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REVIEW

TRIM37: a critical orchestrator of centrosome function

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ABSTRACT

Loss of function mutations in the E3 ubiquitin ligase TRIM37 result in MULIBREY nanism, a disease characterized by impaired organ growth and a high propensity to develop different tumor types. Additionally, increased copy number of TRIM37 is a feature of some breast cancers and neuroblastomas. The molecular role played by TRIM37 in such loss and gain of function conditions has been a focus of research in the last decade, which led notably to the identification of critical roles of TRIM37 in centrosome biology. Specifically, deletion of TRIM37 results in the formation of aberrant centrosomal proteins assemblies, including Centrobin-PLK4 assemblies, which can act as extra MTOCs, thus resulting in defective chromosome segregation. Additionally, TRIM37 overexpression targets the centrosomal protein CEP192 for degradation, thereby preventing centrosome maturation and increasing the frequency of mitotic errors. Interestingly, increased TRIM37 protein levels sensitize cells to the PLK4 inhibitor centrinone. In this review, we cover the emerging roles of TRIM37 in centrosome biology and discuss how this knowledge may lead to new therapeutic strategies to target specific cancer cells.

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Introduction

Centrosomes are key Microtubule Organizing Centers (MTOCs) of animal cells. Centrosomes consist of a pair of centrioles, small barrel shaped microtubule-based organelles, which recruit a proteinaceous cloud of PeriCentriolar Material (PCM). The centrosome is fundamental for cellular processes such as signaling, motility, and division. Centrosome number is strictly regulated so as to ensure the presence of only two centrosomes per mitotic cell, which direct assembly of a bipolar spindle and faithful chromosome segregation (reviewed in) [1,2] (Figure 1(a)). Over a century ago, Theodor Boveri postulated that an excess number of centrosomes promotes the assembly of multipolar spindles, which could lead to anarchic chromosome segregation and thereby induce tumor formation [3]. This postulate has gone from being dispelled for much of the twentieth century to experiencing a renaissance in the last decade. This review discusses recent work on the E3 ubiquitin ligase TRIM37 that sheds new light on how correct regulation of centrosome function is paramount for proper cell physiology and could be exploited therapeutically.

TRIM37 is one of the more than 70 TRIpartite Motif proteins present in the human proteome. TRIM family members all harbor a RING finger, a B-box motif, and a coiled-coiled domain. Like other TRIM proteins, TRIM37 exhibits E3 ubiquitin ligase activity [4]. Importantly, loss of function mutations in the gene encoding TRIM37 cause MULIBREY nanism (from Muscle-Liver-Brain-Eye nanism) [5]. This autosomal recessive disorder is characterized by severe growth failure, dysmorphia and multiple organ pathologies, including hepatomegaly and cardiomyopathy, as well as a higher susceptibility to develop different tumor types [6–89]. What are the relevant TRIM37 substrates that might explain such a vast array of phenotypic manifestations? Initially, MULIBREY nanism was proposed to be a peroxisomal disorder based on the localization of TRIM37 at peroxisomes in HepG2 and human intestinal smooth muscle cell lines [10]. Moreover, further work showed that TRIM37 monoubiquitinates PEX5 to

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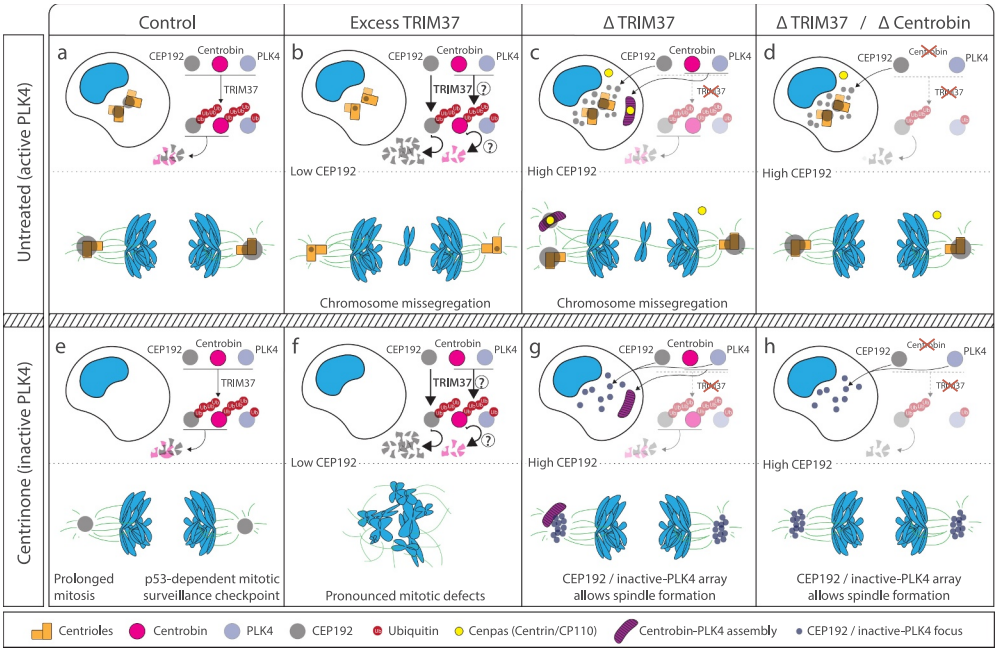

Figure 1. TRIM37 centrosome-related phenotypes. Each panel represents a cell in interphase (G2, top) and anaphase (bottom). A-D: cells not treated with centrinone (i.e. with active PLK4); E-H: cells treated with centrinone (i.e. with inactive PLK4). For simplicity, the distribution of Centrobin and PLK4 at resident centrioles is not represented. (a) Control cell with two pair of centrioles recruiting PCM components such as CEP192, which contributes to ensure bipolar spindle and correct chromosome segregation during mitosis. Current knowledge supports the notion that TRIM37 ubiquitinates CEP192 and Centrobin for degradation, and in addition modifies PLK4 and Centrobin to regulate their function. (b) High levels of TRIM37, as observed in some breast cancers and neuroblastomas, induce CEP192 proteasome dependent degradation and chromosome missegregation. The impact of excess TRIM37 on Centrobin and PLK4 protein levels and function remain to be fully characterized. (c) TRIM37 deficient cells harbor high levels of CEP192 and Centrobin. CEP192 is recruited to centriolar satellites in interphase, and a single Centrobin-PLK4 structure is frequently assembled. In addition, Centrobin-dependent and -independent centriolar protein assemblies (Cenpas) are formed. Centrobin-PLK4 assemblies can recruit CEP192, PCNT, CDK5RAP2, as well as γ-tubulin, and can act as extra MTOCs, resulting in chromosome missegregation. (d) The lack of Centrobin in TRIM37 deficient cells impairs Centrobin-PLK4 structure formation, leading to proper bipolar spindle assembly; chromosome segregation has not been thoroughly characterized in this condition. Note that the Cenpas that are present in the absence of Centrobin do not behave as extra MTOCs. (e) Acentriolar cells rely on CEP192 to perform mitosis. However, such cells undergo prolonged mitosis that activates the p53/USP28/53BP1 mitotic surveillance checkpoint, promoting irreversible-G1 arrest in the following cell cycle. (f) Acentriolar cells with high levels of TRIM37 exhibit pronounced mitotic defects due to low levels of CEP192. (g) Acentriolar cells lacking TRIM37 bypass the p53/USP28/53BP1 mitotic surveillance checkpoint owing to an array of foci containing CEP192 and inactive PLK4. (h) Centrobin depletion does not exacerbate the phenotype of acentriolar cells lacking TRIM37.

regulate peroxisome transport [11]. However, while a *Trim37*-deficient mouse model recapitulates most features of the human disease, peroxisomes appear normal in these mice, suggesting that at least some manifestations of MULIBREY nanism are not caused by peroxisome dysfunction [12]. Therefore, the processes that are altered upon TRIM37 loss and which are relevant in the disease context have remained unclear.

Not only does loss of TRIM37 function result in disease, but increased levels of the protein are correlated with tumorigenesis. TRIM37 is located in the chromosomal region 17q23, which is frequently amplified in several tumor types, including breast cancer and neuroblastoma [13–15]. Several studies have investigated the possible role of TRIM37 in tumor progression. In breast cancer cells, high expression of TRIM37 was reported to promote the mono-ubiquitination of histone H2A, which in turn alters the expression of several oncoproteins that are postulated to promote cancer progression [16,17]. However, Histone H2A was not identified as a proximity interacting partner of TRIM37 [18], and few transcriptional alterations were observed when TRIM37 expression levels were reduced in non-transformed RPE1 cells or in neuroblastoma cells that overexpress TRIM37 [19]. Therefore, it appears that TRIM37 does not have a general role as a transcriptional regulator. In addition to a possible role in regulating

transcription, TRIM37 can activate NF-κB signaling in response to DNA damage, thus favoring cell survival upon genotoxic stress [20]. This could explain how high TRIM37 levels could lead to chemoresistance in cancer patients [20]. Furthermore, TRIM37 can promote epithelial to mesenchymal transition in several cancer cell lines, which might favor tumor metastasis [17,21–23]. Taken together, the above studies suggest that TRIM37 might exert a role in tumor biology by modulating multiple cellular processes.

In this review, we discuss recent work that has revealed the importance of TRIM37 in centrosome biology (Figure 1(b-h)). This has shed light not only on the function of this protein in regulating centrosome numbers in normal physiology, but also on how this role may explain the phenotypic manifestations in MULIBREY nanism, as well as in cancers that overexpress TRIM37. Moreover, we discuss how an excess of TRIM37 leads to synthetic lethality with centrinone, a compound that prevents centriole duplication, which opens novel therapeutic strategies for tumors bearing 17q23 amplification.

Discovery of TRIM37 as an actor in centrosome biology

The connection between TRIM37 and centrosome biology was ~~first~~ revealed in a genome-wide siRNA screen designed to identify regulators of centriole duplication in human cells, using Centrin-1 GFP as a proxy for centriole number [24]. TRIM37 depletion led to an increase of Centrin-1 GFP foci that also harbored the distal centriolar protein CP110, and in some cases the proximal centriolar protein HsSAS-6 [24]. Cells depleted of TRIM37 exhibited pseudobipolar and multipolar spindles during metaphase, as well as chromosome segregation defects during anaphase [24] (Figure 1(c)). Related findings were reported in TRIM37 knock out RPE-1 (TRIM37-ko) cells, with the centriole and PCM protein CEP192 also being abnormally present at centriolar satellites during interphase [25] (Figure 1(c)). Overall, these studies established that TRIM37 negatively regulates the formation of foci that bear several centriolar proteins, but that are not *bona fide* centrioles as judged by serial-section electron microscopy (EM) [26,27], and which have therefore been referred to as Centriolar protein assemblies (Cenpas) [26]. In addition, cells depleted of TRIM37 bear assemblies that harbor Centrobin and PLK4, which can act as an additional MTOC [25,26] (Figure 1(c)). Importantly, Centrobin-PLK4 assemblies are observed likewise in MULIBREY patient fibroblasts [26,27], which also exhibit Cenpas, pseudobipolar and multipolar spindles, as well as chromosome segregation defects [26].

The role of TRIM37 in centrosome biology was also highlighted in screens performed in human cells that lack centrioles [28]. Chronic treatment of cultured cells with the PLK4 inhibitor centrinone leads to a failure of centriole assembly and thereby to cells lacking centrioles and centrosomes [29]. Centrosomes act to catalyze spindle assembly, and consequently, cells lacking centrioles undergo a prolonged mitosis that induces an irreversible G1 arrest through a p53/USP28/53BP1-dependent mitotic surveillance pathway [25,29,30] (Figure 1(e)). Interestingly, knockout of TRIM37 rescues the cell cycle arrest induced by centrinone [25,30]. Such rescue stems from acentriolar TRIM37-ko cells assembling an array of foci containing several centrosomal proteins [25]. These include PLK4, which is inactive in this setting given the presence of centrinone, the PCM component CEP192, which is required for centrosome maturation during mitosis [31,32], and γ-tubulin, which is part of the microtubule-nucleating γ-tubulin ring complex [33,34]. These arrays function as MTOCs during mitosis, which has been proposed to accelerate spindle assembly in acentriolar TRIM37-ko cells, and thereby mitigate the adverse effect of lacking centrioles, satisfying the p53/USP28/53BP1-dependent mitotic surveillance pathway [18,19,25] (Figure 1(g)).

Centrobin-PLK4 assemblies formed upon TRIM37 depletion

Investigation of the root of the phenotype incurred by depletion of TRIM37 led to the discovery that Centrobin, a centriolar protein that normally localizes strictly to newly formed centrioles [35], accumulates in cytoplasmic assemblies that also harbor PLK4 [26,27] (Figure 1(c)). Correlative light EM (CLEM) and super-resolution expansion microscopy revealed that Centrobin-PLK4 assemblies present in

interphase cells contain repeated units that exhibit a striped pattern [26,27]. Additionally, hexagonally packed sheet-like configurations are apparent by CLEM and expansion microscopy [27]. Whether these two forms correspond to intermediates in an assembly pathway, interconverting forms of two mature assemblies, or the same structure imaged from different viewpoints remains to be clarified. Expansion microscopy also revealed that the Centrobin-PLK4 assemblies sometimes contain radial structures positive for centrin, which correspond to a fraction of the above mentioned Cenpas [26] (Figure 1(c)). During mitosis, these assemblies act as MTOCs and recruit PCM components, including CEP192, PCNT, CDK5RAP2 and γ-tubulin [27] (Figure 1(c)). Interestingly, these PCM proteins do not appear to be uniformly present in Centrobin-PLK4 assemblies, but instead are enriched at specific locations herein [27]. Given that most Centrobin-PLK4 assemblies contain associated Cenpas [26,27], one possibility is that the Cenpas located in the Centrobin-PLK4 structure might recruit PCM components and act as MOTCs during mitosis.

Importantly, Centrobin is essential for the formation of Centrobin-PLK4 assemblies [26,27] (Figure 1(d)). This is in contrast to SPICE-1, another centriolar protein present in these assemblies, which is dispensable for their formation [26]. The role of PLK4 in Centrobin-PLK4 assembly formation remains to be fully elucidated. These assemblies remain present upon PLK4 chemical inhibition or PLK4 depletion [26,27], indicating that PLK4 is dispensable for their assembly. Surprisingly, PLK4 depletion from TRIM37-ko cells using either siRNAs or an inducible Crispr-Cas9 knock out strategy (iPLK4-ko) failed to remove the PLK4 signal from Centrobin-PLK4 assemblies [26,27]. Moreover, only one of three PLK4 antibodies tested by immunofluorescence displayed a clear signal in these assemblies, perhaps because of epitope masking in the other two cases [26]. Assuming that the signal detected by the first antibody is specific, these results raise the possibility that, once incorporated into these assemblies, PLK4 is stably retained. Potentially related to this observation, an E3 ligase deficient mutant version of TRIM37 likewise localizes stably to Centrobin-PLK4 assemblies, perhaps trapped there by one of its substrates [27]. Further live imaging experiments are expected to shed light on the dynamics of the proteins present in Centrobin-PLK4 assemblies. Together with biophysical experiments probing the material properties of these entities, this will help to determine whether they should truly be considered as biomolecular condensates as proposed [25].

Regardless of their exact nature, how do Centrobin-PLK4 assemblies form in the first place? Live imaging of a fluorescently tagged E3 ligase mutant TRIM37 uncovered that Centrobin-PLK4 assemblies can grow and detach from the centrosomes in those cells that do not inherit such an assembly after cell division [27]. However, Centrobin-PLK4 assemblies also form in cells lacking centrioles following centrinone treatment [26], suggesting the existence of alternative routes for the biogenesis of Centrobin-PLK4 assemblies. Strikingly, Centrobin-PLK4 assemblies are present as a single structure in most TRIM37-ko cells [27]. This suggests that once an assembly is created, additional centrosomal material is preferentially incorporated into it instead of seeding the formation of a new assembly.

Extra centriolar protein foci and centrioles

Whereas some Cenpas are intimately associated with Centrobin-PLK4 assemblies, others seem independent of them [26,27] (Figure 1(c)). Indeed, depletion or lack of Centrobin does not abolish Cenpas formation [26,27] (Figure 1(d)), but whether the fraction of cells with Cenpas is reduced [26] or not [27], a discrepancy that may reflect differences in the markers used to identify Cenpas. Moreover, a fraction of cells depleted of TRIM37 bear extra *bona fide* centrioles, as judged by CLEM and super-resolution expansion microcopy [26,27]. It has been proposed that such extra centrioles might assemble *de novo* from either Centrobin-dependent or Centrobin-independent Cenpas [26]. Alternatively, extra centrioles may arise from centriole missegregation during an aberrant mitosis, resulting in the generation of daughter cells with an abnormal number of centrioles [27].

Interestingly, PLK1 inhibition in cells synchronized and depleted of TRIM37 dampens Cenpas formation [24]. Moreover, combining PLK1 inhibition and Centrobin depletion completely prevents Cenpas formation in cells lacking TRIM37, supporting the existence of two pathways for Cenpas biogenesis, one reliant on PLK1 and one on Centrobin [26]. Although it was initially proposed that PLK1 could promote centriole reduplication in the absence of TRIM37 [24], evidence for

such a role was not found in a detailed expansion microscopy analysis of TRIM37-ko cells [27]. Overall, how PLK1 promotes Cenpas formation remains to be clarified. Interestingly, the behavior of Cenpas seems to differ depending on whether they are associated with Centrobin-PLK4 assemblies or not. Whereas Centrobin-dependent Cenpas, presumably stemming from Centrobin-PLK4 assemblies, behave as MTOCs that trigger the formation of pseudobipolar and multipolar spindles [26], Cenpas formed in the absence of Centrobin do not [27] (Figure 1d). Overall, these findings established that both Centrobin-PLK4 assemblies and Cenpas form in cells upon TRIM37 depletion and contribute to mitotic abnormalities.

TRIM37 depletion enables successful cell cycle progression in the absence of centrioles

Analysis of centrosomal proteins during mitosis uncovered how TRIM37-ko cells with an intact mitotic surveillance checkpoint can continue proliferating despite the absence of centrioles [18,19,25]. Normally, acentriolar mitotic cells recruit to their spindle poles CEP192 and PLK4, as well as the PCM components CDK5RAP2, PCNT and γ-tubulin [18,19,25,27] (Figure 1e). CEP192 plays a critical role in these acentriolar cells, since its depletion results in pronounced mitotic defects, including mitotic arrest and mitotic slippage [18,19]. In TRIM37-ko cells depleted of centrioles through chronic inhibition of PLK4 activity, CEP192, CDK5RAP2, PCNT and γ-tubulin do not localize to a single focus at each spindle pole, but instead assemble into an array of foci [25] (Figure 1(g)). These arrays act as MTOCs that contribute to bipolar spindle assembly and speed up progression through mitosis, thereby bypassing activation of the mitotic surveillance checkpoint [25]. Interestingly, these arrays also contain inactive PLK4, which is essential for their formation, as TRIM37-ko acentriolar cells generated by iPLK4-ko are devoid of such arrays and undergo prolonged mitosis, which activates the p53/USP28/53BP1-dependent mitotic surveillance pathway [19]. Intriguingly, purified PLK4 can self-assemble in Xenopus extracts into ordered spherical protein condensates that interact with microtubules and can act as MTOCs [36]. However, in this case, this self-assembly potential depends on PLK4 kinase activity. Overall, these results support the notion that in acentriolar human cells, TRIM37 prevents the assembly of inactive PLK4 into an array of small entities that recruit other centrosomal proteins and nucleate microtubules during mitosis.

Centriolar targets of TRIM37 E3 ligase activity

What molecular function of TRIM37 might explain the centrosomal phenotypes described above? An early indication stemmed from the finding that an E3 ligase mutant version of TRIM37 cannot rescue the phenotype incurred by depleting TRIM37 [24], indicating that ubiquitination is key. As discussed above, TRIM37 loss and gain of function phenotypes suggest that CEP192, PLK4 and Centrobin may be substrates of TRIM37. Indeed, TRIM37 negatively regulates CEP192 protein levels through a proteasome dependent mechanism [18,19]. Likewise, TRIM37 negatively regulates Centrobin protein levels and stability [26,27]. By contrast, TRIM37 does not regulate PLK4 protein levels [19]. Nevertheless, co-immunoprecipitation assays showed that an ectopically expressed E3 ligase mutant version of TRIM37 interacts with co-expressed tagged PLK4, as it does with CEP192 and Centrobin [19,27]. Moreover, co-expressed tagged versions of CEP192 and TRIM37 interact with one another [18]. Importantly, co-overexpression of TRIM37, HA-tagged Ubiquitin and either PLK4, Centrobin or a fragment of CEP192, results in the TRIM37-dependent ubiquitination of these three targets [19,27]. Together, these findings suggest that TRIM37 ubiquitination normally keeps CEP192 and Centrobin protein levels in check, and somehow regulates PLK4 function (Figure 1a). It is important to note that Centrobin overexpression alone does not lead to assemblies akin to the ones observed in TRIM37 deficient cells [26]. This suggests that the role of TRIM37 might go beyond simply controlling protein levels, perhaps by disrupting protein assemblies and/or ubiquitinating key interaction domains.

Proximity interacting screens that used as bait centriolar proteins [37,38] or TRIM37 itself [18] have identified potential centrosomal targets of TRIM37, including, as expected, CEP192, Centrobin and SPICE1 [18,37,38]. Further interactors identified included centriolar proteins localizing to the distal end of the mother centriole, such as CEP128 and CEP89 [38], as well as CEP170 and CEP350 [18].

Accordingly, overexpressed GFP-TRIM37 localizes to the distal portion of the mother centriole [26], in addition to a proximal centriole distribution [27]. Further proximity partners of TRIM37 include centriolar satellites proteins [18,37], which might be involved in the recruitment of CEP192 to centriolar satellites in TRIM37-ko cells [25]. Finally, another interesting potential TRIM37 partner is the spindle assembly checkpoint protein BUB1B [18]. Mutations in BUB1B cause mosaic variegated aneuploidy syndrome (MVA), which is characterized by a high rate of chromosome missegregation resulting from a defective spindle assembly checkpoint [39–41]. Characteristic MVA features are slow growth and a high propensity for tumor formation, reminiscent of aspects of MULIBREY nanism. Perhaps impaired TRIM37-mediated regulation of BUB1B could contribute to the chromosome segregation defects observed in cells with either TRIM37 depletion or overexpression [18,24,26,27].

Is MULIBREY nanism a centrosomal disorder?

TRIM37 is involved in several cellular processes, but which of these contribute to the complex pathological features of MULIBREY manism remains unclear. Although some clinical features of the disease overlap with human peroxisome disorders [10], as mentioned above the relevance of this connection was challenged by the observation that peroxisome function is not altered in the MULIBREY mouse model that recapitulates most features of the human disease [11,12]. Likewise, only minimal transcriptional changes were found in cells lacking TRIM37 [19], suggesting that most MULIBREY nanism phenotypes might not be linked to transcriptional alterations. Future experiments are required to shed light on the relevance of these processes and the molecular etiology of the disease.

Importantly, the centrosome-related defects discussed in this review are present in MULIBREY patient-derived cells. This includes the presence of Cenpas, some of which can recruit γ-tubulin and trigger microtubule-nucleation [26]. Moreover, MULIBREY patient cells harbor Centrobin-PLK4 assemblies [26,27], which can act as MTOCs during mitosis [26]. As anticipated, these features are accompanied by spindle abnormalities and high rates of chromosome missegregation [26]. Such chromosome missegregation is expected to compromise cell viability, thus potentially contributing to the impaired growth of MULIBREY patients. In addition, chromosome missegregation is bound to result in abnormal karyotypes in daughter cells. Karyotype abnormalities are a hallmark of cancer cells and might contribute to the augmented predisposition of MULIBREY patients to develop tumors.

A novel therapeutical approach for cancer cells with high TRIM37 expression levels

Two recent studies relying on complementary approaches led to the discovery that high TRIM37 expression levels are synthetically lethal with PLK4 inhibition, potentially offering novel therapeutic avenues for certain cancer types [18,19]. Both MCF-7 breast cancer cells bearing the 17q23 amplicon [18] and RPE-1 cells engineered to conditionally overexpress TRIM37 [19] are hypersensitive to centriole loss induced by centrinone. TRIM37 overexpressing cells in the absence of centrioles exhibit prolonged mitoses and high rates of mitotic errors that compromise cell survival [18,19] (figure 1f). This is because TRIM37 overexpression results in decreased protein levels of CEP192, CDK5RAP2 and PCNT, thus severely compromising mitotic spindle assembly in these acentriolar cells [18,19]. CEP192 seems particularly important in this context, since its partial depletion is sufficient to sensitize cells to centrinone treatment [18,19]. Importantly, both studies validate their findings in several breast cancer cells lines carrying the 17q23 amplicon and neuroblastoma cell lines with 17q gain. Moreover, live imaging established that untreated MCF-7 cells exhibit delayed microtubule nucleation and centrosome separation in late G2, which correlates with a high rate of mitotic errors that is partially suppressed by TRIM37 depletion [18]. Therefore, TRIM37 might contribute to tumor progression by downregulating centrosomal proteins such as CEP192 (Figure 1b). These important findings open the door to using inhibitors that prevent centriole assembly as novel therapeutic avenues to target cancer cells with increased expression of TRIM37.

TRIM37 and centrosome biology: some open questions

In this review, we have highlighted the important role of TRIM37 as an orchestrator of centrosome function, whereby both its absence and its overexpression can alter the levels and/or the activity of key centrosomal components, resulting in abnormal spindle assembly and chromosome missegregation (Figure 1 for a graphical summary). More work will be needed to further the understanding of these findings. For instance, one could expect that TRIM37 depletion might promote tumorigenesis in other contexts than in MULIBREY patients. Perhaps TRIM37 levels and/or function is downregulated in some cancers, leading to the acquisition of Centrobin-PLK4 assemblies. We expect that Centrobin-PLK4 assemblies will be present in the *Trim37*-ko mouse model, which notably recapitulates the propensity of MULIBREY patients to develop tumors [12]. Although Centrobin knock down mouse embryos have been reported to arrest at the 4-cell stage [42], indicating that Centrobin is essential for embryonic development, conditional knock out models could be generated in tissues where *Trim37*-ko mice develop tumors to test whether these are suppressed by Centrobin depletion. Moreover, this could enable one to test if Centrobin-PLK4 assemblies play a role not only in tumor development, but also in other features of MULIBREY nanism present in the mouse model. Many questions also remain regarding the nature of Centrobin-PLK4 assemblies, perhaps the most pressing ones relating to PLK4. First, the presence of PLK4 in these assemblies ought to be validated by generating a fluorescent fusion protein of PLK4 to ensure that the PLK4 signal detected by immunofluorescence in such assemblies is specific. Second, the role of PLK4 in the formation and MTOC activity of these assemblies should be further clarified, as current experimental approaches so far have failed to deplete PLK4 from these assemblies.

What are the relevant centrosomal substrates of TRIM37, and what exact impact does this protein have on their function? Although CEP192, PLK4 and Centrobin are solid candidate substrates, it remains to be determined which specific residues are modified, and whether this entails mono or poly-ubiquitination. Moreover, the impact of these modifications on the function of the targets must be clarified further. TRIM37 limits the proteins levels of CEP192 and Centrobin, but how TRIM37 recognizes its substrates and whether their ubiquitination alters substrate dynamics, structure, or interaction with partner proteins could be explored.

Finally, it is worthwhile to consider if the assemblies observed upon TRIM37 depletion may play a role in a physiological context. In this regard, it is interesting to note that TRIM37 mRNA and protein levels are downregulated in mitosis [18]. Perhaps TRIM37 activity is dampened during mitosis to enable the assembly of functional centrosomal complexes that are suppressed by TRIM37 during interphase. Moreover, a putative modification of Centrobin by TRIM37 during interphase could be required to limit the recruitment of PCM components, a function that has been indeed reported for Centrobin [43]. Hypothetically, the decrease of TRIM37 levels during mitosis could favor the removal of such a putative modification and thus promote centrosome maturation. Additionally, it is tempting to speculate that Centrobin-PLK4 assemblies observed in TRIM37 deficient cells might be present in specific cell types with physiologically low levels of this E3 ubiquitin ligase.

In conclusion, since TRIM37 was first revealed as a centrosome regulator [24], several studies contributed to characterize the mechanisms through which this role is exerted, and the potential links of the corresponding loss and gain of function conditions with tumor progression [18,19,25–27]. Theodor Boveri theorized that an excess number of centrosomes could contribute to tumor formation by inducing abnormal spindle assembly and chromosome missegregation [3]. The current knowledge regarding the role of TRIM37 in centrosome regulation lends further credential to his postulate, albeit in a more complex manner than initially envisaged.

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