Centrosome Defects in Hematological Malignancies: Molecular Mechanisms and Therapeutic Insights

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Abstract
Defects in centrosomes are associated with a broad spectrum of hematological malignancies, such as leukemia and lymphoma. Centrosomes in these malignancies display both numerical and structural aberrations, including alterations in the number and size of centrioles, inappropriate post-translational modification of centrosomal proteins, and extra centrosome clustering. There is accumulating evidence that centrosome defects observed in hematological malignancies result from multiple factors, including dysregulation of the centrosome cycle and impairment of centriole biogenesis. In this review, we discuss the plausible mechanisms of centrosome defects and highlight their consequences in hematological malignancies. We also illustrate the latest therapeutic strategies against hematological malignancies by targeting centrosome anomalies.

Keywords: Centrosome defects, Hematological malignancy, Cell cycle regulators, Cell surveillance pathways, Pharmaceutical inhibitors

1. INTRODUCTION
In animal cells, the centrosome is the major microtubule-organizing center. A centrosome is composed of two centrioles, known as mother and daughter centrioles, surrounded by an amorphous proteinaceous matrix called the pericentriolar material (PCM).\textsuperscript{1} More than 200 centrosome-associated proteins have been identified so far in large-scale proteomic studies.\textsuperscript{2} One essential function of centrosomes is promoting spindle bipolarity, thus ensuring correct chromosome segregation.\textsuperscript{3} Moreover, centrosomes are critical for the formation of cilia, the hair-like cell protrusions essential for cell sensing and motility.\textsuperscript{4,5}

Given the importance of centrosomes in various cellular functions, they are under numerical and structural control. Numerically, centrosome duplication is highly coordinated with the cell cycle, occurring only once per cell cycle.\textsuperscript{6,7} This rigorously regulated centrosome cycle relies on specific evolutionarily conserved core proteins.\textsuperscript{8} For instance, polo-like kinase 4 (Plk4) is an essential protein that serves as a significant regulator of centrosome number.\textsuperscript{9,10} Both the centriole structure and the quantities of PCM components are regulated to maintain normal centrosome function. For example, spindle assembly abnormal protein 4 (SAS-4) is a centriole-associated protein that directly controls centrosome size.\textsuperscript{11} Alterations in the gene expression levels that regulate centrosome duplication or centrosome structure may underlie numerical and structural defects, respectively. For example, deregulation of Plk4\textsuperscript{12} and overexpression of SAS-4 induce centrosome amplification (CA),\textsuperscript{13} the most prevalent centrosome defect. In most cases, numerical and structural defects coexist in carcinomas.\textsuperscript{14}

There are numerous reviews and research articles discussing how centrosome defects impact cancers in general, including both solid tumors and hematological malignancies.\textsuperscript{15-17} In this review, we focus on hematological neoplasms, emphasizing and discussing recent advances in understanding centrosome defects in these malignancies.

2. THE LINK BETWEEN CENTROSOME DEFECTS AND HEMATOLOGICAL MALIGNANCIES
Hematological malignancies differ from solid tumors in that they are primary cancers initiated in or mainly affect the blood, bone marrow, lymph nodes, or immune cells.\textsuperscript{18} There is growing evidence that centrosome abnormalities are universal among hematological malignancies. For example, in one clinical study,\textsuperscript{19} 72\% of patients with B-acute lymphoblastic leukemia presented with centrosome anomalies. In addition, the number of centrosomes closely correlated with tumor grade and...
the proliferative index in a variety of hematological neoplasms, including myeloid leukemia, non-Hodgkin’s lymphoma, and multiple myeloma.

Investigations into the relationship between centrosome defects and hematological malignancies have been carried out for more than a century. In 1914, Theodor Boveri proposed that increased numbers of centrosomes might cause cancers, including hematological malignancies, through the generation of chromosomal instability (CIN) and aneuploidy. These were the first studies to link these two concepts. In the following decades, numerous studies reported that CA is significantly associated with aneuploidy and CIN in various hematological malignancies, including lymphoma, leukemia, and multiple myeloma, supporting Boveri’s postulation. As for the causal relationship, current studies in mammals have presented seemingly paradoxical results. On the one hand, Basto’s group found that CA is not capable of inducing tumorogenesis in embryonic neural progenitors, neither can elevated centrosome numbers in mouse skin facilitate skin-tumor formation. On the other hand, however, Holland and colleagues have successfully demonstrated that CA could initiate hematological malignancies in mammals. They used Plk4 overexpression models to induce chronic and mild CA in mice. After 35 weeks of observation, they noticed an apparent increase in spontaneous lymphoma formation in mice.

Although researchers recently found that centrosome defects may also impact cell physiology independently of chromosome segregation, such as defects in spindle orientation, the consensus remains that centrosome abnormalities play pivotal roles in hematological malignancies. Besides tumorigenesis, centrosome aberrations also contribute to metastasis. Pellman’s group found that CA could enhance Rac1 activity by increasing centrosomal microtubule nucleation, disrupting normal cell-cell adhesion and thus facilitating invasion. Besides its impact on mitosis, supernumerary centrosomes can also promote invasion by disturbing ciliary signaling and inducing interphase cytoskeletal changes.

3. PROTEINS THAT CONNECT CENTROSOME DEFECTS WITH HEMATOLOGICAL MALIGNANCIES

The concept that centrosome anomalies promote the initiation and progression of hematological malignancies is increasingly receiving support. However, the exact mechanism of how centrosome aberrations manage to do so remains unclear. The most promising explanation might involve the deregulation of cancer-associated proteins related to centrosomes. The centrosome cycle starts with two parental centrioles duplicating at the G1/S phase transition to generate two new centrosomes with procentrioles. Replicated centrosomes still bind each other via the G1-G2 tether until the G2/M transition. During the S and G2 phases, proteins such as centrosomal P4.1-associated protein (CPAP) promote procentriole elongation in the late G2 phase, Plk1 and aurora kinase A (AURKA) facilitate centrosome maturation and initiate centrosome separation. Once cells enter mitosis, centrosomes promote bipolar spindle formation and ensure accurate chromosome segregation by moving to the opposite sides of the cell. Centriole disengagement happens during mitosis when the mother and daughter centrioles dissociate entirely from each other following cell division. After the whole cycle, both centrioles remain competent to replicate (Fig. 1). Cell cycle-regulated proteins such as Plk4 and AURKA are pivotal for the centrosome cycle, strictly controlling the accuracy of each step (Fig. 1).

Deregulation of such proteins could induce centrosome defects, especially CA; however, cells with centrosome abnormalities would not necessarily lead to tumorigenesis, and,

![Figure 1](image)
Instead, cells with centrosome alterations, in spite of amplification or loss, usually result in apoptosis or cell arrest due to the surveillance pathways activated by tumor-suppressor proteins such as p53 (Fig. 2). However, in hematological malignancy, deregulation of certain proteins can promote supernumerary centrosomes clustering to form bipolar spindles, resulting in a pseudo-bipolar cell division (Fig. 2). In this way, cancer cells can escape the normal cell surveillance mechanism, surviving and proliferating. Cells with amplified centrosomes can clonally expand; an example is the clonal expansion of malignant plasma cells in multiple myeloma, in which centrosome amplification is frequently observed. Proliferating cells whose extra centrosomes are clustered together increase the frequency of erroneous mitoses, spreading cancerous mutations throughout the population via clonal expansion.

In the following sections, the proteins under detailed discussion are significantly involved in cell-cycle regulation, cell-surveillance pathways, and extra centrosome clustering.

### 4. Plk4-Induced Centrosome Amplification

Plk4 is a vital regulator of centrosome duplication. After localizing to the centrosome by interacting with the centrosomal protein of 192 kDa (Cep192) and Cep152, Plk4 phosphorylates the centriole protein, SCL-interupting locus protein (Stil), triggering the recruitment of SAS-6, a core component of the centriole cartwheel and procentriole formation (Fig. 1). Given its close association with the centrosome cycle, Plk4 overexpression has been developed as a major method to induce CA. Recent research demonstrates that Plk4 levels might tether to the crucial biomarkers of myeloid and lymphoid malignancies, ten-eleven-translocation 2 (TET2) and Janus kinase 2 (JAK2), respectively, suggesting a significance for Plk4 in the initiation, development, and progression of hematological neoplasms. Therefore, Plk4 deregulation has been recognized as a bridge between centrosome abnormalities and hematological malignancies.

Unlike Plk4 overexpression in most solid tumors, the deregulation of Plk4 in hematological malignancies is highly variable. On the one hand, Plk4 protein levels are 35% lower in lymphoproliferative neoplasms, myelodysplastic syndrome (MDS), and leukemia than in normal tissues, which might be the consequence of hypermethylation of the Plk4 promoter found in lymphoma, MDS, and leukemia samples. On the other hand, Plk4 expression has been found to be abnormally elevated in four of five cancer cell lines of classical Hodgkin lymphoma (cHL). Moreover, studies by Zhang’s group have identified Plk4 as one of the co-upregulated genes for relapsed acute lymphoblastic leukemia (ALL), indicating its role as a biomarker for this disease. In addition, as mentioned above, mild Plk4 overexpression can drive overall but low-level CA in mamals, inducing a significant increase in spontaneous lymphoma formation.

So far, researchers have identified various transcription and post-translational factors that modulate Plk4 expression, activity, or stability. Transcriptionally, E2F Transcription Factor 1 (E2F1) and E2F3, two members of the E2F family, function as transcriptional activators for Plk4, while Kruppel-Like Factor 14 (KLF14) has been recognized as a transcriptional repressor. Therefore, it is not surprising that E2F repression leads to cell-growth arrest in Burkitt lymphoma, and the knockout of KLF14 promotes Plk4-induced CA and tumorigenesis in mice. Moreover, KLF14 has been found to be deleted among certain lymphoma patients. Another transcription factor, NF-kB, has been found to bind Plk4 promoter and positively regulate Plk4 expression. In acute myeloid leukemia (AML), more than half of the cases have constitutive NF-kB, and inhibition of NF-kB has dramatically decreased cell proliferation by ~40%. The inhibition of NF-kB has also been associated with apoptosis in primary mantle cell lymphoma (MCL). In fact, certain Plk4 regulators, such as the E2F family and NF-kB, also play essential roles in hematopoiesis, such as controlling hematopoietic cells, hematopoietic differentiation, and lymphopoiesis, which indicates the interplay between hematopoiesis and hematological malignancy. In addition, endoplasmic reticulum (ER) stress...
could significantly reduce Plk4 expression level, and, reversely, Plk4 overexpression prevents ER stress responses such as apoptosis and thus facilitates cell proliferation. There are no classic ER stress response elements in the Plk4 promoter; however, there are the binding motifs of specific transcription factors that react to ER stress, including GATA-1 (binding at −1238 of the Plk4 promoter region), which is a crucial regulator also for hematopoiesis.

As for post-translational modification, Mindbomb E3 ubiquitin-protein ligase 1 (Mib1) and lynine acetyltransferase (KAT) 2A/2B (KAT2A, also known as GCN5) induce ubiquitination and acetylation of Plk4, respectively, decreasing Plk4 activity. Moreover, KAT2A-mediated Plk4 acetylation is capable of preserving centrosome number and, therefore, favors genomic stability. Therefore, it is reasonable for the deregulation of KAT2A/2B to have been observed among various hematological malignancies, and Dent’s group found that inhibition of KAT2 reduces the viability and proliferation of Burkitt lymphoma cells. These findings once again demonstrate that, unlike the situation in solid tumors, Plk4 levels are not consistently up-regulated in hematological malignancies. In addition, Tec protein tyrosine kinase (TEC) can increase Plk4 stability by preventing its auto-ubiquitination, and QL47, a selective inhibitor of TEC kinase, is capable of reducing the proliferation of B-cell lymphoma cell lines. A receptor family with sequence similarity 46 member C (FAM46C) inhibits Plk4 activity, and FAM46C is also known as a tumor suppressor that works specifically for B-lymphocyte lineage. In addition, cullin associated and neddylation dissociated 1 (CAND1) increases Plk4 stability. However, the correlation between CAND1 and hematological malignancies needs further investigation. Moreover, for some leukemia and lymphoma cell lines, associations exist between hypoxic exposure of bone marrow and abnormal Plk4 promoter methylation, indicating the potential impact of environmental stress, hypoxia in this case, on Plk4 during carcinogenesis. Given all the data so far, the role of Plk4 in hematological malignancies seems to switch from an oncogene to a tumor suppressor. Either abnormally high or low levels of Plk4 are associated with centrosome anomalies. The expression level of Plk4 seems to be unassociated with hematological malignancies, but Plk4 inhibitors are therapeutic for hematological neoplasms, as shown in the following subsection on therapeutic insights. These results indicate that Plk4 might be necessary for CA, but it might not be CA’s driving force.

5. p53-DEPENDENT MITOTIC SURVEILLANCE PATHWAY

p53, a well-known tumor suppressor, regulates cell division by preventing cells from proliferating in an uncontrolled way. Recent studies have shown that the mitotic surveillance pathways are also highly p53-dependent. For instance, the ubiquitin carboxyl-terminal hydrolase 28 (USP28) – TP53 binding protein 1 (3SBP1) – p53 – p21 signaling axis has been identified in genome-wide knockout screens as a cellular mechanism for sensing centrosome reduction. The interaction of 3SBP1 with USP28 and p53 leads to USP28dependent de-ubiquitination and activates p53, resulting in apoptosis or cell-cycle arrest. As for centrosome amplification, the large tumor suppressor kinase (LATS2) is another mechanism responsible for sensing supernumerary centrosomes and subsequently stabilizing p53 (Fig. 2). Moreover, researchers have found that PIDDosome, an essential and non-redundant p53 activator, is also crucial in preventing cells with supernumerary centrosomes from proliferating in an alternative pathway (Fig. 2). PIDDosome, consisting of CASH2 and Ripk1 domain-containing adaptor with death domain (CRADD) and p53-induced death domain-containing protein 1 (PIDD1), drives the activation of caspase 2, a pro-apoptotic protease (Fig. 2). Moreover, a recent study found that ankyrin repeat domain containing 26 (ANKRD26) is involved in the activation of the centrosome-PIDDsome-p53 signaling axis by centriolar distal appendages.

Therefore, normally in cultured mammalian cells, centrosome amplification or reduction leads to apoptotic cell death or cell-cycle arrest. The removal of p53 could prevent such a phenomenon, illustrating why hematological neoplasms often lack responses against centrosome defects. Researchers have detected TP53 mutation and p53 expression in various types of hematological malignancies, including but not limited to diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia (CLL), AML, mature T and NK cell lymphomas, aggressive B-cell lymphomas (B-NHL) and MCL. In addition, TP53 mutation and p53 expression tend to indicate a poor prognosis for these diseases. Even the research of Holland’s group found that the thymic tumors from Plk4-overexpressing mice also display a noticeable decrease in p53 expression level, implying that centrosome amplification in spontaneous lymphoma leads, at least, to a partially comprised p53 pathway. However, p53 deficiency alone does not cause centrosome defects. Therefore, loss of p53 does not directly control centrosome numbers or structure. A plausible deduction is that the p53-null environment provides a permissive setting for cells with centrosome abnormalities to proliferate continuously and produce viable progeny.

6. AURKA-ASSOCIATED CENTROsome DEFECTS AND EXTRA CENTROsome CLUSTERING

AURKA contributes significantly to both centrosome maturation and spindle assembly pathways. For example, AURKA phosphorylates the nuclear distribution protein nudeE-like 1 (NDEL1) at the Ser251 site, ensuring appropriate centrosomal maturation and separation. In addition, AURKA is responsible for the Ser467 phosphorylation of another centrosome-associated protein, CPAP, which is essential for the maintenance of centrosome structure and formation of the spindle poles. More importantly, AURKA phosphorylates Plk1, a critical mitotic kinase regulating various cell division processes at the Thr210 site, and is crucial for the proper centrosome duplication cycle. When overexpressed, AURKA promotes CA, chromosome instability, and oncogenic alteration in animal cells. AURKA is also responsible for the phosphorylation of NuMA, whose cortical recruitment plays an essential role in spindle orientation. Given its significance in centrosome replication, it is not surprising that AURKA is deregulated, primarily overexpressed, in various hematological malignancies. The expression level of AURKA dramatically rises in patients with non-Hodgkin lymphoma (nHL), and its expression correlates with disease progression and aggressiveness; high-risk DLBCL and Burkitt lymphoma have the highest AURKA expression. In addition, AURKA is overexpressed in high-risk multiple myeloma, especially in proliferation subgroups. Moreover, studies by Manning’s group have recently found that spindle pole clustering also requires AURKA activity, helping cells with extra centrosomes to obtain pseudo-bipolarity (Fig. 2). In their study, AURKA inhibition promoted a panel of AML cells with extra centrosomes to produce multipolar and disorganized spindles, reducing the proliferation and viability of daughter cells. Various transcription factors regulating AURKA have been identified. Examples include E4TF1, one of the E26 transformation-specific (ETS) family proteins, which can positively regulate AURKA transcriptional levels, and alterations among ETS gene expression are often detected in various hematological malignancies including lymphoma and leukemia. Another factor, forkhead box M1 (FOXM1), which is significantly involved in AML progression and treatment, has been identified as another transcriptional activator for AURKA. In addition, FOXM1 regulates leukemia stem-cell quiescence
and survival in mixed-lineage leukemia (MLL)-rearranged AML. 107 As for post-translational modification, Ajuba LIM protein (AJUBA) efficiently stimulates AURKA phosphorylation at Thr288 and increases its activity. 109 Targeting protein for Xklp2 (TPX2) can also induce AURKA activation. 107 Moreover, Tsai’s group found that, among nHL cell lines, the therapeutic effects of MK-8745, an AURKA inhibitor, are associated with the expression level of TPX2. 110 In addition, glycogen synthase kinase 3b (GSK-3b) functions as a negative regulator that inhibits AURKA activity by phosphorylating AURKA at Ser290/291. 111

As in Plk4 regulation, certain crucial regulators for AURKA also play essential roles in hematopoiesis. Likewise, FOXM1 contributes advantage to chronic myeloid leukemia hematopoiesis, 112 and ETS family proteins also control hematopoiesis and play crucial roles in hematopoietic stem cell (HSC) development. 113 Moreover, GSK-3b regulates hematopoiesis and stem cell function by controlling the Wnt signaling pathway via its main effector β-catenin. 114 Last but not least, AJUBA controls growth factor independent 1 transcriptional repressor (Gfi1), a critical regulator of hematopoiesis. 115 In reverse, AURKA is also involved in the phosphorylation of transcription factors essential for hematopoiesis. An example is that AURKA-induced phosphorylation has been found to promote appropriate mitotic progression by including Runt-related transcription factor from the chromosome. 116 All these examples once again demonstrate the intimate association between hematopoiesis and hematological malignancies.

7. OTHER PROTEINS INVOLVED IN EXTRA CENTROSOME CLUSTERING

Spindle-stabilizing factors also play a crucial role in supernumerary centrosome clustering. One example is transforming acidic coiled-coil-containing protein 3 (TACC3), a key spindle organization regulator. 117 Dedhar’s group identified that an integrin-linked kinase (ILK)-regulated phosphorylation of TACC3 is required for centrosome clustering. 118 Furthermore, Fry and colleagues have found a pathway that functions via NIMA-related kinase 6 (Nek6) and heat shock protein 72 (Hsp72) to facilitate supernumerary centrosome clustering, which is also TACC3 related (Fig. 2). 119 After being phosphorylated by Nek6 and its upstream activators, Plk1 and AURKA, Hsp72 targets the spindle poles of the cells containing supernumerary centrosomes, which may contribute to the assembly of the chTOG-TACC3 complex. 120 This complex, regulated by an ILK, is involved in extra centrosome clustering, and its inhibition prevents centrosome clustering. 119 They also demonstrate the de-clustering effect of an Hsp70 inhibitor for ALL cell lines with supernumerary centrosome clustering; this indicates that Nek6 phosphorylation of Hsp72 is required to cluster amplified centrosomes in ALL. 119

In addition, TACC3 has been found to fuse with fibroblast growth factor receptors (FGFR). 121 FGFR3-TACC3 gene fusion has been detected in various solid tumor types. 122 However, one uniqueness of hematological malignancies different from solid tumors is that, according to Noguera’s group, all samples of hematological malignancies were found to lack such a rearrangement. 122 Therefore, unlike the situation in solid tumors, screening for this phenomenon might not be appropriate for diagnosing hematological malignancies. 122 In addition, elevated levels of TACC3 alter the subcellular localization of FOG family member 1 (FOG-1) and impact its interaction with GATA-1, which, as mentioned before, is a vital regulator in hematopoiesis. 123 Another spindle-stabilizing factor that has been recognized with an important involvement in extra centrosome clustering is hepatoma up-regulated protein (HURP). Verlhac’s group identified the importance of HURP in bipolarity formation, such as stabilizing microtubules in the spindle central domain. 124 They also demonstrated the requirement for HURP to cluster extra centrosomes before cell division. 124 AURKA is a mitotic kinase required for both TACC3 spindle localization 112 and HURP activity. 124 This might explain why AURKA is required for centrosome de-clustering, as mentioned above.

Motor proteins are also critical for extra centrosome clustering. In particular, the removal of minus-end-directed motor dynein leads to de-clustering of centrosomes and thus induces multipolarity establishment among tumor cells or engineered cells with supernumerary centrosomes. 16-18 Besides dynein, kinesin family member C1 (KIFC1), a minus-end-directed kinesin motor protein, also contributes to extra centrosome clustering. 125-127 CW069 and AZB52, inhibitors of KIFC1, have been found to prevent centrosome clustering and reduce cancer-cell viability. 125,126 One plausible reason to explain the involvement of motor proteins in centrosome clustering is that they are responsible for the recruitment of spindle-stabilizing factors. As seen in the study by Verlhac’s group, HURP recruitment to the spindle central region requires kinesin-5 activity. 124 In addition, studies by Delaval and colleagues have demonstrated the requirement of intraflagellar transport protein 88 (IFT88) for effective centrosome clustering in various cancer cell lines with extra centrosomes and revealed the importance of IFT88 for the survival and proliferation of cancer cells. 127 Last but not least, signal transducer and activator of transcription 3 (Stat3) depletion and inhibition in cancer cells lead to a significant reduction in centrosome clustering and viability. 129 Stat3 plays a vital role in hematopoietic cell development and leukemia development. 130 Static, a Stat3 inhibitor, has been found to prevent centrosome clustering and reduce the viability of cancer cells. 129 However, unlike AURKA and Hsp72 inhibitors, their de-clustering effects have not been tested among cell lines or patients with hematological malignancies. 129 Therefore, it is unknown whether these pathways can impact hematological neoplasms, which is a question awaiting further investigation.

8. THERAPEUTIC INSIGHTS

The more we have learned about the role of centrosome defects in hematological malignancies, the more insights we have gained for developing therapeutic targets for anti-cancer treatment. The first feasible approach is to target the gene/protein directly involved in centriole biogenesis or centrosome cycle regulation (Fig. 1). In particular, targeting the abnormal expression of Plk4 by interference or inhibitors offers attractive potential in preventing cancer cell proliferation and inducing apoptotic cancer-cell death. 131 For instance, studies by Wang’s group have shown the up-regulation of Plk4 expression at both transcriptional and translational levels in DLBCL cell lines, and they have demonstrated that CFI-400945, a pharmaceutical inhibitor of Plk4, could successfully prevent DLBCL cell proliferation and induce apoptosis. 132 Several other Plk4 inhibitors have been developed as anti-tumor treatments in solid tumors, such as centrinone and centrinone-B, which are the most selective Plk4 inhibitors. 133 However, their effects on hematological malignancies remain unclear and await investigation. Apart from Plk4, researchers have also developed inhibitors targeting another centrosome regulatory protein, AURKA. Treatment with a high-affinity, selective inhibitor of AURKA, alisertib (MLN8237), leads to mitotic spindle anomalies and mitosis deregulation, resulting in reduced cell proliferation in cell lines and mouse models with lymphoma and myeloma. 19 In fact, inhibitors, such as CFI-400945 and CFI-400437, can target both Plk4 and AURKA. Their anti-tumor therapeutic effects might, in part, result from the dual inhibition of both Plks and AURKs. 131

Another curative possibility is to target supernumerary centrosomes in hematological neoplasms, leading to multipolar division and generating non-proliferative daughter cells with compromised viability (Fig. 2). As mentioned above,
VER-15508, an Hsp70 inhibitor, could reduce extra centrosome clustering and increase the frequency of multipolar spindles in ALL cell lines.119 In addition, CW069 and AZ82, inhibitors of KIFC1, and Statcitc, a Stat3 inhibitor, have been found to cause significant inhibition of centrosome clustering and viability.120,121,122 Still, their de-clustering effects in patients with hematological malignancies need to be further investigated.

In addition, a recent study has demonstrated the association between centrosome amplification and autophagy in malignancies.134 Autophagic degradation of Cep63 induces inhibition of CA.135 CA can also disrupt autophagosome trafficking to lysosomes, resulting in an increased number of autophagosomes.134 Such a connection indicates that amplified centrosomes could protect themselves from degradation by suppressing autophagic flux.134–136 Therefore, the centrosome-autophagy relationship might be another promising precision medicine strategy for anti-tumor therapy targeting centrosome defects. Last but not least, hypoxia also promotes Plk4 overexpression.133 Thus, hypoxia-inducible factor 1α (HIF-1α) could induce CA by directly up-regulating Plk4, another possible therapeutic target available for patients with CA-rich hematological malignancies.137 Given the development of several promising HIF-1α inhibitors, HIF-1α and Plk4 interplay could potentially contribute to the design of new cancer therapies.137

9. FUTURE PERSPECTIVES

Besides inducing chromosome mis-segregation and aneuploidy, centrosome defects can also promote cancer formation by increasing cell invasiveness or defects in spindle orientation.36,38 However, the exact mechanism of these alternative pathways remains ambiguous and needs to be further tested. Moreover, the experiments involving CA depend almost entirely on Plk4 overexpression to induce CA.44 Somepleiotropic effects may arise because Plk4 kinase activity is significantly involved in many other microtubule-dependent cellular processes. Abnormal Plk4 kinase activity may affect these cellular pathways or even impact unknown mechanisms related to this kinase.

As mentioned above, multiple mechanisms underlying the centrosome-related pathogenesis of cancer have been identified, with the corresponding therapeutic strategies explored. However, some therapeutic effects have only been tested in patients with solid tumors. It will be intriguing to investigate whether the same therapeutic targets also work for patients with hematological malignancies. Moreover, the number of patients involved in each clinical study has been limited, usually no more than tens of patients. Such small sample sizes might lead to inaccurate and variations, which would become apparent when Plk4 levels are either up- or down-regulated among limited numbers of patients. In addition, owing to limitations such as the resolution of light microscopy, the structural defects of centrosomes have been rarely studied. Although a recent study has found that over-elongation of centrioles can also promote CA,138 research related to structural defects of centrosomes is inadequate. Given the advanced microscopy technology with higher resolutions, considerable studies have been conducted towards the structural alterations of centrosomes.

Additionally, the centrosome is involved in ciliogenesis; for example, Zhou’s group recently identified O-GlcNAc transferase (OGT) that localized at the PCM outer layer as a critical player in cilium formation, and they have shown the impact of OGT inhibition on aspects such as the number of ciliated cells and ciliary length.139 Therefore, it is not surprising that centrosome dysfunction is also closely associated with ciliopathy.40 Moreover, primary cilia exist in hematopoietic cells and regulate the JH signaling pathway.141 Further, the number of primary cilia in AML cells decreases while the mutation frequency of primary cilia increases.142 Future studies could be conducted to investigate how centrosomes impact on hematological malignancy through ciliogenesis.

In conclusion, centrosome defects, especially centrosome amplification, are hallmarks of hematological malignancies. Various proteins either regulating the centrosome cycle or promoting extra centrosome clustering have been identified as the bridge between centrosome abnormalities and hematological malignancies. Understanding centrosome anomalies helps researchers develop promising therapeutic strategies against various hematological malignancies.

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