Trends in Cancer

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Review

Targeting vulnerabilities of aneuploid cells for cancer therapy

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Aneuploidy is a common feature of cancer that drives tumor evolution, but it also creates cellular vulnerabilities that might be exploited therapeutically. Recent advances in genomic technologies and experimental models have uncovered diverse cellular consequences of aneuploidy, revealing dependencies on mitotic regulation, DNA replication and repair, proteostasis, metabolism, and immune interactions. Harnessing aneuploidy for precision oncology requires the combination of genomic, functional, and clinical studies that will enable translation of our improved understanding of aneuploidy to targeted therapies. In this review we discuss approaches to targeting both highly aneuploid cells and cells with specific common aneuploidies, summarize the biological underpinning of these aneuploidy-induced vulnerabilities, and explore their therapeutic implications.

Highlights

Aneuploidy is a defining hallmark of human cancer, and presents underexploited opportunities for cancer treatment.

Recent discoveries have paved the way to targeting the cellular consequences of high degrees of aneuploidy, as well as those of specific common karyotypes.

Several synthetic lethalities that are induced by aneuploidy have been identified, including the targeting of cell division and chromosome segregation, DNA replication and repair, haploinsufficiency and oncogenic addictions, mechanisms of gene dosage compensation, and metabolic and immune-related alterations.

Aneuploidy creates cell-autonomous and non-cell-autonomous cellular vulnerabilities, and the time is ripe for their clinical translation.

Targeting aneuploidy for precision cancer medicine

Personalized cancer treatment is at the center of the precision medicine paradigm [1] and represents an important advancement in cancer therapy. This paradigm, enabled largely by the genomic revolution, has led to the development of targeted therapies such as vemurafenib against the BRAF V600E mutation [2]. Precision medicine relies heavily on the identification of distinctive characteristics of tumor cells, such as the genetic changes that accumulate in tumors due to their inherent **chromosomal instability (CIN)** (see Glossary).

Genomic instability has been long recognized as one of the 'hallmarks of cancer' and has received much attention in cancer research [3]. It spans a wide range of genetic defects that impact cancer cells, from point mutations to whole-chromosome catastrophes (Figure 1A). One primary type of genomic instability is CIN [4], which can result in structural aberrations, such as **translocations** and **chromothripsis** [5,6]. The therapeutic potential of targeting CIN and its resultant structural aberrations have been extensively reviewed recently [7,8]. Importantly, the main outcome of CIN is **aneuploidy**: an aberrant number of chromosomes or chromosome arms [9]. In recent years, aneuploidy research has boomed due to an improved detection of aneuploidy in tumors through DNA and RNA sequencing, as well as the development of novel techniques to experimentally induce aneuploidy and to computationally integrate aneuploidy within genomic analyses of tumor data (reviewed in [9,10]). This review focuses on the targeting of aneuploidy and its consequences.

A key concept within precision medicine is **synthetic lethality**, defined as a genetic interaction in which two simultaneous genetic alterations lead to cell death although either one of them alone is not lethal [11]. As aneuploidy changes the expression of multiple genes at once, resulting in wide-ranging cellular consequences, it might create novel synthetic lethalities. Specifically, the simultaneous gain or loss of hundreds of genes induces cellular stresses – such as mitotic, replicative, proteotoxic, and metabolic stresses [12] – which have been identified and studied across organisms and model systems (Box 1). In the context of cancer, aneuploid cancer cells successfully

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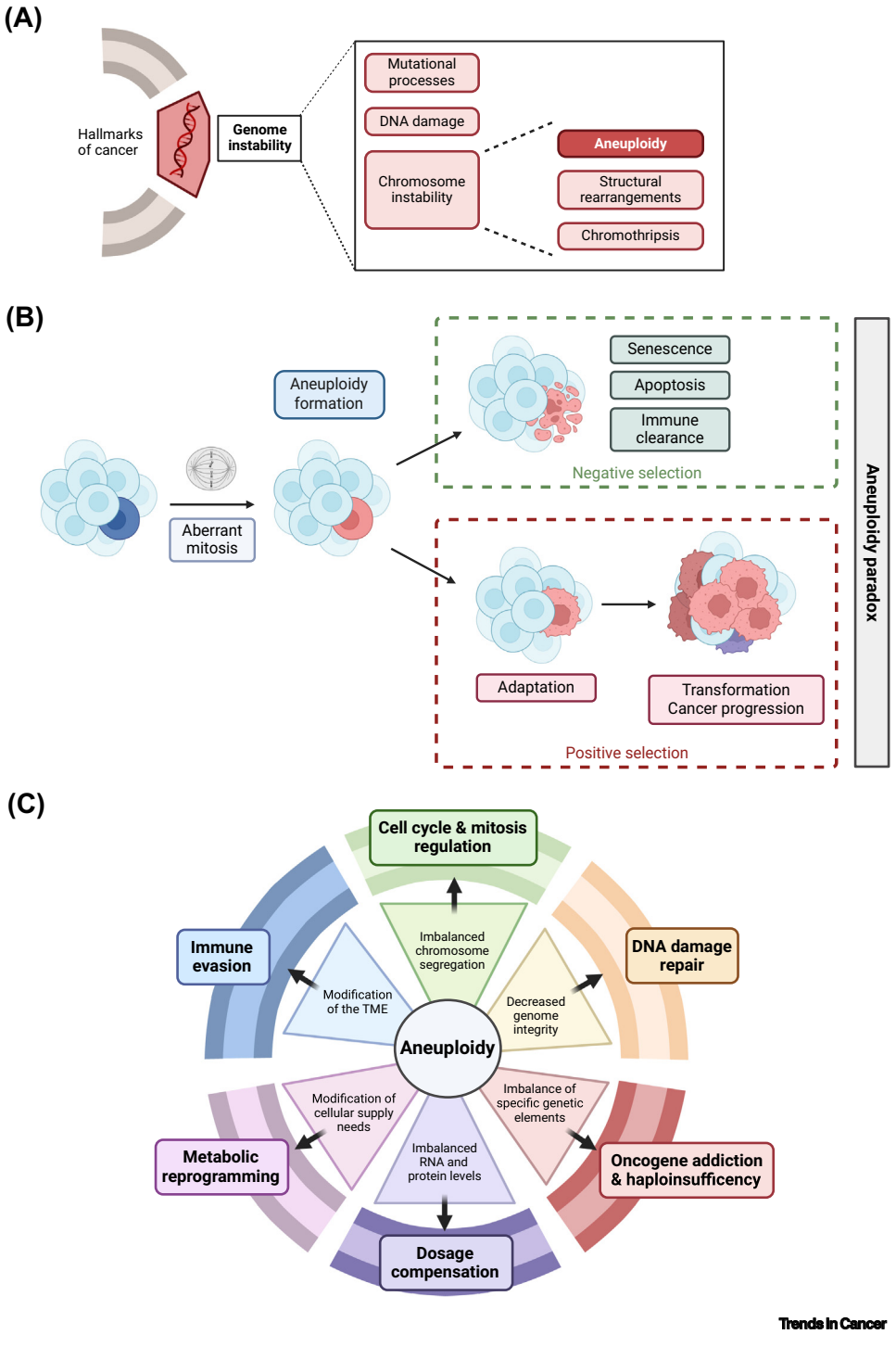

Figure 1. The cellular consequences of aneuploidy may be exploited for cancer therapy. (A) Genomic instability, a characteristic trait of cancer, is an umbrella term for multiple types of mutational processes, DNA damage, and chromosome instability (CIN). Aneuploidy is a common outcome of CIN, but it is important to distinguish CIN (the process) from aneuploidy (the outcome), as aneuploid cells can be CIN-negative (stable karyotypes), or CIN-positive (unstable karyotypes).

(Figure legend continued at the bottom of the next page.)

Glossary

Aneuploidy: an abnormal number of chromosomes or chromosome arms within the cell.
Cancer drivers: genetic alterations – including mutations, amplifications, deletions, or translocations – that provide a selective growth advantage to cells, promoting tumor initiation, progression, and maintenance.
Chromosomal instability (CIN): an increased rate of chromosome mis-segregation during cell division, leading to aneuploidy and structural chromosomal abnormalities.
Chromothripsis: a catastrophic shattering of an entire chromosome or chromosomal region, followed by its erroneous reassembly, leading to complex structural rearrangements and genomic instability.
Dosage compensation: a regulatory mechanism that balances gene expression levels in response to variations in gene copy number, ensuring stable cellular function despite aneuploidy or chromosomal alterations.
Haploinsufficiency: a condition in which a single functional copy of a gene is insufficient to maintain normal cellular function, leading to a partial loss-of-function phenotype.
Immune checkpoint inhibitors (ICIs): monoclonal antibodies that block inhibitory checkpoint proteins, such as PD-1, PD-L1, and CTLA-4, to restore and enhance the immune system's ability to recognize and attack cancer cells.
Oncogenes: mutated or overexpressed genes that drive uncontrolled cell proliferation and tumor development by promoting growth signals, inhibiting apoptosis, or enhancing other cancerous traits.
Proteotoxic stress: a cellular condition caused by the accumulation of misfolded, aggregated, or damaged proteins, overwhelming the protein quality control systems and leading to cellular dysfunction or apoptosis.
Replication stress: a condition characterized by impediments to DNA replication, such as stalled replication forks or DNA damage, leading to genomic instability and increased mutation rates.
Spindle assembly checkpoint (SAC): a surveillance mechanism that ensures proper chromosome alignment and attachment to the mitotic spindle before anaphase onset, preventing chromosomal mis-segregation and aneuploidy.

Box 1. Model systems for the study of aneuploidy

Studying aneuploidy is relevant to multiple fields, from developmental and regenerative biology to cancer therapy. Therefore, the models most appropriate for aneuploidy research depend on the question one wants to address. Some of the mechanisms required for the adaptation to aneuploidy are conserved across organisms: for example, the response to disrupted mitotic checkpoint [37,109,116,117,247] or the need for dosage compensation [107,116,170–172,177,180]. Yeast can be a suitable model to study conserved cellular consequences, as it is a simple eukaryotic model with advanced tools for genetic and chromosomal engineering. However, yeast is a unicellular model, its chromosomes are very different from mammalian chromosomes, and it lacks mechanisms of epigenetic regulation. Drosophila and zebrafish can serve as models to study aneuploidy in small multicellular organisms [111,195,200,248–252], but their chromosomes are also different from mammalian chromosomes, and they deploy distinct mechanisms for sex chromosome regulation. Therefore, mammalian models such as murine and human cells are needed for studying advanced mechanisms of aneuploidy adaptation, such as the involvement of epigenetics [186] or the interaction with the environment [235]. The mouse system allows for perturbational *in vivo* studies [224,253,254], but the synteny between mouse and human chromosomes is incomplete, and all mouse chromosomes are acrocentric. Studying aneuploidy in human cells is obviously the most relevant for cancer therapy, but *in vivo* manipulations are naturally limited. Human systems for aneuploidy research include patient-derived cell lines, organoids, or xenografts, all of which originally exhibit the karyotypes of their tumor-of-origin. However, all of these model systems evolve, and the fitness value of specific karyotypes might be different in the model. Therefore, it is important to take the karyotypic heterogeneity and genetic evolution of these models into account [255–257]. In addition, it is also possible to genetically engineer aneuploidy *in vitro*, as reviewed elsewhere [10,258], generating 'karyotypes-on-demand' that could be very useful for aneuploidy research [164,259].

When focusing on aneuploidy in cancer, one must also consider the differences between untransformed and cancer cell lines. As CIN and aneuploidy are highly detrimental for normal cells [107,167], untransformed models tend to respond to aneuploidy by activating compensatory mechanisms, while cancer models are already adapted to tolerate aneuploidy (Figure 1B in the main text). Untransformed models also tend to be more chromosomally stable, enabling us to detangle the consequences of aneuploidy from CIN [24,180]. Further, untransformed models have a simpler genetic background, allowing the study of a single chromosome gain or loss [24,180,187,226,260], as well as of gradual karyotypic evolution leading to cellular transformation [156,226]. By contrast, aneuploid cancer cell lines [21,180] and tumors [14] are highly chromosomally unstable, and they are likely more suitable models for studying cancer dependencies.

Finally, when modeling aneuploidy one must consider the potentially distinct impact of chromosome gains (trisomies) and chromosome losses (monosomies). Due to their unstable karyotypes, most cancer models carry both trisomies and monosomies [14,21]. Therefore, separate models that harbor only one type of aneuploidy [24,41,187,211,260,261] are needed to study the distinct effects of chromosome gains and losses.

Synthetic lethality: a condition in which the simultaneous loss or inhibition of two genes leads to cell death, whereas the loss of either gene alone is non-lethal.
Translocation: a structural chromosomal abnormality in which a segment of one chromosome is rearranged and attached to a different chromosome or to a different location on the same chromosome.
Triplosensitivity: a condition in which an extra copy of a gene leads to a dosage imbalance that disrupts normal cellular function.
Tumor microenvironment (TME): the complex network of cancer cells, immune cells, stromal cells, blood vessels, extracellular matrix, and signaling molecules that interact to influence tumor growth, immune evasion, and therapy resistance.
Tumor suppressor genes (TSGs): genes that regulate cell growth and division by preventing uncontrolled proliferation; their inactivation or loss of function can lead to tumor development and cancer progression.
Whole-genome doubling (WGD): duplication of the entire genome of the cell, resulting in a tetraploid state that promotes chromosomal instability, aneuploidy, and tumor evolution.

overcome these stresses and even turn them into a proliferative advantage [13] (Figure 1B). However, aneuploid cells might become dependent on the mechanisms that they deploy to cope with aneuploidy-induced cellular stresses, which might create therapeutic opportunities.

The quest for aneuploidy-induced synthetic lethalities

Most solid and hematological tumors are in fact highly aneuploid [14,15]. CIN and aneuploidy are associated with a poor clinical outcome [16], rapid tumor evolution [17], cancer progression and aggressiveness [18,19], and both general and specific drug resistance [20–24]. The effect of aneuploidy is not merely cell-autonomous; rather, aneuploidy also alters the interaction of cancer cells with other cells in the **tumor microenvironment (TME)** [25–30]. Identifying synthetic lethalities of aneuploid cells could therefore inform the development of new therapies for patients with a variety of cancer types.

Two complementary conceptual frameworks have been proposed to target aneuploid cancer cells. The first approach aims to identify non-chromosome-specific dependencies of highly

(B) Chromosome mis-segregation during an aberrant mitosis results in the acquisition of aneuploidy. The fate of the emerging aneuploid cell depends on its ability to adapt to aneuploidy-induced stresses. In healthy dividing cells, aneuploidy is selected against, so that the aneuploid cells experience cell cycle arrest, senescence, apoptosis, and/or clearance by the immune system. However, if the aneuploid cells succeed in overcoming these stresses, their aneuploidy could become beneficial, and contribute to cellular transformation and to tumor development and progression. (C) Schematic representation of the variety of aneuploidy-induced cellular consequences (inner circle) and the resultant cellular vulnerabilities induced by these consequences (outer circle). Abbreviation: TME, tumor microenvironment. Figure created with BioRender.

aneuploid cells, independently of the affected chromosome(s). As aneuploid cancer cells are generally more resistant to drug treatment, partly due to their reduced proliferation [20,31], the identification of drugs to which aneuploid cells are more sensitive is a long-sought-after goal. The second approach aims to identify chromosome-specific dependencies. Each cancer type displays a characteristic pattern of recurring aneuploidies [14,15,32,33], suggesting that some aneuploidies serve as **cancer drivers** [10]. The cellular consequences of specific aneuploidies are very much context-dependent [9], and have been shown to be associated with drug responses [23,34]; identifying therapeutically relevant vulnerabilities induced by specific, common aneuploidies is therefore of much interest as well. In this review, we discuss recent discoveries on the cellular vulnerabilities created by aneuploidy, and explore potential opportunities to leverage these vulnerabilities to target aneuploid cancer cells, using both non-chromosome-specific and chromosome-specific approaches (Figure 1C).

Targeting cell division and chromosome segregation

Dividing cells must keep a very tight control of the cell cycle, carefully regulating cell division in general and chromosome segregation in particular. This task is more challenging in aneuploid cells, which need to propagate an unbalanced number of chromosomes (as reviewed in [35]), potentially making the aneuploid cells more dependent on various cell cycle components (Figure 2A). The link between aneuploidy and cell proliferation is complicated. On the one hand, aneuploidy characterizes more aggressive tumors, which also tend to proliferate faster [13,14]. On the other hand, highly aneuploid cells seem to divide more slowly than nearly euploid cells across human cancer cell lines [20], and in mouse [36] and human isogenic systems [24,25,37], potentially explaining their increased resistance to drug treatments that target proliferation.

Aneuploidy is tightly associated with CIN, in a bidirectional manner: CIN is obviously the mechanism that leads to aneuploidy [38,39], but aneuploidy can also increase CIN, thereby promoting further aneuploidy [40–44]. Even a single mis-segregated chromosome can trigger massive chromosome catastrophes and genomic rearrangements such as chromothripsis [45]. Targeting cell division and chromosome segregation-related mechanisms is the most advanced therapeutic strategy proposed to target aneuploid cells to date.

Aneuploidy patterns are shaped by segregation errors involving specific chromosomes, followed by selection for the fittest karyotypes. Several factors have been shown to affect chromosome mis-segregation rates, including centromeric features [46–48] and the nuclear location of the chromosome [49]. Despite the chromosome-specific aneuploidy emergence rate, however, the eventual karyotypes that are commonly seen in cancer seem to be shaped mostly by positive and negative selection [26,50–52]. Importantly, both the mechanistic and the selective pressures associated with specific chromosomes may result in chromosome-specific cellular vulnerabilities.

Mechanisms to target highly aneuploid cells

Aneuploid cells often experience CIN, so that induction of further CIN in aneuploid cells can result in unfit karyotypes that can lead to cell cycle arrest and cell death [25,53,54]. Therefore, increasing CIN in aneuploid cancer cells can push them past a tolerable ‘CIN threshold’, resulting in deadly mitotic catastrophes.

Targeting the spindle assembly checkpoint: The **spindle assembly checkpoint (SAC)** is the main mitotic checkpoint, ensuring the proper attachment of chromosomes to the spindle microtubules, and regulating the progression from metaphase to anaphase [55]. Chemical inhibition of the SAC using MPS1 inhibitors promotes CIN and aneuploidy levels in the cells [56]. This is particularly detrimental for aneuploid cells, as they can override the checkpoint inhibition, resulting

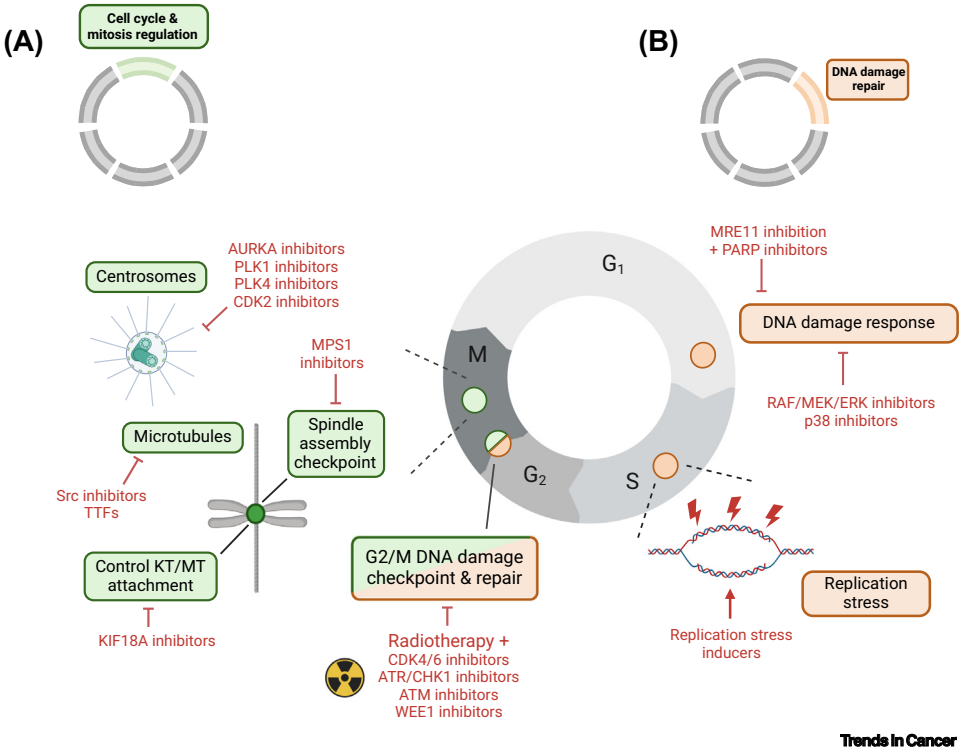

Figure 2. Targeting the genomic instability of aneuploid cancer cells. (A) Mitosis is a central node to target aneuploid cancer cells by interfering with chromosome segregation and its regulation. Several molecular targets have been reported to be preferentially essential in aneuploid cells. These targets govern the regulation of the G2/M checkpoint, the mitotic checkpoint (spindle assembly checkpoint, SAC), the centrosomes, and the microtubules. Aneuploid cancer cells may be more vulnerable to these perturbations, as they may push the cells towards intolerable karyotypes. (B) DNA damage repair is required for the adaptation to aneuploidy, and is required throughout the cell cycle. Inhibition of the DNA damage response (DDR), induction of replication stress, or targeting the G2/M DNA damage checkpoint may therefore preferentially target aneuploid cells. Abbreviation: TTF, tumor-treating fields. Figure created with BioRender.

in abnormal cell cycle progression [21]. Mechanistically, CDC20 activity is particularly important for regulating SAC dependency, and high levels of CDC20 expression – often observed in aneuploid cancer cells – are associated with increased sensitivity to SAC inhibition (SACi) [57].

Targeting the kinetochore–microtubule attachment and microtubule dynamics: The SAC is associated with multiple spindle-related proteins, including the superfamily of motor proteins kinesins (KIFs). Multiple studies recently found an increased dependency of highly aneuploid and chromosomally unstable cancer cells on KIF18A [21,58,59] through its destabilization of the kinetochore–microtubule attachment [60]. KIF18A inhibitors demonstrated *in vivo* preclinical efficiency against multiple highly aneuploid *TP53*-mutated tumor types, such as triple-negative breast cancer (TNBC) and high-grade serous ovarian cancer (HGSOC) [61,62]. KIF18A inhibitors are currently undergoing clinical trials for treating highly aneuploid, chromosomally unstable cancers (clinical trials NCT05902988, NCT06084416, and NCT06799065) (Table 1), opening the door to the clinical targeting of such tumors.

Microtubule stabilization and destabilization can also be targeted directly, with a potentially elevated impact in aneuploid cells. For example, altering microtubule dynamics by Src kinase inhibition was shown to preferentially stabilize the microtubules of SAC-impaired cells [63]. Further, the common microtubule stabilizer paclitaxel was recently shown to kill tumor cells by inducing

Table 1. Ongoing clinical trials to target highly aneuploid cancers[a,b]

Targeted mechanism	Specific targeted process	Molecular target	Molecule	Cancer type	Clinical phase	Refs and/or clinical trial
Cell cycle proteins	KT/MT interaction	KIF18A	VLS-1488	Highly aneuploid CIN+ solid tumors	1/2	NCT05902988
			Sovilnesib	High-grade serous ovarian cancer (HGSOC)	1b	NCT06084416
			ATX-295	Mainly high-grade serous ovarian cancer (HGSOC)	1/2	NCT06799065
	Microtubule dynamics	Microtubules	TTF	Metastatic non–small-cell lung cancer (NSCLC)	3	NCT02973789 [262] (LUNAR trial)
			TTF + pembrolizumab	Metastatic non–small-cell lung cancer (NSCLC)	3	NCT06216301 (LUNAR-2 trial)
			TTF + paclitaxel + gemictabine	Pancreatic adenocarcinoma (PDAC)	3	NCT03377491 (PANOVA-3 trial)
	Centrosomes	PLK1	Onvansertib + paclitaxel	Triple-negative breast cancer (TNBC)	1/2	NCT05383196
			Onvansertib + FOLFIRI + bevacizumab	Metastatic colorectal cancer (CRC)	2	NCT05593328
			Onvansertib + abiraterone	Metastatic castration-resistant prostate cancer (PC)	2	NCT03414034
		PLK4	RP-1664	Advanced solid tumors	1/2	NCT06232408 (LIONS trial)
			CFI-400945	Acute myeloid leukemia (AML)	1	NCT03187288 [76]
				Triple-negative breast cancer (TNBC)	2	NCT01954316
	CIN	CDK4/6	Ribociclib + RT	Diffuse intrinsic pontine glioma (DIPG)	1/2	NCT02607124 [99]
			Palbociclib + RT+ cetuximab	Advanced local head and neck squamous-cell cancer (HNSCC)	1	NCT03024489 [100]
			Palbociclib + RT + hormonotherapy	Breast cancer bone metastasis	2	NCT03691493 (ASPIRE trial)
DNA damage response proteins	Replication stress	WEE1	Adavosertib + RT + temozolomide	Glioblastoma	1	NCT01849146
			Adavosertib + RT + gemcitabine	Advanced pancreatic cancer	1	NCT02037230 [101]
		ATR	Berzosertib + RT + cisplatin	Head and neck squamous-cell cancer (HNSCC)	1	NCT02567422
			Berzosertib + RT	HNSCC brain metastasis, neuroendocrine tumors, chemotherapy-resistant breast cancer	1	NCT02589522 NCT04052555
			Ceralasertib + RT	Solid tumors	1	NCT02223923 (PATRIOT trial)
		ATM	AZD1390 + RT	Glioblastoma (GBM)	1	NCT03423628
Immune-related proteins	Interferon type 1	PARP7	RBN-2397	Small-cell lung cancer (SCLC), HNSCC, hormone receptor-positive breast cancer	1	NCT05127590 [238]

[a]A list of the ongoing clinical trials to target highly aneuploid cancers, detailing the targeted mechanism, process and molecular target, the name of the drug, the cancer type on which it is tested, the clinical phase, and the reference for the trial.
[b]Abbreviations: FOLFIRI, combination therapy of folic acid, 5-fluorouracil and irinotecan; RT, radiotherapy; TTF, tumor-treating fields.

chromosome mis-segregation [64], and CIN and aneuploidy were both shown to increase the sensitivity to this drug in breast cancer [65,66].

Finally, Tumor-Treating Fields (TTF), a US Food and Drug Administration (FDA)-approved therapy that interferes with mitosis by perturbing microtubule polarity [67], was shown to induce aneuploidy

and to act synergistically with SAC inhibitors [68]. Notably, TTF is currently FDA-approved for treating glioblastoma (GBM) and mesothelioma patients [69,70], and is undergoing multiple clinical trials against various solid tumors (Table 1).

Targeting centrosomes: Interfering with the centrosomes, for example by overexpressing PLK1 or PLK4, results in elevated CIN, increased aneuploidy, and promotion of tumorigenesis [71,72]. Several *in vitro* and *in vivo* studies show a specific vulnerability of highly aneuploid breast cancer cells to PLK1 inhibition [73,74]. Combination therapies using PLK1 inhibitors (NCT05383196, NCT05593328, NCT03414034) [75] and PLK4 inhibitors (NCT03187288[76], NCT06232408) are currently in trial for advanced aneuploid tumors (Table 1). Further, AURKA and TPX2, a major AURKA cofactor that is necessary for its localization at the centrosome during the G2/M phase [77], were both suggested to be more essential in highly aneuploid *BRCA2*-deficient/p53-deficient cancer cells [78]. Similarly, CDK2 inhibition, which disrupts centrosome clustering and induces multipolar spindles [79], was suggested to selectively inhibit aneuploid lung cancer cells [80] while not disrupting mitosis in diploid primary alveolar epithelial cells [81].

Targeting cell cycle regulators in combination with radiotherapy: Radiotherapy is known to cause structural aberrations and aneuploidies through CIN [82,83]. Therefore, combining cell cycle inhibitors with radiotherapy prevents the attenuation of the cell cycle in response to DNA damage, leading to CIN and cell death [84]. CIN was recently shown to increase the sensitivity of cancer cells to radiation [85] by leading to aneuploidy levels that cannot be tolerated. Consistent with this notion, the combination of an MPS1 inhibitor with radiotherapy improved the survival of mice with breast cancer [86]. Synergistic effects were also demonstrated when radiotherapy was combined with other cell cycle inhibitors such as CDK4/6 inhibitors [87–90], ATR/CHK1 inhibitors [91–94], ATM inhibitors [95], or WEE1 inhibitors [96–98]. Therefore, therapies combining radiotherapy with cell cycle inhibitors to induce intolerable CIN levels are now in clinical trials, mainly for solid tumors (Table 1) (NCT03691493, NCT01849146) [99–102].

Mechanisms to target specific aneuploidies

Specific aneuploidies that alter the cell cycle may also lead to changes in the cellular sensitivity to cell cycle inhibitors and anti-mitotic drugs.

Targeting chr17p loss and chr17q gain: The loss of the short arm of chromosome 17 (chr17p loss) is one of the most common aneuploidies in breast cancer, and in cancer in general, whereas the long arm of that chromosome is often gained (chr17q gain) [14,103]. Chr17p loss is a common way to biallelically inactivate the key cell cycle regulator *TP53*, which can render breast cancer cells vulnerable to perturbation of p53-regulated mechanisms [104]. Interestingly, chr17q gain has been associated with centrosomal ubiquitin ligase TRIM37 overexpression, and shown to render breast cancer cells more sensitive to PLK4 inhibition by triggering centrosome catastrophes [105,106].

Targeting chr10q gain: RPE1 cells represent a common non-transformed cellular model for aneuploidy research due to their relative chromosomal stability [21,24]. RPE1 cells harbor a clonal gain of chr10q. Whereas under standard culture conditions chr10q gain is not selected against [24,49], the loss of this aneuploidy was associated with paclitaxel resistance, suggesting that this aneuploidy may confer sensitivity to paclitaxel [22].

Targeting DNA replication and repair

Acquisition of DNA damage as a result of chromosome mis-segregation is an evolutionarily conserved consequence of aneuploidy, which was demonstrated in aneuploid yeast [107–109],

Drosophila melanogaster [110–112], mouse [113–115], and human cells [41–44,116]. DNA damage and aneuploidy act in a vicious cycle, occurring throughout the cell cycle (Figure 2B). DNA damage can promote aneuploidy by inducing chromosome translocations [42], whole-chromosome mis-segregation [82,117], or **replication stress** [118]. Further, DNA damage can lead to aneuploidy through mutations in key regulators of DNA damage repair, such as p53 [119,120], BRCA1/2 [121,122], or other **oncogenes** and **tumor suppressor genes (TSGs)** [10], which enable cell cycle progression of DNA-damaged cells, resulting in high levels of aneuploidy [123,124]. Further, prolonged activation of the DNA damage response during mitosis increases the rate of chromosome mis-segregation [82,125]. Aneuploidy can also cause DNA damage and elevate the DNA damage response (DDR). Chromosome segregation errors can cause DNA damage and structural chromosome aberrations [42], as well as chromothripsis [126,127]. Aneuploidy itself can lead to DNA replication stress and further genomic instability [41,43], and cells experiencing replication stress can complete replication through mitotic DNA synthesis (MiDAS), which is associated with elevated DNA damage [44].

The increased levels of DNA damage and the resultant DDR induction in aneuploid cancer cells likely underlie their increased resistance to DNA-damage-inducing chemotherapies [20–24,128–130]. Hence, to exploit the DNA damage in aneuploid cancer cells, it is their adaptation to DNA damage that should be targeted, rather than the direct induction of additional DNA damage.

Mechanisms to target highly aneuploid cells

Aneuploid cells cope with higher levels of DNA damage by activating various DDR mechanisms [24,44,131]. Therefore, inhibition of these DDR processes could be a viable strategy to target aneuploid cancer cells.

Targeting DDR pathways: Adaptation to aneuploidy often involves chronic activation of the DDR [21,24], starting from the first cell cycle following aberrant mitosis [44,111]. Therefore, aneuploid cells present relatively high basal levels of DDR, both in cell lines [24,44] and in tumors [132], which may make them particularly vulnerable to perturbation of DNA damage repair. For example, high levels of aneuploidy are associated with increased response to poly(ADP-ribose) polymerase inhibition (PARPi) in BRCA-mutant aneuploid pancreatic cancer cells [130].

Targeting MAPK signaling: MAPK signaling, via the RAF–MEK–ERK cascade or the p38 cascade, plays an important role in complex cellular programs, including proliferation, differentiation, transformation, and apoptosis [133,134]. Interestingly, increased activity of both p38 and RAF–MEK–ERK pathways are implicated in resistance to DNA damage induction in aneuploid cells [23,24,135]. Importantly, targeting either p38 [136] or the RAF–MEK–ERK pathway [24] can attenuate the DDR in aneuploid cells, thereby re-sensitizing them to DNA damage-inducing drugs.

Targeting DNA replication stress: Acquisition of DNA damage during the S phase is due mainly to replication stress, triggered by the abnormal DNA content of aneuploid cells [44,111,137]. Replication stress also fuels CIN and aneuploidy [138–142]. To cope with the replication stress, aneuploid cells increase their DNA replication and repair activity [143]. Enhancing replication stress increases the rate of chromosome mis-segregation and CIN [125,139,142], which might be particularly detrimental for aneuploid cells as they experience replication stress and CIN to begin with. In p53-deficient cells, SAC inhibition suppresses the mitotic arrest induced by replication stress, reducing mitotic death but increasing multipolar cell divisions [144]. Elevated DNA content due to trisomies is also associated with increased pressure on the nucleotide synthesis pathways that are essential

for proper DNA replication, potentially rendering aneuploid cells more sensitive to perturbations of the nucleotide pool [145].

Mechanisms to target specific aneuploidies

Specific aneuploidies can alter chromosomes that encode key genes involved in DNA replication and repair, which in turn can make those aneuploid cells more sensitive to perturbation of the affected mechanism(s).

Targeting copy-number-altered DDR pathways: The dysregulated DDR in aneuploid cells may make them more sensitive to perturbation of specific DDR pathways that are directly affected by aneuploidy. For example, in Ewing sarcoma, trisomy 8 mitigates *EWS-FLI1*-induced replication stress through the gain of a copy of *RAD21* [146], potentially rendering the cells more sensitive to the perturbation of double-strand break (DSB) repair. In neuroblastoma, chr11q loss is a common event, which results in the copy number loss of DDR-associated genes located on this chromosome-arm (*MRE11A*, *H2AFX*, and *CHEK1*), potentially affecting homologous recombination repair and inducing sensitivity to PARP inhibitors [147].

Targeting copy-number-induced replication stress: Several common aneuploidies directly affect DNA replication-associated genes. For example, the frequent gain of chr8q results in elevated levels of *MYC* [148], which drives excessive replication origin firing, overwhelming the replication machinery and resulting in replication stress [149–151]; the common gain of chr17q leads to overexpression of TOP2A, which might disrupt DNA replication dynamics, contributing to replication stress [152]; and the common loss of chr13q perturbs the function of *RB1*, causing premature S-phase entry and increased replication stress [153]. Therefore, specific recurrent aneuploidies may exacerbate replication stress, potentially making the tumors that harbor them sensitive to replication stress targeting.

Targeting haploinsufficiency and oncogenic addictions

Aneuploidy is driven largely by selection pressures to overexpress oncogenes that reside on gained chromosomes, or to downregulate TSGs that reside on lost chromosomes [10,14,51,52,154–156]. Co-occurring aneuploidies are similarly selected for due to their combined effect on gene expression patterns [15,157]. The transcriptional changes induced by aneuploidy-mediated copy number alterations (CNAs) of affected genes may therefore create cellular vulnerabilities of therapeutic relevance (Figure 3A).

Targeting haploinsufficient genes: Recurrent chromosome losses can be driven by the loss of specific TSGs [51,52,154]. However, large CNAs often include copies of genes that reside near the driver TSGs, whose loss is not beneficial for the cancer cells. If such genes are essential, there might even be a negative selection against their loss [50,52]. Importantly, losing a single copy of a gene may render the cells more sensitive to the perturbation of the remaining allele, a phenomenon known as **haploinsufficiency** [158]. Therefore, multiple recent studies aimed to identify such 'collateral damage' within recurrent chromosome losses [10]. For example, *WRN* was identified as a haploinsufficient TSG on chr8p, which is recurrently lost across human cancers [50]. In prostate cancer, chr17p loss, where POLR2A resides, renders the cells sensitive to the RNA polymerase inhibitor, α-amanitin [159].

Chromosome losses can also create cellular vulnerabilities by affecting multiple genes that function in the same pathway, or by broadly affecting cellular physiology or metabolism beyond the genes that are directly altered. For example, the common loss of chr16q reduces the expression of multiple metallothionein genes, thereby impacting their response to the metal chelator drug,

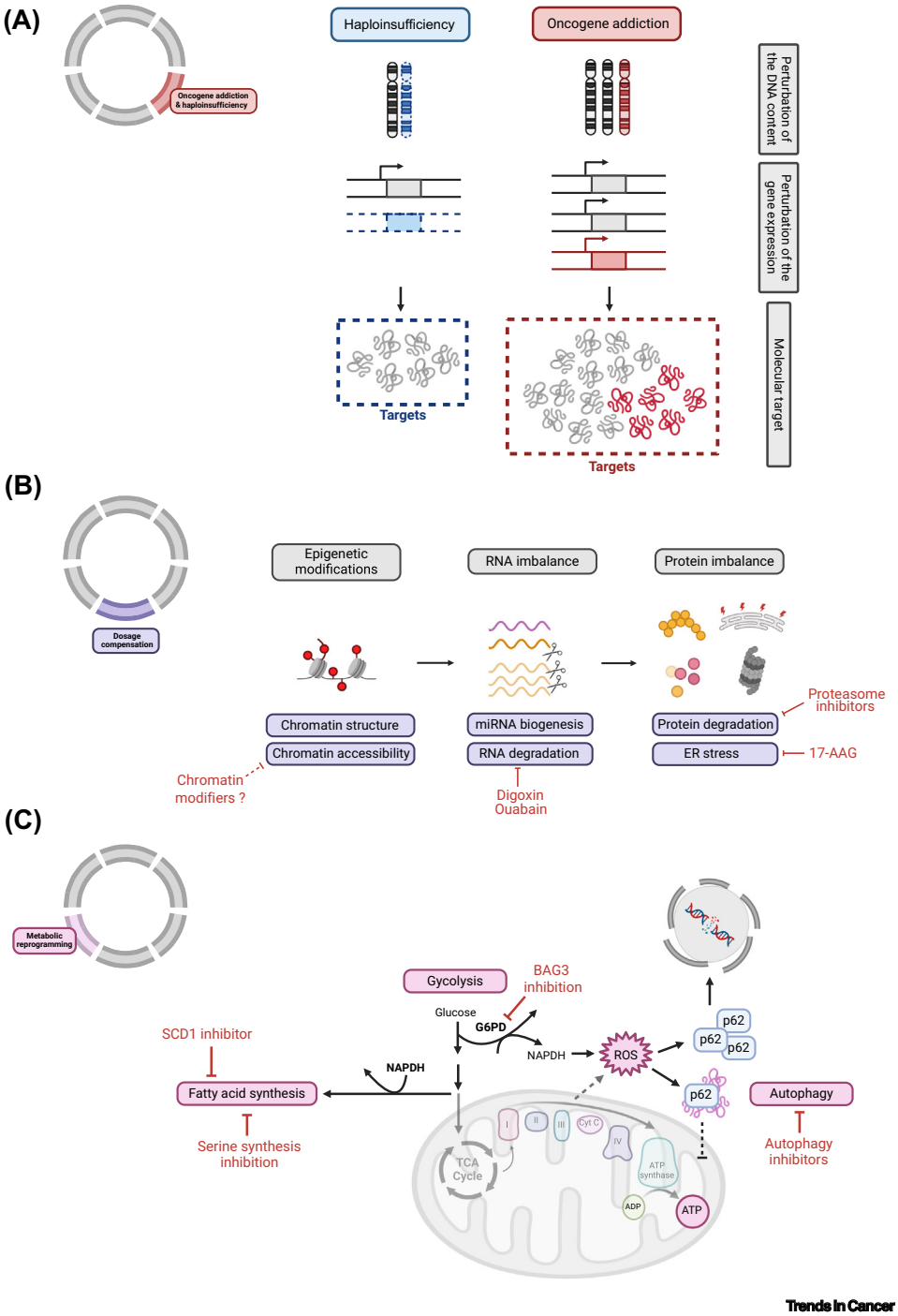

Figure 3. Targeting the gene expression consequences of aneuploidy. (A) Monosomies and trisomies could alter the gene expression of haploinsufficient genes and oncogenes, respectively. Cells may consequently become dependent on the continuous overexpression of the oncogenes ('oncogene addiction') or on the residual expression of the haploinsufficient genes. (B) Aneuploidy can render cells dependent on mechanisms of gene dosage compensation, such as epigenetic modifications that alter chromatin structure and accessibility (left), RNA degradation to cope with transcriptional burden

(Figure legend continued at the bottom of the next page.)

disulfiram [160]. Another example is chr17p loss, a common mechanism for p53 inactivation, which increases fatty acid synthesis (FAS) and renders breast cancer cells sensitive to FAS inhibition [104]. Interestingly, increased lipid metabolism was also observed in breast cancer cells with chr8p loss [161], suggesting that they might be more sensitive to FAS inhibitors as well.

Chromosome losses can also increase the dependency of cancer cells on paralog genes that reside on other chromosomes. For example, in liver cancer cells, chr8p loss induces dependency on the gene *NUDT17*, a paralog of the chr8p-residing gene *NUDT18* [162], and also on *MFRN2*, a paralog of the chr8p-residing gene *MFRN1* [163]. More broadly, essential genes are more likely to be lost if their paralog is gained [52], suggesting paralog-targeting as a potentially effective strategy in tumors with chromosome losses.

Targeting 'oncogene-like' addictions to aneuploidy: Chromosome gains are usually associated with the activation of oncogenes [52,154], thereby increasing the sensitivity of the cells to inhibition of these oncogenes. For example, chr1q is one of the most commonly gained chromosomes across all cancer types [14]. MDM4 has been shown to be a *bone fide* driver of chr1q gain in cancer cells [164], where its upregulation inhibits the p53 pathway. Importantly, cells with chr1q gain become dependent on the increased activity of MDM4, and a single copy number loss of this gene is sufficient to inhibit cell growth across multiple cell types [164]. In line with the notion that multiple genes drive the recurrence of common aneuploidies, chr1q gain was also shown to drive the transformation of mammary cells through the activation of Notch signaling [156], suggesting that cells with chr1q gain may be more sensitive to inhibitors of this pathway as well. Another cancer-type-specific oncogene addiction was recently shown in colorectal cancer, which is uniquely characterized by a recurrent gain of chr13q [14]. Chr13q gain was shown to be associated with WNT pathway activation [165] and with *KLF5* overexpression [52]; importantly, cells with chr13q gain were preferentially sensitive to *KLF5* knockdown, suggesting it as a vulnerability of this aneuploid state.

Recurrent aneuploidies can also create 'collateral vulnerabilities' due to the overexpression of non-driver genes that reside on the altered chromosome, a phenomenon known as **triplosensitivity** (the mirror image of haploinsufficiency). A prominent example is once again that of chr1q, which harbors the pyrimidine salvage kinase *UCK2*. This gene is overexpressed in human cancers with chr1q gain, and it creates a collateral sensitivity to UCK2-dependent nucleotide analogs [164].

Finally, whole-chromosome gains can also arise following drug exposure [22,23,166], creating further aneuploidy-induced vulnerabilities in the drug-resistant cells. For example, drug treatment can select for the gain of mouse chr6, which contains the oncogene cMet. Pharmacological inhibition of cMet in mouse tumors that harbor this trisomy reduces proliferation and increases cell death [166].

Targeting gene dosage compensation

Gene **dosage compensation** is a crucial mechanism of adaptation to aneuploidy. Dosage compensation was first studied in the context of chromosome gains in yeast, where it was shown to

(middle), and protein degradation to cope with proteotoxic stress (right). Aneuploid cells are therefore more sensitive to the perturbation of these mechanisms (e.g., cardiac glycosides digoxin and ouabain) that inhibit the nonsense-mediated decay (NMD) pathway, reducing mRNA degradation, proteasome inhibitors that attenuate protein imbalance, or 17-AAG that targets ER stress-related protein folding. (C) Aneuploid cells exhibit targetable metabolic changes. Several metabolic vulnerabilities of aneuploid cells have been proposed, including serine and sphingolipid synthesis, glucose uptake and glycolysis, ROS detoxification, autophagy, and p62-dependent micronucleus membrane collapse. Abbreviations: BAG3, Bcl-2 associated athanogene 3; Cyt C, cytochrome C; G6PD, glucose 6-phosphate dehydrogenase; ROS, reactive oxygen species; SCD1, stearoyl-CoA 9-desaturase; TCA, tricarboxylic acid. Figure created with BioRender.

be limited in yeast strains grown in the laboratory [107,167,168], but to alleviate protein imbalance in wild yeast strains [169,170]. The extent of dosage compensation seems to gradually increase with the complexity of the organism: aneuploid yeast strains mainly modify their gene expression at the protein level [170–172]; aneuploid drosophila cells modify their gene expression mostly, but not solely, at the mRNA level [173,174]; and aneuploid human cancer cells adjust their gene expression both at the mRNA and at the protein levels [175–180].

Importantly, aneuploidy affects not only the expression of genes that are located on the aneuploid chromosomes (*cis* effects) but also that of genes that reside elsewhere in the genome (*trans* effects). Even a single aneuploidy can lead to global gene expression alterations that go well beyond the aneuploid chromosome [181]. For example, aneuploidy affects the function of large protein complexes that include proteins encoded from the aneuploid chromosomes [178–180]. Another source of global gene expression changes are the aneuploidy-induced cellular stresses, such as mitotic, replicative, proteotoxic, and metabolic stresses [12,24]. Recent studies also suggested that altered epigenetic regulation affects the gene expression of aneuploid human cells [51,182–186], indicating epigenetic regulation as a key mechanism for gene dosage compensation (Figure 3B).

Interestingly, gene dosage compensation is not limited to gained chromosomes, and the expression of genes that reside on lost chromosomes is also compensated [177,187]. However, the cellular pathways that are altered by dosage compensation differ between chromosome gains and losses [24,177,187], suggesting that different cellular vulnerabilities are associated with each type of aneuploidy.

Mechanisms to target highly aneuploid cells

Targeting RNA metabolism: Human cells carrying trisomies tend to downregulate their transcript abundance [177,180], while ones carrying monosomies tend to upregulate the expression of the affected genes [187]. Multiple compensation mechanisms have been proposed: in trisomic human cells there is a faster RNA turnover associated with increased RNA degradation activity [180], through multiple pathways of RNA degradation. The miRNA-mediated degradation machinery was implicated in degrading the extra mRNA transcripts in both chromosome-specific and non-chromosome-specific manners [180,188]. Moreover, higher levels of DNA damage induce high levels of aberrant transcripts, which in turn triggers the nonsense-mediated decay pathway [180]. Consequently, cardiac glycosides, a group of drugs that indirectly inhibit the nonsense-mediated decay (NMD) pathway [189], are preferentially effective against aneuploid cells [180]. Finally, monosomies often impact the abundance of rRNAs and ribosomal proteins, resulting in defects in protein synthesis [187].

Targeting the unfolded protein response (UPR) and protein metabolism: Multiple mechanisms have been proposed to mitigate the **proteotoxic stress** of aneuploid cells, and they seem to be largely conserved throughout evolution. Both yeast and mammalian aneuploid cells need to compensate for the dysregulated protein expression of proteins that function in large complexes [178–180], as the extra subunits tend to form aggregates [190]. It was recently proposed that UBR4 mediates the degradation of these remaining subunits [191], identifying it as a potential vulnerability of aneuploid cells. However, protein dosage compensation is incomplete, so that aneuploid cells suffer from endoplasmic reticulum (ER) stress due to the accumulation of unfolded proteins [29,180,187,190,192]. Therefore, it has been suggested that aneuploid cells become more sensitive to the inhibition of protein-folding-related and ER-stress-related regulators, such as the chaperone protein HSP90 [192,193]. Finally, aneuploid cells upregulate their proteasome activity to alleviate the protein burden by degrading extra proteins. This adaptation is a conserved mechanism as it is found in aneuploid yeast [194], drosophila [195], and human

cells [180,192]. Therefore, proteasome inhibitors might be effective in targeting highly aneuploid tumors across a variety of cancer types [180].

Targeting epigenetic silencing mechanisms: Aneuploidy-induced dosage compensation often involves mechanisms of epigenetic regulation. For example, a single additional chromosome was sufficient to modify the global histone marking patterns, resulting in genome-wide gene expression dysregulation, in a mouse model of Down's syndrome [182]. Further, **whole-genome doubling (WGD)**, a common precursor of high aneuploidy, can lead to altered chromatin organization, resulting in oncogenic transcriptional changes [185]. Further, chromosome mis-segregation itself causes nuclear deformation and heterochromatin alterations that leads to a p53 activation response but can also promote cellular transformation [196]. The aberrations in the 3D chromatin conformation are not restricted to the primary nucleus, as they were also found in micronuclei following chromosome mis-segregation, and could be propagated into the next mitosis [184,186]. Epigenetic alterations can also compensate for CNAs by silencing gained genes whose overexpression is toxic for the cell [197]. For example, a recent study demonstrated that tumor-toxic effects of gene dosage changes of 'passenger' gained genes can be compensated by their selective methylation [198]. Therefore, interfering with aneuploidy-associated nuclear organization, or with general mechanisms of epigenetic regulation and chromatin organization, may be particularly detrimental for aneuploid cells.

Mechanisms to target specific aneuploidies

Dosage compensation of genes that reside within recurrently gained regions can create unique cellular vulnerabilities. We recently characterized amplification-related gain of sensitivity (ARGOS) genes in human cancer [197]. These are 'bystander' genes that are commonly gained because they reside within common copy-number gains; however, the overexpression of such genes is toxic, and they consistently escape overexpression when gained. For example, this is the case of RBM14, which resides within the frequently gained chr11q. The reactivation of such genes in tumors in which they are genetically gained but epigenetically silenced could therefore be toxic for the cancer cells [197].

Co-occurring genetic events can also compensate for aneuploidy-induced aberrant gene expression, creating further vulnerabilities. A prominent example was recently reported in glioma cells, which often gain a copy of chr7 to compensate for the loss of chr10 [157]. Compensatory genetic alterations can even occur within the aneuploidy itself: for example, deletions of TSGs within large chromosomal gains were recently described in multiple myeloma [199]. These secondary genetic events can in turn create a cellular vulnerability to the perturbation of genes that reside on the co-occurring, compensatory CNAs.

Targeting metabolic consequences of aneuploidy

Various aspects of cellular metabolism can be altered in aneuploid cells, including increased glucose uptake [107], higher levels of reactive oxygen species (ROS) [113], and altered fatty acid metabolism [104,161] (Figure 3C). Such metabolic changes were associated with aneuploidy across multiple species, including yeast [107], drosophila [200], mouse [36], and human [201]. Aneuploid cells were also reported to exhibit hypo-osmotic stress, leading to plasma-membrane stress and impaired endocytosis. This phenomenon, which was observed in yeast and human cancer cells, may disrupt the intracellular nutrient homeostasis [202].

Mechanisms to target highly aneuploid cells

Studies on the metabolic consequences of aneuploidy were mostly conducted in non-human systems that are amenable to whole-animal experiments, as cell metabolism is largely affected

by the environmental conditions (e.g., nutrient availability). Nonetheless, several metabolic liabilities have been described in aneuploid cells, with high potential relevance to cancer.

Targeting sphingolipid synthesis: In aneuploid yeast, increased synthesis of serine and the resulting high levels of sphingolipids are associated with increased cellular fitness [203]. Sphingolipid levels are tightly linked to serine synthesis, and inhibiting either serine or sphingolipid synthesis, as well as increasing ceramide levels, impaired the fitness of aneuploid cells. In both aneuploid yeast and transformed human cells, disrupted nuclear morphology was improved by increased levels of long-chain bases, the structural units of sphingolipids. Further, inhibition of ceramide synthesis improved the fitness of human Down's syndrome cells [204]. Finally, a ceramide analog was shown to inhibit proliferation, increase apoptosis, and increase the cytotoxic effect of paclitaxel in mouse and human aneuploid cells [205].

Targeting energy metabolism and ROS: The link between aneuploidy and energy metabolism is bidirectional. Whereas ATP depletion in non-transformed cells leads to cell cycle arrest, in transformed cells ATP depletion can result in chromosome mis-segregation [206]. Aneuploid human cancer cells produce more ATP, either by upregulating glycolysis or by increasing oxidative phosphorylation (OXPHOS), in comparison to their diploid counterparts [135,145]. Oxidative stress and increased production of ROS have also been observed in aneuploid cells. Recent studies revealed that high levels of ROS can lead to micronuclei membrane collapse, inducing genomic instability, inflammation, cancer progression, and metastasis in a p62- and CHMP7-dependent manner [207,208]. Furthermore, aneuploidy-induced proteotoxic stress was recently shown to lead to the sequestration of mitochondrial precursor proteins into cytosolic p62-bodies, leading to abnormal mitochondrial network and defects in OXPHOS functions [201].

Aneuploid cells are preferentially dependent on several aspects of mitochondrial function. Mitotic NADPH upsurge was observed in aneuploid cancer cells with high levels of ROS, while it was nearly absent from near-diploid cancer cells. Consequently, aneuploid cancer cells were shown to depend on a glucose 6-phosphate dehydrogenase (G6PD)-mediated NADPH increase in mitosis to protect them from ROS-induced chromosome mis-segregation [209]. The mitochondrial RNA methyltransferase enzyme TRMT61B was also proposed as a potential biomarker and therapeutic target in highly aneuploid cancers. TRM61B depletion reduces the expression of several mitochondrially encoded proteins and limits mitochondrial function, specifically in highly aneuploid tumors [210]. Finally, inhibition of the p38 stress response kinase promoted cell survival following aneuploidy induction through the upregulation of hypoxia-inducible factor 1α (HIF1α), which alleviates aneuploidy-induced metabolic collapse [135]. Additional liabilities of aneuploid cells on mitochondrial function, and on energy production, remain to be elucidated.

Targeting autophagy: Aneuploidy is known to induce autophagy [211,212] and reduce lysosomal degradation [143]. As discussed earlier, multiple studies have linked the autophagy receptor SQSTM1/p62 to aneuploidy via distinct, yet complementary, mechanisms [201,207,208]. This is consistent with previous findings linking autophagy and cyclic GMP-AMP synthase– stimulator of interferon genes (cGAS–STING) pathway activation [213,214], as well as with work in drosophila that also showed increased autophagy and impaired mitochondrial activity in response to aneuploidy [195]. Together, these studies suggest that aneuploid cells might be more sensitive to autophagy inhibitors under certain circumstances [193].

Mechanisms to target specific aneuploidies

Recurrent aneuploidies can affect cellular metabolism in a chromosome-dependent manner. For example, chr5q loss leads to increased glycolysis in squamous-cell carcinoma [215], and chr18

gain following BRG1 loss in colon cancer leads to a hypoxia-like response with elevated levels of glycolysis and upregulation of glucose transporters [216].

Fatty acid metabolism is also altered by specific aneuploidies. Loss of *TP53* in breast cancer cells following chr17p loss results in enhanced FAS, which is required for breast cancer brain metastasis. Consequently, *TP53*-deficient cells exhibit greater sensitivity to FAS inhibitors in comparison to *TP53*-proficient cells, suggesting FAS as a unique liability of tumors with chr17p loss [104].

Interestingly, a single aneuploidy can sometimes induce multiple metabolic vulnerabilities. Chr8p loss, which is associated with an aggressive phenotype and increased metastasis in human hepatocellular cancer cell lines [162], increases the sensitivity to the inhibition of the ROS-associated enzyme NUDT17, due to the copy-number loss of its chr8p-residing paralog NUDT18 [162]. The same aneuploidy is also associated with altered fatty acid and ceramide metabolism in breast cancer. The altered metabolism triggers increased autophagy, rendering cells with chr8p loss more dependent on autophagy – and more sensitive to autophagy inhibitors – likely due to the decreased levels of acid ceramidase ASAH1 [161].

Targeting aneuploidy-induced immune evasion

Highly aneuploid tumors can evade immune surveillance, leading to strong negative correlations between aneuploidy and immune activation [14,26]. Indeed, highly aneuploid tumors have fewer infiltrating leukocytes in their microenvironment [14,26], and are more resistant to **immune checkpoint inhibitors (ICIs)** [28,217,218]. Specific recurrent aneuploidies can further alter their TME and reduce the response to immunotherapy [28,30,219,220].

Aneuploid cells are actually highly immunogenic in non-transformed cells and during the early stages of tumorigenesis [25,27,221]. Emerging aneuploid cells can be eliminated by natural killer (NK) cells via nuclear factor κB (NF-κB) activation [27], or by CIN-induced triggering of the cGAS–STING pathway [222,223]. However, aneuploid cells become less immunogenic as tumors develop. First, specific immune-suppressing karyotypes are selected for during tumorigenesis, resulting in clonal expansion of aneuploid cells that are able to evade the immune system [224,225]. Second, aneuploid cancer cells develop mechanisms to evade NK cell detection [26,27]; to reduce major histocompatibility complex (MHC) class I presentation, thus diminishing their reactivity to cytotoxic T lymphocytes [26]; and to polarize macrophages to the pro-tumorigenic state [26,29]. Third, CIN and inflammation are sometimes reduced during adaptation to aneuploidy in human cells *in vitro* [226]. Alternatively, the chronic activation of innate immune pathways by ongoing CIN can paradoxically lead to immune suppression and promote metastasis [227,228]. Therefore, understanding the underlying mechanisms of the aneuploidy-driven switch in tumor immunogenicity could uncover viable approaches to target aneuploid cells (Figure 4A).

Mechanisms to target highly aneuploid cells

Targeting the cGAS–STING pathway: Chromosome mis-segregation during mitosis can lead to DNA breaks, resulting in lagging chromosomes or anaphase bridges [127,192], which lead to formation of micronuclei. The rupture of micronuclei, or of chromatin bridges, may trigger the cGAS–STING pathway [229], although recent studies suggested that micronuclei might not be a common source for cGAS activation [230–233]. In any case, once activated, cGAS synthesizes cyclic GMP-AMP (cGAMP), which in turn activates STING [222,223]. Several studies have shown that cGAS–STING pathway activation promotes the survival of chromosomally unstable aneuploid cancer cells due to chronic inflammation [234–236]. Suppressing cGAS or STING reduced CIN-driven metastasis in melanoma, breast, and colorectal cancers [227]. Interestingly, the

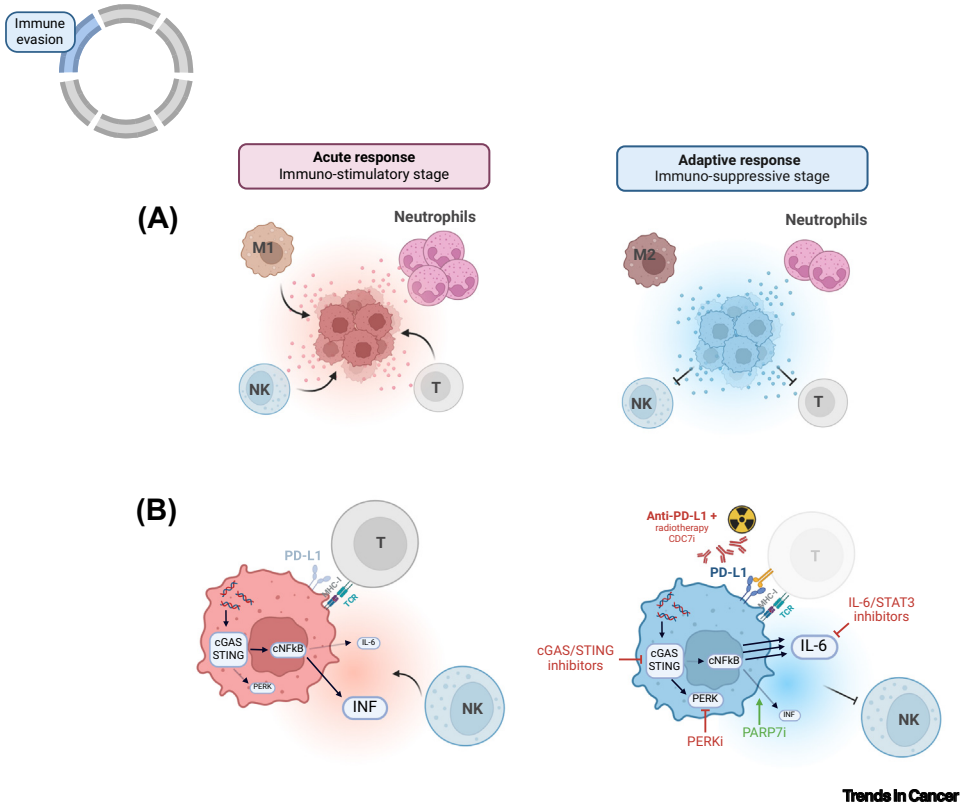

Figure 4. Targeting aneuploidy-induced immune evasion. (A) Aneuploidy emergence triggers an acute immune-stimulatory response, whereas long-term adaptation to aneuploidy involves immune suppression. During the 'acute' immune response (left), aneuploid cells trigger a strong inflammatory phase and recruit the infiltration of leukocytes, including M1 macrophages, natural killer (NK) and T cells, to effectively eliminate the emerging aneuploid cells. During adaptation to aneuploidy (right), aneuploid cells develop immune evasion strategies, reducing the leukocyte infiltration, inducing a shift from M1 to M2 macrophages, and suppressing their immune clearance. (B) During the acute response stage (left), cyclic GMP-AMP synthase–stimulator of interferon genes (cGAS–STING) activation triggers nuclear factor κB (NF-κB) signaling and interferon (IFN) secretion, promoting immune surveillance. During the adaptive response stage (right), the cGAS–STING pathway activation is decoupled from the inflammatory response and triggers endoplasmic reticulum (ER) stress that can jeopardize neo-antigen presentation. Moreover, the cells activate the programmed death protein 1 (PD1)/PD ligand 1 (PD-L1) checkpoint and increase secretion of interleukin 6 (IL-6), to effectively suppress the immune surveillance. Several strategies have been proposed to reactivate the immune response in the adapted aneuploid cells, including the targeting of cGAS–STING, IL3/STAT3, protein kinase R-like ER kinase (PERK), poly(ADP-ribose) polymerase 7 (PARP7), and CDC7 in combination with PDL1. Abbreviations: MHC1, major histocompatibility complex class I; TCR, T-cell receptor. Figure created with BioRender.

cGAS–STING pathway can also be perturbed by an inhibitor of PARP7, a negative regulator of nucleic acid sensing in tumor cells [237], which can restore the interferon (IFN) response and reactivate antitumor immune activity [237,238] (Table 1). These and other approaches to target CIN in cancer have recently been comprehensively reviewed [7]. However, the degree to which aneuploidy – rather than merely CIN – also plays a role in inducing these drug sensitivities is not completely understood. For example, aneuploid cells activate the UPR, as described earlier, and UPR activation was linked to local immune dysregulation via its effect on macrophages and T cells in the TME [29]. Tumors with high levels of STING1 also show increased UPR activity, and blocking the ER stress sensor PERK increases T cell and NK cell infiltration [227]. Together, these findings suggest that CIN-induced cGAS–STING dependency and aneuploidy-induced UPR dependency may have combined immunosuppressive effects (Figure 4B).

Targeting non-canonical NF-κB and IFN signaling: The NF-κB pathway plays a role in NK cell-mediated immune clearance [25,27]. However, NF-κB signaling can also suppress the immune IFN response, leading to immune suppression [228]. It was recently shown that aneuploid cells are dependent on non-canonical NF-κB signaling: chronic exposure of aneuploid cells to aneuploidy-related stressors leads to the secretion of cytokines, such as interleukin-6 (IL-6), to create a tumor-permissive microenvironment that suppresses effective immune clearance [26,29,235]. Blocking the IL6–STAT3 axis successfully inhibited the growth of chromosomally unstable aneuploid tumors [235] (Figure 4B).

Targeting the senescence-associated secretory phenotype (SASP) phenotype: Chromosomally unstable aneuploid cells tend to acquire the SASP, secreting pro-tumorigenic cytokines [239]. Possible interventions to target SASP cells are extensively reviewed elsewhere [240], and might be relevant also for targeting highly aneuploid tumors. Aneuploidy-induced SASP can also be induced by CDC7 inhibitors, resulting in an increased sensitivity of aneuploid cells to a combination of CDC7 inhibitors and ICIs [241].

Mechanisms to target specific aneuploidies

Targeting chr9p loss: Chr9p loss is specifically linked to immune dysregulation in cancer. Tumors with chr9p loss exhibit a 'cold' tumor-immune environment with a lower number of tumor-infiltrating lymphocytes (TILs), decreased immune cell activation, and decreased programmed death protein ligand 1 (PD-L1) expression and ICI response [28,218]. This phenomenon was further studied in HPV^- head and neck squamous cancer, where the effect of chr9p loss on the response to anti-PD1 therapy was molecularly dissected [219,220]. In renal-cell carcinoma, where chr9p loss is common, this aneuploidy leads to inhibition of IFN signaling; enhancing the IFN response could promote senescence and limit tumor progression of these aneuploid cells [242].

Targeting other aneuploidies: Very little is known about the effect of other common aneuploidies on the tumor–immune interactions. Gain of chr1q, which is very common in multiple cancer types, was reported to be associated with low PD-L1 expression and reduced response to ICIs in non–small-cell lung cancer, but whether this is causative or strictly correlative is currently unknown [218]. More research is needed to demonstrate a causal link between specific aneuploidies and reduced immune response, which might enable aneuploidy-informed immunotherapy.

Concluding remarks

These are exciting times for aneuploidy research, with multiple aneuploidy-induced vulnerabilities identified in recent years. The advance of chromosome engineering technologies, and the ample sequencing data now available for studying aneuploidy in cancer, all but guarantee that additional therapeutically relevant liabilities will be associated with aneuploidy in the coming years. However, translating these biological insights into cancer therapies remains a formidable challenge (see Outstanding questions). Targeting a specific aneuploidy may result in rapid emergence of resistance due to ongoing CIN and the selection for the loss of the targeted event. Furthermore, the integration of aneuploidy detection and analysis into clinical models and clinical trials, as done in the seminal TRACERx studies [16], is still not a common practice, and might be necessary for successful outcomes. Several promising drugs, such as ATR and AURK inhibitors, exhibited limited success in clinical trials [243–246], highlighting the complexity of targeting basic mechanisms of genomic instability. Nonetheless, recent studies suggest that stratifying patients based on their CIN and aneuploidy status could greatly improve the response to well-established drugs such as paclitaxel [66] and bortezomib [180], to more recent drugs like PARP inhibitors [130], or to novel drugs like KIF18A inhibitors [21,61,62]. Therefore, future clinical trials will determine whether aneuploidy can be used as a *bone fide* biomarker for existing

Outstanding questions

How can we effectively translate aneuploidy-induced vulnerabilities into targeted cancer therapies?

Can specific chromosome gains or losses serve as predictive biomarkers for drug response in precision oncology?

How does aneuploidy influence the tumor microenvironment and immune evasion, and what are the best strategies to counteract it?

Can gene dosage compensation mechanisms that are deployed by aneuploid cells be leveraged to selectively target aneuploid cells?

How do different aneuploidies impact metabolic adaptation, and which metabolic pathways present actionable vulnerabilities?

To what extent can synthetic lethal interactions with aneuploidy be used to develop effective combination therapies?

What are the clinical implications of aneuploidy for immunotherapy, and how should aneuploidy status be integrated into patient stratification for immune checkpoint inhibitors?

therapies, and whether new therapies that target the cellular consequences of this hallmark of cancer can make it from bench to bedside.

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