2003, Jia et al., 2003, Pantalacci et al., 2003, Udan et al., 2003, Wu et al., 2003), *Warts* (Large tumor suppressor kinases 1 and 2 (*LATS1* and *LATS2*) orthologs in mammals) (Justice et al., 1995, Xu et al., 1995), *Salvador* (*SAV1* ortholog in mammals) (Kango-Singh et al., 2002, Tapon et al., 2002), and *Mats* (Mps1 binder (*MOB*) ortholog in mammals) (Lai et al., 2005). Loss of function mutations in these genes lead to increased cell proliferation, reduced cell death, and increased organ size in flies (*e.g.* overgrown eyes and wings). Similarly, loss of Hippo pathway activity promotes tissue overgrowth and tumor development in mice (Camargo et al., 2007, Dong et al., 2007, Lu et al., 2010, Song et al., 2010, Zhou et al., 2009a). For simplicity, the mammalian gene/protein names will be used for the purposes of this review.

The main function of the Hippo pathway is to negatively regulate the oncogenic transcriptional co-activators yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ) (Pan, 2010, Yu and Guan, 2013). This regulation is primarily accomplished through activation of the kinases LATS1 and LATS2, which phosphorylate YAP and TAZ to promote their inactivation (Figure 2) (Yu and Guan, 2013, Zhao et al., 2010a). Phosphorylated YAP and TAZ bind to 14-3-3, which sequesters

YAP/TAZ in the cytoplasm where they are subsequently proteasomally degraded (Hong and Guan, 2012). YAP/TAZ can also be sequestered at both tight and adherens junctions through direct binding to proteins that localize there (Avruch et al., 2012, Bertini et al., 2009, Zhao et al., 2010b, Zhao et al., 2011, Oka et al., 2008). Ultimately, activation of the Hippo pathway prevents YAP and TAZ from entering the nucleus and activating the transcriptional enhancer activation domain (TEAD)-family of transcription factors to initiate the expression of genes important for cell growth and survival (Pan, 2010, Yu and Guan, 2013, Zhao et al., 2010a, Zhao et al., 2010b, Zhao et al., 2011).

The upstream regulatory pathways that mediate LATS1/2 phosphorylation and activation are complex and not yet fully understood. In the classical signaling cascade (reviewed in (Pan, 2010, Yu and Guan, 2013, Zhao et al., 2010a, Zhao et al., 2010b, Zhao et al., 2011)), MST1 and MST2 kinases form heterodimers with the adaptor protein SAV1, which enhances MST1 and MST2 kinase activities. The MST/SAV1 complexes directly phosphorylate and partially activate LATS1/2 kinases. MST/SAV1 also phosphorylate MOB1, which enables it to bind to the autoinhibited regions of LATS1/2. MOB binding releases LATS1/2 of their inhibitory state and enables autophosphorylation within their activation loops. Together, the coordinated actions of MST1/2, SAV1, and MOB fully activate LATS1/2 (Figure 2). Loss of function of any of these components can inactivate the Hippo pathway, and all core members of this signaling pathway (MST1/2, LATS1/2, SAV1, and MOB) have tumor suppressive activities in mammals (Cai et al., 2010, Lee et al., 2010, McPherson et al., 2004, Nishio et al., 2012, Song et al., 2010, St John et al., 1999, Yabuta et al., 2007, Zhou et al., 2009b, Zhou et al., 2011).

In addition to the classical, linear MST1/2 signaling cascade, it is now recognized that regulation of YAP/TAZ can be achieved through MST1/2-independent processes in certain contexts. For example, disruption of the actin cytoskeleton and/or reduced RhoA activity, which occur upon cell detachment, serum starvation, tetraploidy, and contact inhibition, all activate LATS1/2 in an MST1/2-independent manner (Ganem et al., 2014, Mo et al., 2012, Wada et al., 2011, Yu et al., 2012, Zhao et al., 2012). This implies that additional regulatory mechanisms exist to activate LATS1/2 and inactivate YAP/TAZ, and new studies demonstrate that this regulation may involve other members of the Ste-20 family of kinases (Li et al., 2014, Zheng et al., 2015).

In addition to negatively regulating YAP/TAZ, activation of the Hippo pathway can also engage the p53 pathway. Phosphorylated, active LATS2 (but not LATS1) can bind and inhibit the E3 ubiquitin ligase mouse double minute 2 (MDM2), which normally targets p53 for destruction (Aylon et al., 2006). Consequently, LATS2 activation leads to p53 stabilization and the expression of downstream target genes that reinforce cell cycle arrest (*e.g. cyclin dependent kinase inhibitor 1A (CDKN1A)*). *LATS2* itself is a p53 target gene, and its activation thus initiates a feedback loop to enforce Hippo pathway activity (Aylon et al., 2006). Activation of the Hippo pathway therefore limits cellular proliferation in at least two ways: by inactivating YAP/TAZ and by stabilizing p53 (Figure 2).

Activation of the Hippo Pathway Impairs the Proliferation of Cells with Extra Centrosomes

Extra centrosomes primarily arise from cytokinetic failures that give rise to tetraploid cells or from deregulation of mechanisms that control centriole overduplication (Figure 1). It has long been recognized that tetraploid cells activate the p53 pathway and fail to proliferate (Andreassen et al., 2001, Fujiwara et al., 2005, Ganem and Pellman, 2007). Interestingly, a recent study by Holland et al. demonstrates that centrosome amplification alone, independent of tetraploidy, similarly activates the p53 pathway and impairs long-term cell growth (Holland et al., 2012). This suggests that extra centrosomes, *per se*, can impair cell proliferation.

To induce extra centrosomes in non-transformed diploid cells, Holland et al. transiently overexpressed wild-type or degradation-resistant forms of the centriole duplication regulator Polo-like kinase 4 (PLK4) (Habedanck et al., 2005, Kleylein-Sohn et al., 2007). Clonogenic growth assays revealed that the resulting diploid cells, now containing numerous supernumerary centrosomes, exhibited severely impaired proliferation. Upon closer inspection, it was revealed that the cells had activated the p53 pathway. This stabilization of p53 was not simply an indirect effect of deregulated PLK4 kinase phosphorylating unidentified substrates, as expression of a non-degradable version of spindle assembly abnormal protein 6 homolog (SAS6) similarly led to centrosome amplification and reduced cell proliferation. Inactivation of the p53 pathway restored proliferation to the cells with extra centrosomes (Holland et al., 2012).

Recently, it has been shown that activation of the p53 pathway in both tetraploid cells and cells with centrosome amplification can be explained, at least in part, by activation of the Hippo pathway (Ganem et al., 2014). Extra-centrosomal cells display increased phosphorylation of LATS2 and subsequent inactivation of YAP (Figure 3). As described above, phosphorylated LATS2 binds to and inhibits MDM2, thus indirectly promoting the accumulation of p53 (Aylon et al., 2010). Importantly, depletion of LATS2 in cells with extra centrosomes mitigates p53 accumulation and activation of the p53 pathway (Ganem et al., 2014).

Defining the mechanism through which extra centrosomes activate the Hippo pathway remains an important area of investigation. Several recent studies have demonstrated that disruption of the actomyosin cytoskeleton and/or reduction in the activity of small G-protein RhoA have a major role in activating LATS in a MST-independent manner (Aragona et al., 2013, Dupont et al., 2011, Halder et al., 2012, Mo et al., 2012, Wada et al., 2011, Yu et al., 2012, Mana-Capelli et al., 2014). Indeed, cells with extra centrosomes exhibit a significant reduction in active RhoA (Ganem et al., 2014, Godinho et al., 2014). This reduction in RhoA is triggered, at least in part, by the indirect effects of increased microtubule nucleation from extra centrosomes. Dynamic microtubules are known to stimulate the activity of the small G-protein Rac1, and it has been reported that the increased microtubule nucleation from extra centrosomes hyperactivates Rac1 (Godinho et al., 2014). As active Rac1 antagonizes RhoA (Sander et al., 1999), increased Rac1 activity provides one molecular explanation for the observed loss of RhoA activity in cells with extra centrosomes.

An alternative possibility is that the centrosome may act as a scaffold that mediates LATS2 activation in the cell by physically localizing regulatory components of the Hippo pathway to a distinct subcellular space, and centrosome amplification would enhance this activation. Supporting this view, many core members of the Hippo pathway, including MST, MOB, SAV1 and LATS all localize to the centrosome throughout the cell cycle (Morisaki et al., 2002, McPherson et al., 2004, Nishiyama et al., 1999, Mardin et al., 2010, Guo et al., 2007, Wong et al., 2015, Hergovich et al., 2006, Hergovich et al., 2007, Hergovich et al., 2009). This localization is similar in principle to how LATS2 is activated at the plasma membrane, where it is recruited by neurofibromin 2 (NF2) so that it may more efficiently interact with MST/SAV complexes (Yin et al., 2013). The idea of the centrosome as a signal platform is not new; centrosomes are known to anchor hundreds of regulatory proteins that mediate activation of diverse cellular networks (Jackman et al., 2003, Sluder, 2005). It is interesting to speculate that the subcellular localization of LATS2 may dictate which regulatory proteins activate it. For example, while it is known that LATS2 is phosphorylated and activated by MST1/2 at the plasma membrane, centrosomal-localized LATS2 may be responsive to different regulatory proteins. To date, the kinases responsible for activating LATS in response to centrosomal defects remain unknown. It is possible that such kinases are specifically recruited or localized to centrosomes.

Regulation of Centrosome Number and Function by Hippo Pathway Components

In addition to acting as signaling conduits to regulate cell proliferation, many key members of the Hippo pathway moonlight as regulators of various aspects of centrosome biology. For example, MST1 and MOB1A/B play keys roles in centriole duplication (Hergovich et al., 2009). Depletion of either MST1 or MOB1A/B results in impaired centriole duplication, while overexpression of MOB1A/B promotes centriole amplification (Hergovich et al., 2009). Mechanistically, MOB1A/B bind to N-Myc downstream regulated 1 and 2 (NDR1/2) kinases, which facilitates their subsequent phosphorylation and activation by MST1 (Hergovich et al., 2009). Active NDR1/2 have been shown to be important for centriole duplication, though the mechanisms remain to be defined (Hergovich et al., 2009, Hergovich et al., 2007, Cook et al., 2014).

MST kinases, in complex with SAV1, also play an essential role in centrosome disjunction (Mardin et al., 2010). Replicated centrosomes are bound to one another during interphase by the linker proteins C-Nap1 and rootletin (Fry et al., 1998, Yang et al., 2006). Upon entry into mitosis, these linker proteins are phosphorylated by the kinase NIMA-related kinase (Nek2A), which leads to their disassembly (Bahe et al., 2005, Faragher and Fry, 2003). This process, termed centrosome disjunction, enables centrosome separation and bipolar mitotic spindle assembly. A complex of MST2/SAV1 mediates this process by directly phosphorylating and activating Nek2A (Mardin et al., 2010). Thus, loss-of-function of MST2 or SAV1 impairs normal centrosome disjunction and has the capacity to promote abnormal mitosis (Mardin et al., 2010).

LATS1 and LATS2 kinases also localize to centrosomes throughout the cell cycle, yet their function there remains poorly understood (Morisaki et al., 2002, McPherson et al., 2004,

Nishiyama et al., 1999, Guo et al., 2007, Wong et al., 2015, Toji et al., 2004). Cells depleted of LATS1/2 show no defects in centriole duplication or centrosome disjunction. However, it has been reported that depletion of LATS2 impairs the recruitment of γ-tubulin to centrosomes, thus limiting microtubule nucleation during mitosis and hindering chromosome alignment (Abe et al., 2006).

Most strikingly, loss of Hippo pathway components indirectly deregulates centrosome numbers by disrupting normal cytokinesis. Knock-out studies in mice demonstrate that loss of Hippo pathway components LATS1, LATS2, MOB1A and MOB1B all promote cytokinesis failure and the production of tetraploid cells with extra centrosomes (McPherson et al., 2004, Nishio et al., 2012, St John et al., 1999, Yabuta et al., 2007). Tetraploid cells, by virtue of their extra centrosomes, are genetically unstable and are known to be significant contributors to tumorigenesis (Boveri, 1914, Davoli and de Lange, 2012, Fujiwara et al., 2005, Ganem et al., 2007, Zack et al., 2013). Combatting this potentially oncogenic effect of tetraploidy, it has been demonstrated that activation of the Hippo pathway in tetraploid cells limits their growth (Ganem et al., 2014). Thus, inactivation of Hippo pathway components not only promotes the generation of oncogenic tetraploid cells, but also imparts them with the ability to proliferate (Figure 3). Unsurprisingly, deletion of *LATS1* and *LATS2* is significantly more common in high-ploidy tumors than neardiploid tumors (Ganem et al., 2014).

Concluding Remarks

Both centrosome amplification and Hippo pathway inactivation are common in human tumors. New data suggest that these two phenotypes may be intertwined: Functional inactivation of the Hippo pathway may not only promote cytokinesis failure and/or centrosome overduplication, but also impart the resulting cells with an increased tolerance for the extra centrosomes. Understanding how cancer cells adapt to tolerate extra centrosomes has the potential to reveal new vulnerabilities that can be therapeutically exploited.

Acknowledgments

Abbreviations

CIN	chromosome instability
CDKN1A	cyclin dependent kinase inhibitor 1A
LATS1, LATS2	Large tumor suppressor kinases 1 and 2
Mats	Mps1 binder (MOB)
Mps1	Monopolor spindle 1

MST1, MST2	Mammalian sterile 20-like kinases 1 and 2
NDR1/2	N-Myc downstream regulated 1 and 2 kinases
Nek2A	NIMA-related kinase 2A
NF2	neurofibromin 2
SAS6	spindle assembly abnormal protein 6
TAZ	transcriptional co-activator with PDZ-binding motif
TEAD	transcriptional enhancer activation domain
YAP	transcriptional co-activator yes-associated protein

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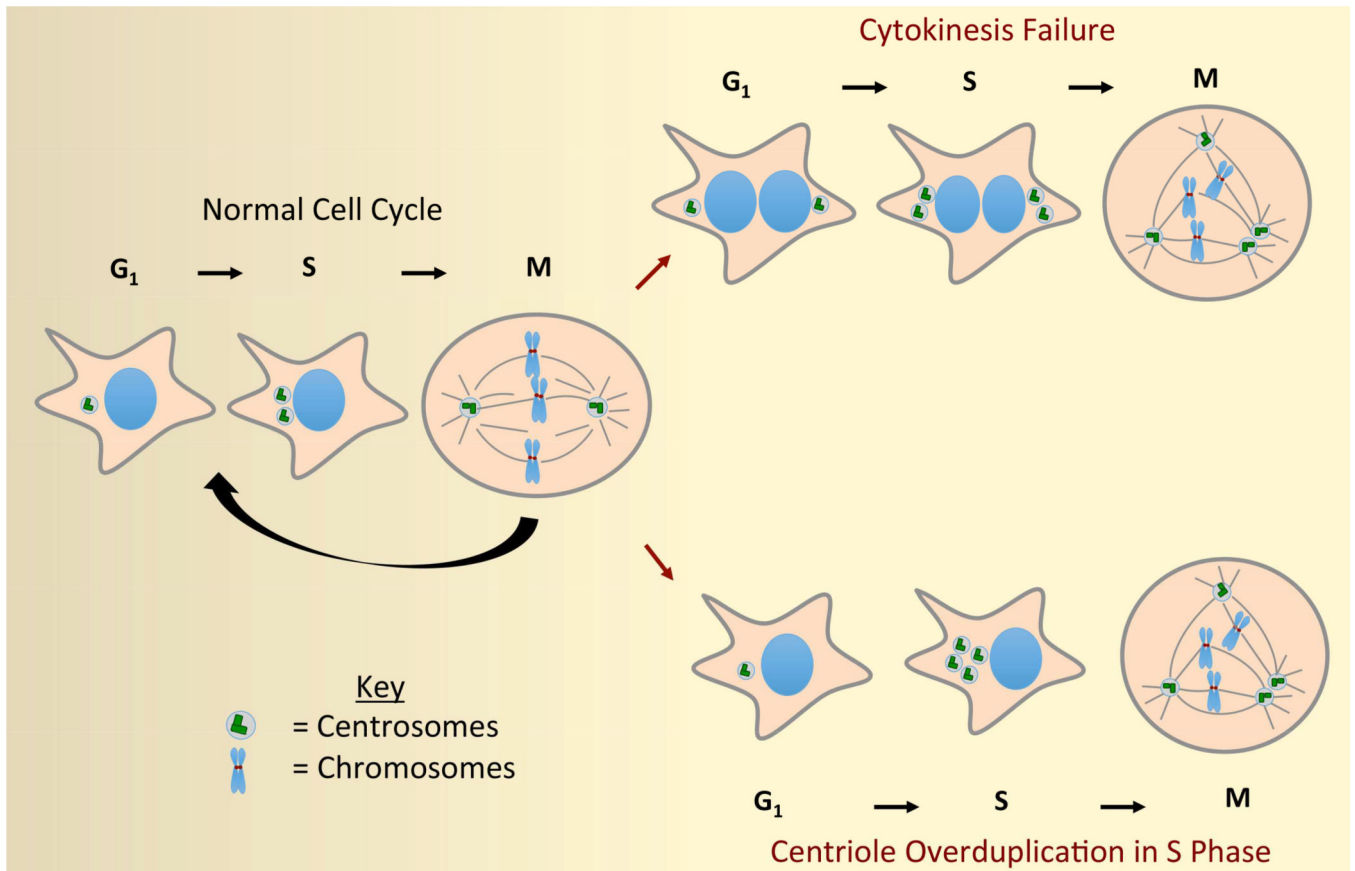
Figure 1. Mechanisms of centrosome amplification

Extra centrosomes predominantly arise from cytokinesis failure or centriole overduplication. Following cytokinesis failure, two centrosomes are present in G_1 interphase cells. These centrosomes replicate during S-phase and the resulting 4 centrosomes promote multipolar cell division during the next mitosis. Abnormal centriole duplication arises during S-phase and can produce a variable number of centrosomes in the subsequent mitosis.
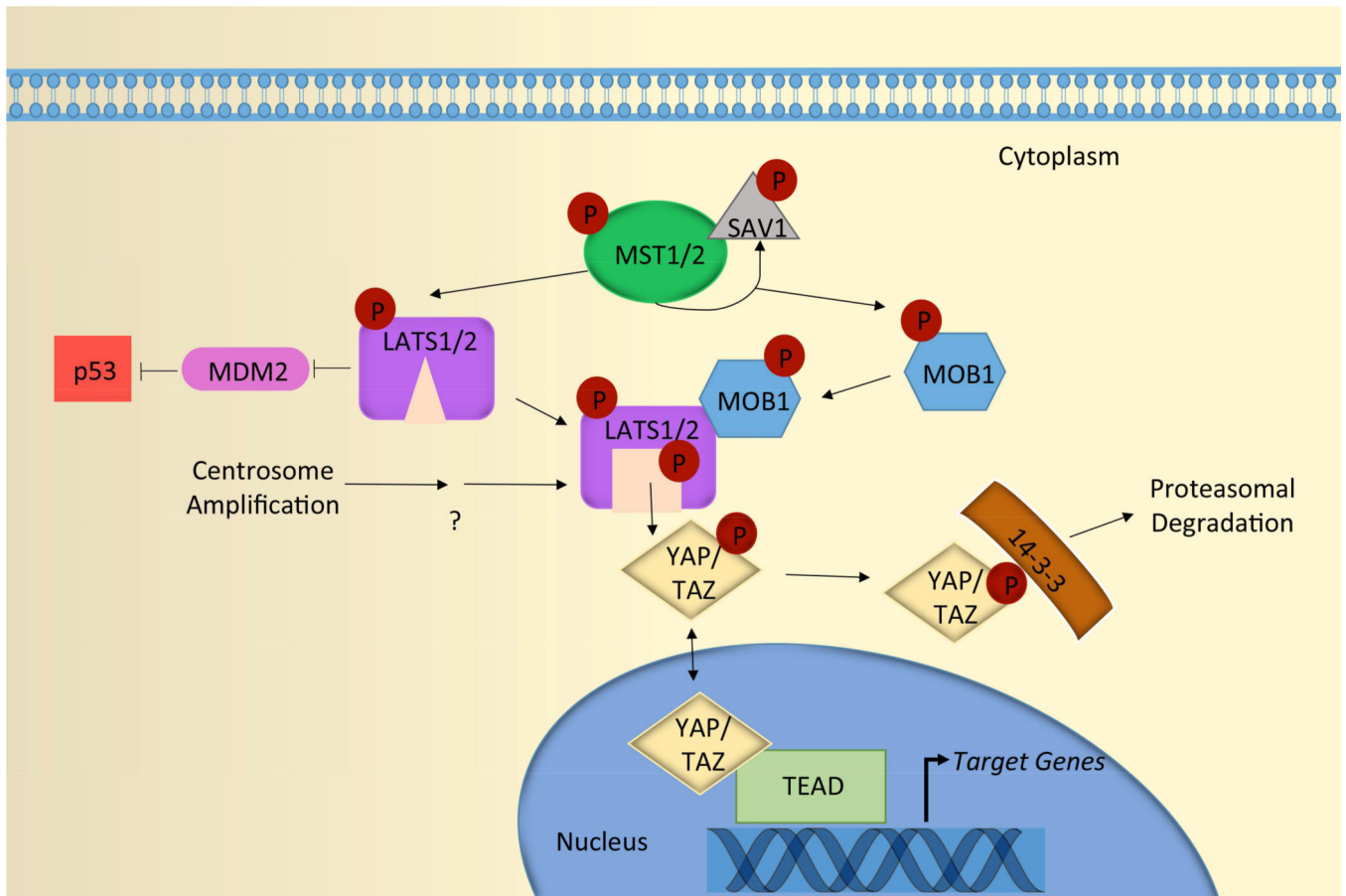
Figure 2. Canonical Hippo pathway signaling

MST1/2 kinases, in complex with the scaffolding protein SAV1, directly phosphorylate LATS1/2 and MOB1. Phosphorylated MOB1 binds to the auto-inhibitory regions of LATS1/2, which releases LATS1/2 from their inhibitory state and enables auto-phosphorylation on their activation loops. Together, the coordinated actions of MST1/2 and MOB fully activate LATS1/2. Active LATS1/2 then phosphorylate both YAP and TAZ. Phosphorylated YAP and TAZ are sequestered in the cytoplasm through binding to 14-3-3, where they are subsequently proteasomally degraded. Consequently, activation of the Hippo pathway prevents YAP and TAZ from entering the nucleus and activating the TEAD-family of transcription factors to initiate the transcription of genes important for cell growth and survival. In addition, active LATS2 binds to and inhibits MDM2, which is an E3 ubiquitin that targets p53 for proteasomal degradation. Thus, activation of LATS2 also indirectly increases p53 levels. Centrosome amplification is known to promote LATS1/2 activation in an MST1/2-independent manner; however, the mechanisms leading to LATS1/2 activation in this context remain to be determined.
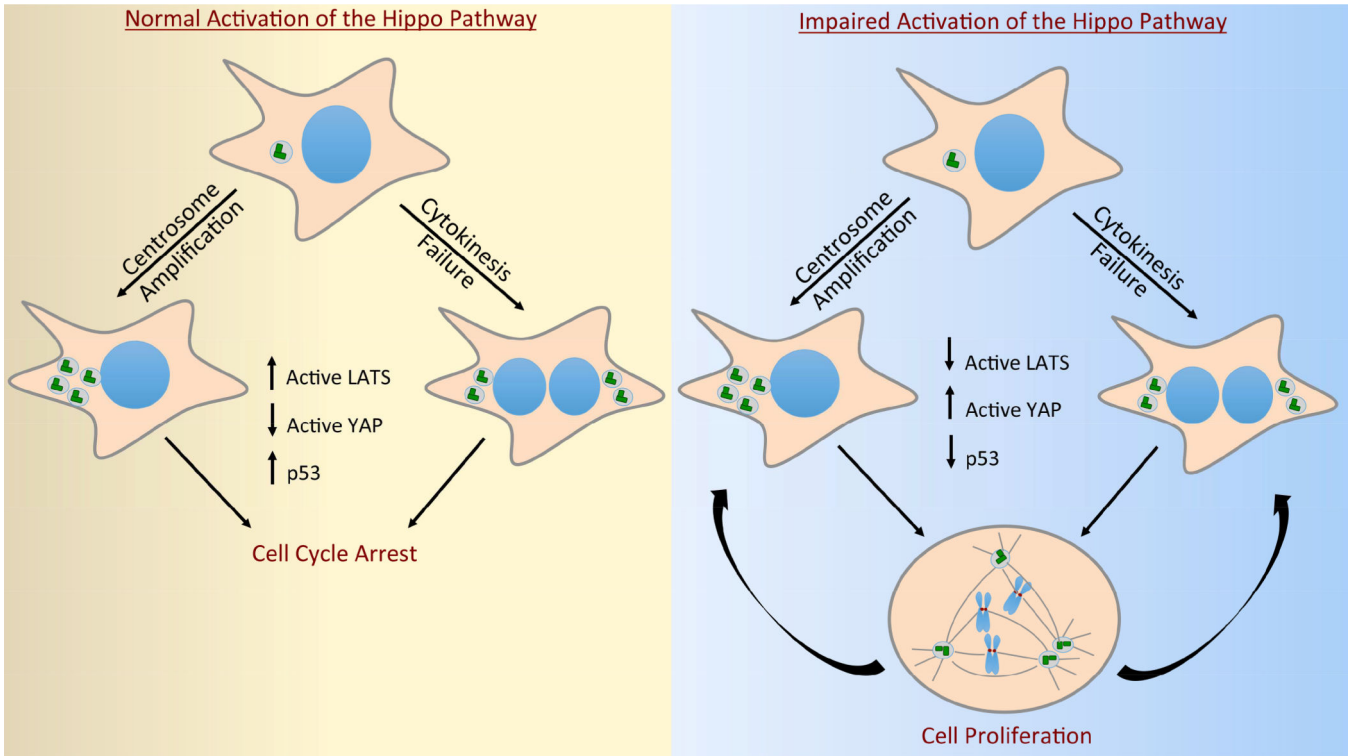
Figure 3. Inactivation of the Hippo pathway enables the proliferation of cells with extra centrosomes

Centrosome amplification, either caused by centriole overduplication or cytokinesis failure, engages the Hippo pathway through increased activation of LATS1/2 kinases (left panel). Consequently, cells with extra centrosomes have decreased YAP activity and exhibit stabilization and accumulation of p53. These cells fail to proliferate (left panel). By contrast, cells that have functionally inactivated the Hippo pathway are capable of proliferation even if they possess supernumerary centrosomes (right panel). In addition to imparting cells with an increased tolerance for extra centrosomes, deregulation of many Hippo pathway core components can also promote further cytokinesis failure and centriole overduplication.