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Review

Targeting Thyroid Hormone Receptor Interacting Protein (TRIP13) for Cancer Therapy: A Promising Approach

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Abstract: TRIP13 is a member of the large AAA+ ATPase protein superfamily that plays a crucial role in the precise segregation of chromosomes during mitosis. The abnormal function of TRIP13 has diverse functions, including mitotic processes, DNA repair pathways, and spindle assembly checkpoints, which may contribute to chromosomal instability (CIN). Emerging evidence suggests that the overexpression of TRIP13, observed in many cancers, plays a significant role in drug resistance, autophagy, and immune invasion. Recently, significant advances have been made in identifying TRIP13-associated signaling pathways that have been implicated in cancer progression. Several small molecules that specifically inhibit TRIP13 function and reduce cancer cell growth have been developed. Combination treatments, including TRIP13 inhibitors and other anticancer drugs, have shown promising results. While these findings are promising, TRIP13 inhibitors are awaiting clinical trials. This review discusses recent progress in understanding the oncogenic function of TRIP13 and its possible therapeutic targets, which could be exploited as an attractive option for cancer management.

Keywords: TRIP13; cancer; DNA repair; mitosis; chromosomal instability; drug resistance

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1. Introduction

Millions of new cases of cancer are diagnosed each year, making it one of the greatest global health challenges [1]. The identification of genes, such as tumor suppressor genes and oncogenes that affect the development of tumors, has been a subject of research for many years [2]. In recent years, chromosomal instability (CIN) has garnered considerable attention owing to its critical role in the diagnosis and development of cancer [3]. An estimated 60–80% of human cancers show chromosomal abnormalities that could be indicative of CIN [4]. Errors in chromosome segregation during anaphase are the most common cause of CIN, although radiation, mitotic toxins, and impairments in DNA repair can also cause CIN [5]. According to previous research, the spindle assembly checkpoint (SAC) is a widely used defense mechanism that guarantees the accuracy of chromosomal separation during cell division [6,7]. Many SAC proteins have been reported to be the source of CIN in tumors and are extensively expressed in various malignancies [8,9]. The literature has documented that various thyroid hormone receptor-interacting proteins (TRIPs, including TRIP4, TRIP11, TRIP12, and TRIP13) perform diverse cellular functions in an organism. TRIP4 is a component of the ribonucleoprotein complex called the transcriptional coregulator ASC-1, which plays a role in RNA processing and transcriptional coactivation [10]. There is limited information on the tumor-promoting role of TRIP4. Only a few studies

have demonstrated that TRIP4 promotes tumor growth in cervical [11] and melanoma [12] cancers. The *TRIP11* gene encodes a protein known as GMAP-210, which is crucial for the function of the Golgi apparatus [13]. TRIP12 belongs to the E3 ubiquitin ligase family homologous to the E6-AP carboxyl terminus (HECT). It regulates various essential biological processes, including chromatin remodeling, cell proliferation, cell division, and DNA damage repair [14–16]. Recent evidence indicates that TRIP12 expression is associated with the development of breast cancer [17] and pancreatic cancer [18]. Among all, TRIP13 is the most extensively studied gene in relation to cancer. TRIP13 (also known as PCH2) was first discovered in *Saccharomyces cerevisiae* using a yeast two-hybrid screening method. This study also showed that a lack of TRIP13 induces cell cycle arrest [19]. Recently, several studies have documented that TRIP13 is one of the most frequently overexpressed genes related to CIN in human tumors and is associated with poor prognosis in various tumor types [20–23]. TRIP13 is a member of the large AAA+ protein superfamily of ring-shaped P-loop NTPases. This superfamily is involved in a number of cellular processes, such as chromosome synapsis, checkpoint signaling, and DNA break repair and recombination [24]. According to recent data, TRIP13 is involved with more than meiosis and mitosis, including the regulation of tumorigenesis [25]. Numerous studies have shown that elevated levels of TRIP13 are linked to various types of cancer, such as bladder [26,27], colon [28,29], pancreatic [30], breast [31], prostate [32], head and neck [25], chronic lymphocytic leukemia (CLL) [33], liver [34], ovarian [35], brain [36], renal cell carcinoma [37], Wilms tumor [38] and thyroid tumor [39].

Based on these accumulating findings, it is evident that TRIP13 plays a role in the development of cancer and drug resistance. In this review article, we provide an overview of some recently identified underlying mechanisms that explain how TRIP13 increases resistance to anticancer drugs. A novel role for the overexpression of TRIP13 in inducing autophagy and promoting immune suppression is also discussed in this review article. Recently, several molecules and drugs have been developed to target TRIP13 for cancer treatment; however, none have entered clinical trials yet. Therefore, more studies are needed to elucidate the underlying molecular mechanism of TRIP13's involvement in cancer progression and to develop strategies to utilize TRIP13-targeting drugs for cancer management. The aim of this review is to summarize the role of TRIP13 in cancer progression and its therapeutic potential, focusing on studies on its inhibitors in human cancers. The information presented in this review article is based on a literature search of articles published during the past ten years. This search utilized various electronic databases, including Scopus, Google Scholar, and PubMed. The keywords used in the search were TRIP13, chromosomal instability, cancer, DNA repair, autophagy, TRIP13 inhibitor, spindle assembly checkpoint, drug resistance, and immunity.

2. Biological Function of TRIP13

The human TRIP13 gene is located on chromosome 5 and encodes a protein of 432 amino acids. Pch2 is a mouse ortholog of TRIP13, which is located on chromosome 13 of mouse [40]. This protein contains an ATP-binding site within the AAA+ ATPase region and a small N-terminal domain that may participate in substrate recognition. In addition to its complex structure, TRIP13 performs a wide range of cellular functions, such as activating the SAC, regulating cell cycle progression, and repairing DNA within cells. In addition, recent findings have revealed that the overexpression of TRIP13 is involved in regulating immunity, autophagy, and cancer development (Figure 1).

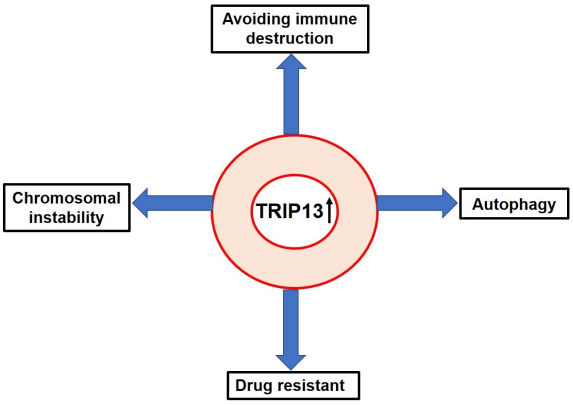

Figure 1. The schematic diagram shows the overexpression of TRIP13 involved in regulating various functions.

2.1. TRIP13 and Spindle Assembly Checkpoint

During mitosis, a spindle checkpoint ensures proper chromosome segregation through a cell cycle surveillance system. TRIP13 is known to play a crucial role in maintaining genomic stability by delaying chromosomal separation (anaphase) until every chromosome is securely attached to the spindle [41]. The anaphase-promoting complex or cyclosome connected to its mitotic activator Cdc20 (APC/CCdc20) is inhibited by checkpoint proteins that are activated by unattached kinetochores [42]. The mitotic checkpoint complex (MCC), which is composed of various proteins, including Mad2, Cdc20, and BubR1–Bub3, is a significant effector of the spindle checkpoint [43]. This complex prevents the recognition and ubiquitination of securin and cyclin B1 by APC/CCdc20 binding to its substrate binding site. As a consequence of the stabilization of securin and cyclin B1, sister-chromatid separation and mitotic exit are delayed [43]. Once the checkpoint has been reached, TRIP13 could use the energy from ATP hydrolysis to change the conformation of a stable closed-MAD2 to a less stable open-MAD2, allowing the APC/C to initiate anaphase. Recently, a novel mechanism involving ATP hydrolysis was discovered. This mechanism involves the disassembly of MCC through the combined action of TRIP13 and p31comet (Figure 2) [44,45].

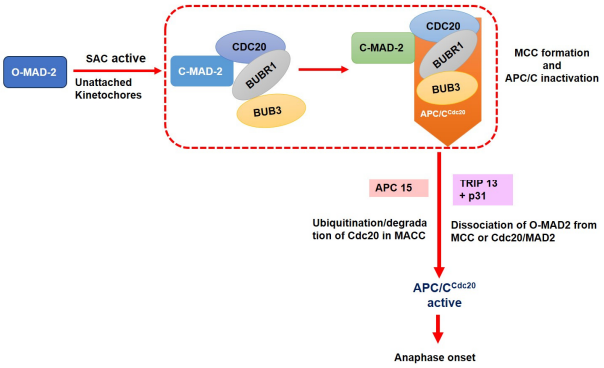

Figure 2. Model for the role of TRIP13 in SAC inactivation. Unattached kinetochores catalyze the formation of mitotic checkpoint complex (MCC) through the conversion of O-MAD2 to C-MAD2 with CDC20. The disassembly of free MCC and the removal/disassembly of MCC bound to APC/CCdc20 are catalyzed by TRIP13 and p31comet during checkpoint silencing. In MCC, Cdc20 can be ubiquitinated by APC15-mediated conformational changes in the APC/C, which can reactivate APC/CCdc20. Created with Microsoft PowerPoint.

The two mechanisms work differently: TRIP13 and p31comet dominate the disassembly free of MCC, while APC15 facilitates the ubiquitination of Cdc20 in MCC and the subsequent reactivation of APC/CCdc20 [41,46]. A study also demonstrated that cells

lacking TRIP13 cannot trigger the SAC despite having C-MAD2, thus suggesting that TRIP13 is essential for the silencing of the SAC [47]. TRIP13 regulates meiosis by removing HORMAD proteins from synapsed chromosomes and facilitating the conversion of MAD2 protein [48].

2.2. TRIP13 and DNA Repair

Our genomes have numerous risks, including DNA damage and abnormalities during cell division. These genomic alterations can eventually lead to oncogenic transformations if the genome is unprotected [49]. Double-strand breaks (DSBs) are a highly hazardous form of DNA damage, which can be repaired through two pathways: non-homologous end-joining (NHEJ) and homology-directed repair (HDR) [49]. Recent studies have shown that the upregulation of TRIP13 promotes both these repair pathways. This may lead to chromosomal instability, increased survival, metastasis, and increased drug resistance in cancer cells [50]. MAD2L2 (Rev7), which contains a HORMA domain, is a component of shieldin that protects DSBs while promoting DSB end-joining. It is also involved in DNA translation synthesis as a member of the Pol-ζ complex. A high-throughput yeast two-hybrid screen revealed an interaction between TRIP13 and MAD2L2 (Rev7) [51]. Recent studies have documented that the interaction between Rev7 and Rev3 proteins, essential for the activation of Pol-ζ, is actively regulated in cells [52]. TRIP13 alters Rev7 conformation, blocking its ability to interact with Rev3 to generate active Pol ζ, which is necessary for translesion synthesis, as well as with the shieldin complex, which triggers NHEJ [51]. Thus, TRIP13 overexpression promotes error-free HDR over mutagenic NHEJ through pathway choice. This is essential for the development of interhomolog-biased HR and DSB repair via the DNA-PKcs and Lupus-Ku autoantigen proteins p70 and p80 (KU70, KU80). Therefore, DNA damage is caused by the absence of TRIP13 [52]. This accumulating evidence suggests that TRIP13 may be involved in the NHEJ pathway, thereby contributing to CIN and tumor development.

2.3. TRIP13 and Autophagy

Autophagy is a catabolic process that has been conserved throughout evolution. It involves the lysosomal degradation pathway to regulate the turnover and removal of proteins and cellular organelles, including the endoplasmic reticulum, mitochondria, and peroxisomes [53]. This process involves cytosolic vesicles containing double membranes, called autophagosomes, which are essential for the lysosomal targeting of organelles during autophagy. In general, autophagy is considered a survival mechanism; however, its dysregulation has been associated with non-apoptotic deaths.

Some recent studies have shown that autophagy plays an essential role in maintaining genomic stability [54]. As a result of starvation or stress, abnormal mitochondria can produce high levels of reactive oxygen species (ROS), causing DNA damage. Autophagy aids in the elimination of all biomolecules that are irreversibly oxidized within cells and plays a major role in preserving redox equilibrium, which in turn preserves genomic stability [54]. A previous study showed that higher ROS production in CIN cells damages DNA and causes cell death. The autophagic activity was also more sensitive in CIN cells. In CIN cells, the knockdown of the autophagy-related proteins Atg1 and Atg18 led to a marked increase in oxidative stress and DNA damage levels [55]. Recent research has demonstrated that TRIP13 has the potential to influence autophagy in specific scenarios. However, the specific relationship between TRIP13 and autophagy remains unclear. A study reported that TRIP13 overexpression in HCC827 cells increased the number of autophagosome-like structures, indicating stimulated autophagy (Figure 3). Gefitinib enhanced TRIP13's autophagy-promoting ability, while 3-MA, an autophagy inhibitor,

decreased this ability [56]. A study indicated that TRIP13 functions as a conserved generic HORMA remodeler; however, its association with autophagy remains unestablished [57]. In addition, it is unclear whether ATP-dependent remodeling of the HORMA domains would be required to silence autophagosome biogenesis during disassembly of the ATG9-13-101 complex [58]. Further studies are required to understand the relationship between TRIP13 and autophagy to use TRIP13 as a biomarker and therapeutic target for autophagy.

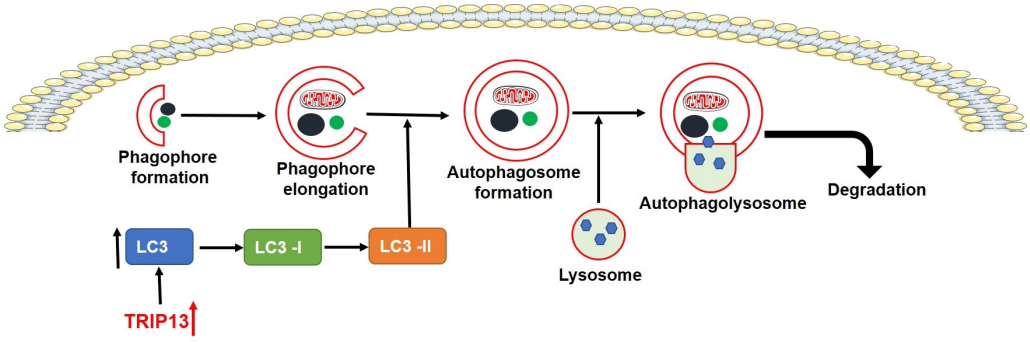

Figure 3. An illustration showing TRIP13 expression induces autophagy in cancer cells. This figure was created using Servier Medical Art, CC BY 4.0 (http://smart.servier.com).

2.4. TRIP13 and Immunity

There is strong evidence supporting the connection between CIN, poor prognosis, and reduced immune cell activity against tumors [59]. In CIN, there is a high frequency of chromosome missegregation, leading to micronuclei and aneuploidy—an abnormal chromosome ratio [60]. Several clinical studies have demonstrated a correlation between tumor aneuploidy and immune evasion, local immunity suppression, and reduced immunotherapeutic responses [59,60]. As a result, the activation or suppression of the immune system caused by tumor aneuploidy function is found to be dependent on the carcinogenic stage and the complex microenvironment [61]. Furthermore, TRIP13-expressing tumors had increased aneuploidy and tended to have a lower CD8+/Treg ratio, resulting in a worse survival outcome [62]. This study also found that TRIP13-expressing tumors negatively influence immune cells, such as T cells, B cells, dendritic cells, granulocytes, NK cells, and monocytes. A recent study indicated that elevated TRIP13 expression was associated with enhanced infiltration of Th2 cells and decreased infiltration of neutrophils, Th17 cells, and dendritic cells [63]. In addition, inhibiting TRIP13 increases cytotoxic mediator production, which stimulates the immune system to fight cancer [63]. The results suggest that an overexpression of TRIP13 suppresses immunity, and targeting TRIP13 has the potential to activate immunity in tumors.

3. TRIP13 Role in Cancer

Several types of cancers have been reported to overexpress TRIP13, including head and neck cancer [25], bladder cancer [26,27], pancreatic [30], breast cancer [31], prostate cancer [32], chronic lymphocytic leukemia [33], ovarian cancer [35], brain tumors [36], renal cell carcinoma [37], Wilms tumor [38], and thyroid cancer [39]. Several studies and online tools, such as the analysis of TNMplot (https://www.tnmplot.com, accessed on 6 November 2024), have demonstrated that TRIP13 expression is increased in various human tumors compared to normal tissues. It was observed that TRIP13 was highly expressed in lung cancer, uterus cancer, bladder cancer, ovary cancer, and esophageal cancer (Figure 4A) [64]. In the last five years, researchers have made significant progress in identifying the molecular mechanism/signaling involved in tumor development associated with TRIP13 (Figure 4B).

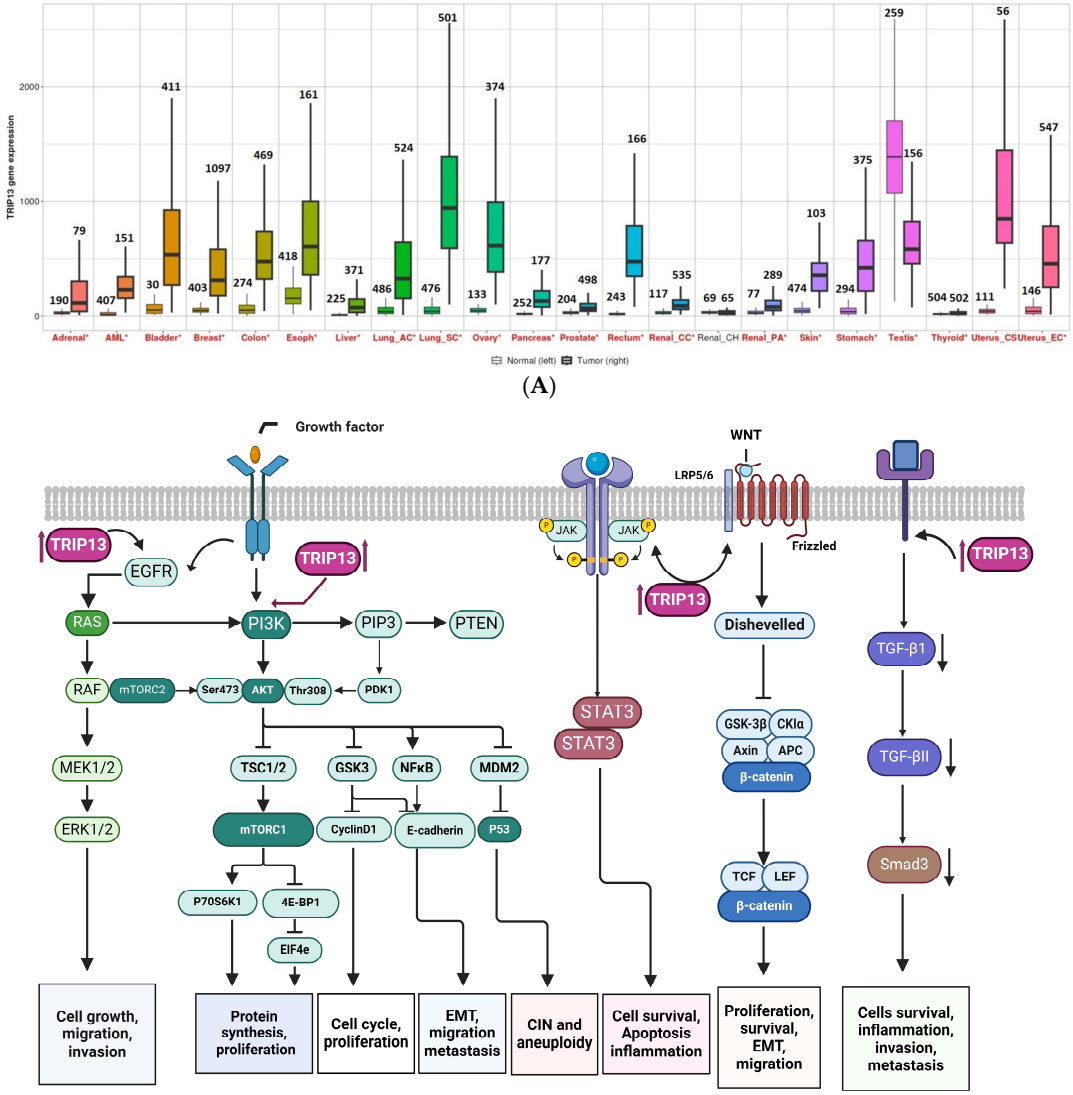

Figure 4. Expression of TRIP13 in human cancers. (**A**) TGCA data analysis of TRIP13 expression in various cancer types using TNMpolt (www.tnmplot.com). The number indicated on the graph shows the sample number, the left graph shows the normal, and the right graph shows the tumor in each individual tumor. Red color * denotes significantly different ($p < 0.05$) expression in cancer compared to corresponding normal tissue expression, analyzed using the Mann–Whitney test. (**B**) Possible interactions between TRIP13 and other signaling pathways involved in cancer development. Created with BioRender.com.

Based on the immunohistochemical assay, TRIP13 was found to be abnormally expressed in gastric cancer, which correlated with the tumor grade [65]. This study provided mechanistic evidence that TRIP13 interacts with the HDAC1-TRIP13/DDX21 axis, stabilizing its expression by inhibiting ubiquitination degradation and accelerating the spread of gastric cancer [65]. Another study revealed that TRIP13 functions as an oncogene, facilitating the growth and spread of pancreatic ductal adenocarcinoma (PDAC). In addition, TRIP13 overexpression in PDAC samples activates FGFR4, a receptor tyrosine kinase. Furthermore, PDAC samples with high TRIP13 expression showed elevated STAT3 phosphorylation at Tyr705 and high levels of active β-catenin [21]. In CRC, a high level of TRIP13 expression is associated with a lower survival rate in patients at all stages [66]. A critical signaling pathway involved in the growth and metastasis of CRC involves EGFR and AKT tyrosine kinases and WNT/b-catenin signaling [66]. TRIP13 stimulates the signal-

ing pathways involved in CRC growth and metastasis by interacting with FGFR4 tyrosine kinase [28,29]. Furthermore, p53 is the most frequently mutated protein across many cancers, with a strong link to carcinogenesis. The activity of p53 can also be abrogated by other proteins, such as MDM, which is also frequently overexpressed in several cancers and functions as an oncogene. MDM2 can bind to the transcriptional activation domain of p53 or degrade it, leading to its loss of function. Unfortunately, targeting the p53 pathway directly has been very challenging. Some studies have explored the possible connection between TRIP13 and p53. Using gene set expression analysis, TRIP13 was identified as an upstream regulator of the p53 gene [67]. In thyroid cancer cells, the sh-RNA-mediated knockdown of TRIP13 resulted in a significantly elevated ratio of p-p53 to p53 [39]. Similarly, in B cell lymphoma, *TRIP13* knockdown led to increased apoptosis with an increase in MDM4 protein levels [68]. Thus, targeting TRIP13 has an indirect effect on p53 activation; the effect on MDM2 is not well understood yet. These data indicate that TRIP13 targeting may be beneficial in p53 wild-type tumors; in another study, TRIP13 inhibition was shown to inhibit tumor metastasis to be independent of p53 mutation [29]. Thus, TRIP13 can serve as a promising target for both p53 wild-type as well as mutant tumors.

Additionally, TRIP13 overexpression activated the AKT/mTORC1/cMyc pathway to trigger lung adenocarcinoma [69]. A study analyzing 124 esophageal cancer patients found that TRIP13 overexpression was only associated with a poor prognosis in early-stage disease [70]. Gene expression profiling and RNA-sequencing data from the Cancer Genome Atlas (TCGA) revealed that TRIP13 expression was elevated in bladder cancer (BC) tissues and that TRIP13 overexpression was substantially linked to poor prognosis in BC patients. In addition, TRIP13 overexpression triggers the cell cycle phase, resulting in increased cell viability, proliferation, and colony formation in BC cell lines [26,71]. High TRIP13 expression is associated with clinical progression and is an independent prognostic indicator for prostate cancer. It modulates YWHAZ and EMT-associated genes to promote prostate cancer cell proliferation, migration, and invasion [32]. According to a study, TRIP13 was found to be significantly elevated in multiple myeloma (MM) cells and is recognized as a CIN gene in the etiology of MM [72]. Overexpression of TRIP13 has been observed to interfere with the DNA SAC and facilitate the proteasome-mediated degradation of MAD2 through the AKT-signaling pathway [72]. In breast cancer, TRIP13 activated PI3K-AKT-mTOR signaling, enabling the cells to proliferate and migrate more effectively [22]. Another study showed similar findings in hepatocellular carcinoma (HCC) and found that TRIP13 promotes the PI3K/AKT/mTOR signaling pathways and accelerates the growth of HCC cells [73]. The link between TRIP13 and Wnt signaling has been studied in multiple cancers [74–76]. TRIP13 was found to enhance the activation of the Wnt/β-catenin signaling pathway via regulation of ACTN4, thus promoting cervical cancer [74]. In breast cancer cells, it was shown that KIF18B promotes proliferation, migration, and invasion by targeting TRIP13 and activating the Wnt/β-catenin signaling pathway, also linking these two pathways [76]. In lung cancer cells, overexpression of TRIP13 resulted in the upregulation of active β-catenin and other proteins of the Wnt pathways, such as LRP6 and transcription factors TCF4 and LEF1. Furthermore, TRIP13 overexpression also caused the upregulation of N-cadherin, Snail, and vimentin, and the downregulation of E-cadherin. As expected, these effects were reversed after knocking down the expression of TRIP13. Most importantly, co-immunoprecipitation and immunofluorescence imaging experiments revealed that TRIP13 directly interacts with LRP6, which is the receptor and upstream activator of the Wnt signaling pathway [75]. These studies collectively demonstrate the role of TRIP13 in regulating the Wnt pathway, thus making it an important target in Wnt pathway-dependent cancers.

4. TRIP13 Contributes to Drug Resistance

Drug resistance is a major cause of cancer treatment failures. There is evidence that tumors overexpressing TRIP13 exhibit lower sensitivity to anticancer drugs (bortezomib and cisplatin) [25]. It has also been demonstrated that TRIP13 plays a role in nedaplatin resistance in esophageal squamous cell carcinoma [77]. Squamous cell carcinoma of the head and neck (SCCHN) with high TRIP13 levels is aggressive, resistant to treatment, and retains DNA damage even after treatment [25]. A more thorough investigation was recently conducted, revealing a unique function of TRIP13-PKCδ/PRS3 in persistently triggering NF-κB in patients with MM who develop resistance to proteasome inhibitor therapy [78]. Furthermore, EGFR interacts with TRIP13, implicating EGFR-mediated phosphorylation of TRIP13 at Tyr56 as a mechanism of radiation resistance in HNSCC. It is also shown that tumors expressing TRIP13 respond to radiation only when cetuximab is present [79]. The overexpression of TRIP13 in NSCLC promotes gefitinib resistance by regulating autophagy and triggering EGFR signaling [56]. A research study also demonstrated that TRIP13 functions as an oncogene in gastric cancer and that the knockdown of TRIP13 inhibits stemness and cisplatin resistance by regulating the FBXW7/ENO1 signaling pathway [80]. A previous study described TRIP13 as an error-prone, non-homologous end-joining protein that induces chemoresistance in head and neck cancers [25]. Research shows that the TRIP13/Mad2 axis damages the checkpoint surveillance system and causes anticancer drug resistance by activating the PI3K Akt-signaling pathway [72]. In drug-treated BC cells, TRIP13 overexpression mitigated cisplatin- and doxorubicin-induced DNA damage and enhanced DNA repair, as suggested by the reduced H2AX and increased RAD50 expression [26]. TRIP13 upregulation correlates with poor survival and accelerates tumor growth in B-cell lymphoma. As a result of binding to USP7, TRIP13 induces intracellular deubiquitination, which leads to the accumulation of diverse proteins. Through USP7, TRIP13 regulates NEK2, p53, MDM2, and PTEN, which are implicated in oncogenesis and resistance to bortezomib [81]. Collectively, these studies indicate an association between TRIP13 overexpression and anticancer drug resistance, further supporting the idea of targeting TRIP13 or using it as adjuvant therapy to enhance anticancer treatments.

5. Recent Advancements in Targeting TRIP13 for Cancer Therapies

As discussed above, overexpression of TRIP13 is linked to cancer development and drug resistance, thus making it a potential target for cancer therapy. Few small-molecule inhibitors of TRIP13, such as DCZ0415, TI17, DCZ5417, and DCZ5418, have been developed to block the function of the TRIP13 protein and are currently being studied in various cancer types (Figure 5).

Among all, DCZ0415 is one of the most widely studied small-molecule inhibitors in different types of cancer. Biological assays and molecular docking studies demonstrated that DCZ0415 can interact directly with the ATP-binding pocket of TRIP13. DCZ0415 treatment also induced DNA damage and apoptosis in myeloma cells. Additionally, this study reported that DCZ0415 increased the CD3+, CD4+, and CD8+ immune cells in immunocompetent myeloma models and inhibited nuclear factor kappa B (NF-kB) activity, suggesting that inhibition of TRIP13 could have immunotherapeutic potential [82]. Another study reported that DCZ0415 inhibited EMT and reduced NF-KB and Wnt/β-catenin signaling pathway activation in colorectal cancer [28]. This study also showed that DCZ0415 induced G2/M phase arrest and promoted apoptosis by inhibiting the FGFR4/STAT3/NF-KB axis in a colorectal cancer cell line. In addition, DCZ0415 administration increased the levels of cytotoxic mediators, which enhanced the antitumor immune response in xenografted NSG mice [28]. DCZ0415 showed an inhibitor effect on cell proliferation, migration, invasion, tumor growth, and metastasis in PDAC by targeting the TRIP13/FGFR4/STAT3 axis

and downregulating the Wnt/β-catenin and EMT signaling pathways [30]. Furthermore, DCZ0415 (25 mg/kg) was injected into immunocompetent syngeneic KPC mice, which showed enhanced granzyme B/perforin levels, suppressed PD/PD-L1, and promoted T cell infiltration, leading to tumor eradication [30]. DCZ0415 inhibits the progression of hepatocellular carcinoma by targeting TRIP13 and impairing non-homologous end-joining repair [83]. Recently, our results also showed that DCZ0415 significantly suppressed bladder cancer cell proliferation and induced apoptosis [71]. Overall, these findings suggested that targeting TRIP13 with DCZ0415 could be a potential therapeutic option against many cancers.

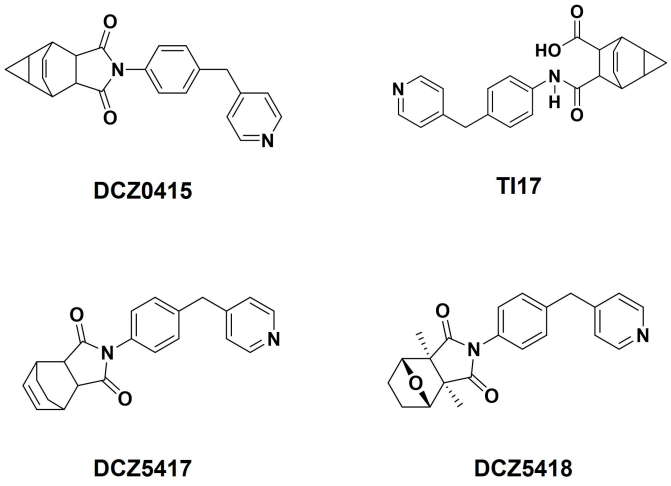

Figure 5. Chemical structures of small-molecule TRIP13 inhibitors reported in the literature.

Another TRIP13 inhibitor, TI17, inhibits the proliferation of MM cells and induces cell cycle arrest and apoptosis in multiple myeloma. A study using mouse xenografts showed that TI17 inhibits tumor growth without causing apparent side effects in mice. Additionally, TI17 reduces TRIP13 activity during DNA double-strand break repair and enhances DNA damage responses in multiple myeloma [84].

DCZ5417 is a Norcantharidin derivative that has been found to be less toxic, safer, and more effective than NCTD against primary MM and MM cell lines. Multiple tests, including surface plasmon resonance, cellular thermal shift assays, and pull-down assays, demonstrated that DCZ5417 binds to TRIP13 and inhibits its ATPase function. This study also revealed that DCZ5417 inhibited cell proliferation by targeting TRIP13, disrupting the TRIP13/YWHAE complex, and blocking the ERK/MAPK signaling axis [85]. Recently, another cantharidin derivative, DCZ5418, was developed, which showed significant anticancer activity against multiple myeloma both in vitro and in vivo. Further xenograft model studies showed that DCZ5418 has a more substantial effect on multiple myeloma than DCZ0415 [86].

In addition to small-molecule inhibitors, a study also reported that cruciferous vegetables containing the isothiocyanate compound sulforaphane decreased TRIP13 expression and induced apoptosis in leukemia cells using the U93 cell line [87]. The curcumin metabolite, tetrahydrocurcumin, selectively targets TRIP13, disrupting the TRIP13/USP7/c-FLIP interaction. This leads to the ubiquitination of c-FLIP, which consequently triggers extrinsic apoptosis in triple-negative breast cancer [88]. A recently published article showed that an FDA-approved drug (Selinexor, KPT-330) also suppresses TRIP 13 expression in Wilms tumor (WT) [89]. Aside from the small-molecule inhibitors and drugs, several studies have reported that slicing the *TRIP13* gene suppresses cancer growth. A study demonstrated that silencing *TRIP13* with a plasmid decreased cell proliferation, migration, and invasion

and induced apoptosis in the hepatocellular carcinoma cell lines HepG2 and MHCC97H cells [90]. Additionally, this study indicated that *TRIP13* knockdown reduced tumor formation in vivo. Knockdown of *TRIP13* using lentiviruses expressing TRIP13 shRNA reduced the invasion and metastasis of colorectal cancer (CRC) cells by decreasing the expression of MMP2 and MMP9 [29]. *TRIP13* knockdown decreased cell migration and invasion and induced apoptosis in the osteosarcoma cell line U2OS [91]. Lentivirus-induced *TRIP13* knockdown in NSCLC cell lines A549 and H1299 causes G2/M phase cell cycle arrest and inhibits the proliferation and invasion of cells [92]. Another study indicated that knocking down *TRIP13* reduced the colony formation of MIA PaCa-2 and S2VP10 pancreatic ductal adenocarcinoma cells. Furthermore, this knockdown also decreased FGFR4 expression and STAT3 phosphorylation at Tyr705 in PDAC cells [30]. These findings suggest that silencing the *TRIP13* gene offers a promising strategy for cancer management.

6. Combination Therapies

Despite the progress made by small-molecule inhibitors in targeted drugs, their effectiveness against tumors is limited, mainly because of the high levels of clonal heterogeneity in cancer, intratumor genetic heterogeneity in tumors, and the complexity of cell signals and resistance to drugs [93]. Preserving genomic integrity requires the efficient repair of DSBs after a DNA damage response. However, in cancer patients, treatment resistance and recurrence increase when anticancer agent-induced DSBs are repaired by either homologous recombination (HR) or NHEJ repair pathways [94]. To address this significant problem, researchers have combined TRIP13 inhibitors with inhibitors of DNA repair proteins and reported positive results. Synergistic effects of the TRIP13 inhibitor DCZ0415 and PARP1 inhibitor olaparib showed encouraging results in suppressing HCC cell proliferation when compared to single treatment groups [81]. In HPV-positive cervical cancer cells, the combination of Aurora kinase inhibition and TRIP13 depletion caused extensive apoptosis, as a loss of Rb protein expression leads to high levels of Mad2 [95]. As a result of overexpressing TRIP13, SCCHN became more susceptible to DNA-PKcs inhibitors, and impairment of TRIP13 ATPase activity diminished DSB repair efficiency [25]. Moreover, DCZ0415 was synergistically active against multiple myeloma when combined with the HDAC inhibitor panobinostat or the multiple myeloma chemotherapy melphalan [82]. A study demonstrated that the combination of DCZ0415 with gemcitabine significantly reduced tumor size and weight in an immunocompetent syngeneic PDAC mouse model [30]. Recent studies found that KPT-330 can act synergistically with doxorubicin, identifying this combination as a potential therapeutic option for treating patients with favorable histology Wilms Tumor (FHWT) [89]. These findings suggest that combining TRIP13 inhibitors with anticancer drugs could be an effective strategy for cancer management.

7. Conclusions and Perspectives

TRIP13 is crucial for numerous biological processes, such as DNA repair and cell division, and it ensures the alignment of chromosomes during mitosis. The overexpression of TRIP13 causes genomic instability due to SAC weakening. This allows cancer cells to multiply faster and become aneuploid, immune envision, and promotes resistance to chemotherapy and other drugs. Recently, there has been a significant increase in the possibility of employing TRIP13 as a therapeutic target owing to several important findings; the most important finding was reported by multiple groups that inhibition of TRIP13 with a small-molecule inhibitor resulted in decreased tumor growth. It is essential to find more small-molecule inhibitors that target TRIP13 specifically, as only a few small-molecule inhibitors are available. A few combination studies have shown a considerable effect on drug-resistant cancer cells. Additionally, some new areas are anticipated to gain significant

development over the next decade, such as a combination of small-molecule targeted TRIP13 with tumor immunotherapy. Although most in vitro tests have shown positive results, further preclinical and clinical studies are necessary to develop a TRIP13 inhibitor for clinical use.

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Abbreviations

The following abbreviations are used in this manuscript:

BC	Bladder Cancer
CIN	Chromosomal Instability
CLL	Chronic Lymphocytic Leukemia
CRC	Colorectal Cancer
DSBs	Double Strand Breaks
FHWT	Favorable Histology Wilms Tumor
HCC	Hepatocellular Carcinoma
HDR	Homology Directed Repair
HECT	E6-AP carboxyl Terminus
MCC	Mitotic Checkpoint Complex
NHEJ	Non-homologous End Joining
PDAC	Pancreatic Ductal Adenocarcinoma
ROS	Reactive Oxygen Species
SAC	Spindle Assembly Checkpoint
TCGA	Cancer Genome Atlas
TRIP4	Thyroid Hormone Receptor Interacting protein 4
AML	Acute Myeloid Leukemia
Renal CC	Renal Cell Carcinoma
Renal CH	Renal Cell Hyperplasia

References

1. Wild, C.P.; Weiderpass, E.; Stewart, B.W. *World Cancer Report: Cancer Research for Cancer Prevention*; International Agency for Research on Cancer: Lyon, France, 2020.
2. Tijhuis, A.E.; Johnson, S.C.; McClelland, S.E. The Emerging Links between Chromosomal Instability (CIN), Metastasis, Inflammation and Tumour Immunity. *Mol. Cytogenet.* **2019**, *12*, 17. [CrossRef] [PubMed]
3. Chandrakasan, S.; Ye, C.J.; Chitlur, M.; Mohamed, A.N.; Rabah, R.; Konski, A.; Heng, H.H.Q.; Savaşan, S. Malignant fibrous histiocytoma two years after autologous stem cell transplant for Hodgkin lymphoma: Evidence for genomic instability. *Pediatr. Blood Cancer* **2011**, *56*, 1143–1145. [CrossRef] [PubMed]
4. Carter, S.L.; Cibulskis, K.; Helman, E.; McKenna, A.; Shen, H.; Zack, T.; Laird, P.W.; Onofrio, R.C.; Winckler, W.; Weir, B.A.; et al. Absolute Quantification of Somatic DNA Alterations in Human Cancer. *Nat. Biotechnol.* **2012**, *30*, 413–421. [CrossRef] [PubMed]
5. Holland, A.J.; Cleveland, D.W. Boveri Revisited: Chromosomal Instability, Aneuploidy and Tumorigenesis. *Nat. Rev. Mol. Cell Biol.* **2009**, *10*, 478–487. [CrossRef]
6. Lara-Gonzalez, P.; Westhorpe, F.G.; Taylor, S.S. The Spindle Assembly Checkpoint. *Curr. Biol.* **2012**, *22*, R966–R980. [CrossRef]
7. Chao, W.C.H.; Kulkarni, K.; Zhang, Z.; Kong, E.H.; Barford, D. Structure of the Mitotic Checkpoint Complex. *Nature* **2012**, *484*, 208–213. [CrossRef]

8. Sotillo, R.; Schvartzman, J.-M.; Socci, N.D.; Benezra, R. Mad2-Induced Chromosome Instability Leads to Lung Tumour Relapse after Oncogene Withdrawal. *Nature* **2010**, *464*, 436–440. [CrossRef] [PubMed]
9. Bargiela-Iparraguirre, J.; Prado-Marchal, L.; Pajuelo-Lozano, N.; Jiménez, B.; Perona, R.; Sánchez-Pérez, I. Mad2 and BubR1 modulates tumourigenesis and paclitaxel response in MKN45 gastric cancer cells. *Cell Cycle* **2014**, *13*, 3590–3601. [CrossRef] [PubMed]
10. Töpf, A.; Pyle, A.; Griffin, H.; Matalonga, L.; Schon, K.; Sickmann, A.; Schara-Schmidt, U.; Hentschel, A.; Chinnery, P.F.; Kölbel, H.; et al. Exome Reanalysis and Proteomic Profiling Identified TRIP4 as a Novel Cause of Cerebellar Hypoplasia and Spinal Muscular Atrophy (PCH1). *Eur. J. Hum. Genet.* **2021**, *29*, 1348–1353. [CrossRef]
11. Che, Y.; Li, Y.; Zheng, F.; Zou, K.; Li, Z.; Chen, M.; Hu, S.; Tian, C.; Yu, W.; Guo, W.; et al. TRIP4 Promotes Tumor Growth and Metastasis and Regulates Radiosensitivity of Cervical Cancer by Activating MAPK, PI3K/AKT, and HTERT Signaling. *Cancer Lett.* **2019**, *452*, 1–13. [CrossRef] [PubMed]
12. Hao, J.; Xu, H.; Luo, M.; Yu, W.; Chen, M.; Liao, Y.; Zhang, C.; Zhao, X.; Jiang, W.; Hou, S.; et al. The Tumor-Promoting Role of TRIP4 in Melanoma Progression and Its Involvement in Response to BRAF-Targeted Therapy. *J. Investig. Dermatol.* **2018**, *138*, 159–170. [CrossRef]
13. Ramos-Morales, F.; Vime, C.; Bornens, M.; Fedriani, C.; Rios, R.M. Two Splice Variants of Golgi-Microtubule-Associated Protein of 210 KDa (GMAP-210) Differ in Their Binding to the Cis-Golgi Network. *Biochem. J.* **2001**, *357*, 699–708. [CrossRef] [PubMed]
14. Brunet, M.; Vargas, C.; Larrieu, D.; Torrisani, J.; Dufresne, M. E3 Ubiquitin Ligase TRIP12: Regulation, Structure, and Physiopathological Functions. *Int. J. Mol. Sci.* **2020**, *21*, 8515. [CrossRef] [PubMed]
15. Gudjonsson, T.; Altmeyer, M.; Savic, V.; Toledo, L.; Dinant, C.; Grøfte, M.; Bartkova, J.; Poulsen, M.; Oka, Y.; Bekker-Jensen, S.; et al. TRIP12 and UBR5 Suppress Spreading of Chromatin Ubiquitylation at Damaged Chromosomes. *Cell* **2012**, *150*, 697–709. [CrossRef]
16. Gatti, M.; Imhof, R.; Huang, Q.; Baudis, M.; Altmeyer, M. The Ubiquitin Ligase TRIP12 Limits PARP1 Trapping and Constrains PARP Inhibitor Efficiency. *Cell Rep.* **2020**, *32*, 107985. [CrossRef]
17. Lee, K.K.; Rajagopalan, D.; Bhatia, S.S.; Tirado-Magallanes, R.; Chng, W.J.; Jha, S. The Oncogenic E3 Ligase TRIP12 Suppresses Epithelial–Mesenchymal Transition (EMT) and Mesenchymal Traits through ZEB1/2. *Cell Death Discov.* **2021**, *7*, 95. [CrossRef]
18. Brunet, M.; Vargas, C.; Fanjul, M.; Varry, D.; Hanoun, N.; Larrieu, D.; Pieruccioni, L.; Labrousse, G.; Lulka, H.; Capilla, F.; et al. The E3 Ubiquitin Ligase TRIP12 Is Required for Pancreatic Acinar Cell Plasticity and Pancreatic Carcinogenesis. *J. Pathol.* **2024**, *263*, 466–481. [CrossRef] [PubMed]
19. Herruzo, E.; Lago-Maciel, A.; Baztán, S.; Santos, B.; Carballo, J.A.; San-Segundo, P.A. Pch2 Orchestrates the Meiotic Recombination Checkpoint from the Cytoplasm. *PLoS Genet.* **2021**, *17*, e1009560. [CrossRef]
20. Zhou, W.; Yang, Y.; Xia, J.; Simchi-Levi, D.; Salama, M.; Xiong, W.; Xu, H.; Shetty, S.; Chen, T.; Shi, L.; et al. NEK2 Induces Drug Resistance Mainly through Activation of Efflux Drug Pumps and Is Associated with Poor Prognosis in Myeloma and Other Cancers. *Cancer Cell* **2013**, *23*, 48–62. [CrossRef] [PubMed]
21. Wang, K.; Sturt-Gillespie, B.; Hittle, J.C.; Macdonald, D.; Chan, G.K.; Yen, T.J.; Liu, S. Thyroid Hormone Receptor Interacting Protein 13 (TRIP13) AAA-ATPase Is a Novel Mitotic Checkpoint-Silencing Protein. *J. Biol. Chem.* **2014**, *289*, 23928–23937. [CrossRef] [PubMed]
22. Chen, C.; Li, P.; Fan, G.; Yang, E.; Jing, S.; Shi, Y.; Gong, Y.; Zhang, L.; Wang, Z. Role of TRIP13 in Human Cancer Development. *Mol. Biol. Rep.* **2024**, *51*, 1088. [CrossRef]
23. Carter, S.L.; Eklund, A.C.; Kohane, I.S.; Harris, L.N.; Szallasi, Z. A Signature of Chromosomal Instability Inferred from Gene Expression Profiles Predicts Clinical Outcome in Multiple Human Cancers. *Nat. Genet.* **2006**, *38*, 1043–1048. [CrossRef] [PubMed]
24. Li, X.C.; Bolcun-Filas, E.; Schimenti, J.C. Genetic Evidence That Synaptonemal Complex Axial Elements Govern Recombination Pathway Choice in Mice. *Genetics* **2011**, *189*, 71–82. [CrossRef] [PubMed]
25. Banerjee, R.; Russo, N.; Liu, M.; Basrur, V.; Bellile, E.; Palanisamy, N.; Scanlon, C.S.; Van Tubergen, E.; Inglehart, R.C.; Metwally, T.; et al. TRIP13 promotes error-prone nonhomologous end joining and induces chemoresistance in head and neck cancer. *Nat. Commun.* **2014**, *5*, 4527. [CrossRef]
26. Lu, S.; Guo, M.; Fan, Z.; Chen, Y.; Shi, X.; Gu, C.; Yang, Y. Elevated TRIP13 drives cell proliferation and drug resistance in bladder cancer. *Am. J. Transl. Res.* **2019**, *11*, 4397–4410.
27. Gao, Y.; Liu, S.; Guo, Q.; Zhang, S.; Zhao, Y.; Wang, H.; Li, T.; Gong, Y.; Wang, Y.; Zhang, T.; et al. Increased Expression of TRIP13 Drives the Tumorigenesis of Bladder Cancer in Association with the EGFR Signaling Pathway. *Int. J. Biol. Sci.* **2019**, *15*, 1488–1499. [CrossRef] [PubMed]
28. Agarwal, S.; Afaq, F.; Bajpai, P.; Kim, H.; Elkholy, A.; Behring, M.; Chandrashekar, D.S.; Diffalha, S.A.; Khushman, M.; Sugandha, S.P.; et al. DCZ0415, a Small-Molecule Inhibitor Targeting TRIP13, Inhibits EMT and Metastasis via Inactivation of the FGFR4/STAT3 Axis and the Wnt/β-Catenin Pathway in Colorectal Cancer. *Mol. Oncol.* **2022**, *16*, 1728–1745. [CrossRef]

29. Agarwal, S.; Behring, M.; Kim, H.; Chandrashekar, D.S.; Chakravarthi, B.V.S.K.; Gupta, N.; Bajpai, P.; Elkholy, A.; Al Diffalha, S.; Datta, P.K.; et al. TRIP13 Promotes Metastasis of Colorectal Cancer regardless of P53 and Microsatellite Instability Status. *Mol. Oncol.* **2020**, *14*, 3007–3029. [CrossRef] [PubMed]
30. Afaq, F.; Agarwal, S.; Bajpai, P.; Diffalha, S.A.; Kim, H.-G.; Peter, S.; Khushman, M.; Chauhan, S.C.; Mukherjee, P.; Varambally, S.; et al. Targeting of Oncogenic AAA-ATPase TRIP13 Reduces Progression of Pancreatic Ductal Adenocarcinoma. *Neoplasia* **2024**, *47*, 100951. [CrossRef] [PubMed]
31. Lan, J.; Huang, J.; Tao, X.; Gao, Y.; Zhang, L.; Huang, W.; Luo, J.; Liu, C.; Deng, Y.; Liu, L.; et al. Evaluation of the TRIP13 Level in Breast Cancer and Insights into Potential Molecular Pathways. *J. Cell. Mol. Med.* **2022**, *26*, 2673–2685. [CrossRef]
32. Dong, L.; Ding, H.; Li, Y.; Xue, D.; Li, Z.; Liu, Y.; Zhang, T.; Zhou, J.; Wang, P. TRIP13 is a predictor for poor prognosis and regulates cell proliferation, migration and invasion in prostate cancer. *Int. J. Biol. Macromol.* **2018**, *121*, 200–206. [CrossRef] [PubMed]
33. Zhou, K.; Zhang, W.; Zhang, Q.; Gui, R.; Zhao, H.; Chai, X.; Li, Y.; Wei, X.; Song, Y. Loss of Thyroid Hormone Receptor Interactor 13 Inhibits Cell Proliferation and Survival in Human Chronic Lymphocytic Leukemia. *Oncotarget* **2017**, *8*, 25469–25481. [CrossRef]
34. Garcia, M.R.; Meissburger, B.; Chan, J.; De Guia, R.M.; Mattijssen, F.; Roessler, S.; Birkenfeld, A.L.; Raschzok, N.; Riols, F.; Tokarz, J.; et al. TRIP13 depletion in liver cancer induces a lipogenic response contributing to PLIN2-Dependent mitotic cell death. *Adv. Sci.* **2022**, *9*, 2104291. [CrossRef] [PubMed]
35. Zhou, X.y.; Xm, S. TRIP13 Promotes Proliferation and Invasion of Epithelial Ovarian Cancer Cells through Notch Signaling Pathway. *Eur. Rev. Med. Pharmacol. Sci.* **2019**, *23*, 522–529. [PubMed]
36. Hu, L.; Shen, D.; Liang, D.; Shi, J.; Song, C.; Jiang, K.; Ren, M.; Du, S.; Cheng, W.; Ma, J.; et al. Thyroid Receptor-Interacting Protein 13 and EGFR Form a Feedforward Loop Promoting Glioblastoma Growth. *Cancer Lett.* **2020**, *493*, 156–166. [CrossRef] [PubMed]
37. Kowalewski, A.; Jaworski, D.; Antosik, P.; Smolińska, M.; Ligmanowska, J.; Grzanka, D.; Szylberg, Ł. TRIP13 predicts poor prognosis in clear cell renal cell carcinoma. *Am. J. Cancer Res.* **2020**, *10*, 2909. [PubMed]
38. Yost, S.; De Wolf, B.; Hanks, S.; Zachariou, A.; Marcozzi, C.; Clarke, M.; de Voer, R.M.; Etemad, B.; Uijttewaal, E.; Ramsay, E.; et al. Biallelic TRIP13 Mutations Predispose to Wilms Tumor and Chromosome Missegregation. *Nat. Genet.* **2017**, *49*, 1148–1151. [CrossRef]
39. Yu, L.; Xiao, Y.; Zhou, X.; Wang, J.; Chen, S.; Peng, T.; Zhu, X. TRIP13 Interference Inhibits the Proliferation and Metastasis of Thyroid Cancer Cells through Regulating TTC5/P53 Pathway and Epithelial-Mesenchymal Transition Related Genes Expression. *Biomed. Pharmacother.* **2019**, *120*, 109508. [CrossRef]
40. Ye, Q.; Kim, D.H.; Dereli, I.; Rosenberg, S.; Hagemann, G.; Herzog, F.; Tóth, A.; Cleveland, D.W.; Corbett, K.D. The AAA + ATP Ase TRIP 13 Remodels HORMA Domains through N-Terminal Engagement and Unfolding. *EMBO J.* **2017**, *36*, 2419–2434. [CrossRef]
41. Ma, H.T.; Poon, R.Y.C. TRIP13 Functions in the Establishment of the Spindle Assembly Checkpoint by Replenishing O-MAD2. *Cell Rep.* **2018**, *22*, 1439–1450. [CrossRef]
42. Musacchio, A. The molecular biology of spindle assembly checkpoint signaling dynamics. *Curr. Biol.* **2015**, *25*, R1002–R1018. [CrossRef]
43. Sudakin, V.; Chan, G.K.T.; Yen, T.J. Checkpoint Inhibition of the APC/c in HeLa Cells Is Mediated by a Complex of BUBR1, BUB3, CDC20, and MAD2. *J. Cell Biol.* **2001**, *154*, 925–936. [CrossRef]
44. Miniowitz-Shemtov, S.; Teichner, A.; Sitry-Shevah, D.; Hershko, A. ATP is required for the release of the anaphase-promoting complex/cyclosome from inhibition by the mitotic checkpoint. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 5351–5356. [CrossRef] [PubMed]
45. Eytan, E.; Sitry-Shevah, D.; Teichner, A.; Hershko, A. Roles of Different Pools of the Mitotic Checkpoint Complex and the Mechanisms of Their Disassembly. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 10568–10573. [CrossRef]
46. Kim, D.H.; Han, J.S.; Ly, P.; Ye, Q.; McMahon, M.A.; Myung, K.; Corbett, K.D.; Cleveland, D.W. TRIP13 and APC15 drive mitotic exit by turnover of interphase- and unattached kinetochore-produced MCC. *Nat. Commun.* **2018**, *9*, 4354. [CrossRef]
47. Snider, J.; Thibault, G.; Houry, W.A. The AAA+ superfamily of functionally diverse proteins. *Genome Biol.* **2008**, *9*, 216. [CrossRef] [PubMed]
48. Ye, Q.; Rosenberg, S.C.; Moeller, A.; Speir, J.A.; Su, T.Y.; Corbett, K.D. TRIP13 Is a Protein-Remodeling AAA+ ATPase That Catalyzes MAD2 Conformation Switching. *Elife* **2015**, *4*, e07367. [CrossRef]
49. Tubbs, A.; Nussenzweig, A. Endogenous DNA damage as a source of genomic instability in cancer. *Cell* **2017**, *168*, 644–656. [CrossRef]
50. Ceccaldi, R.; Rondinelli, B.; D'Andrea, A.D. Repair pathway choices and consequences at the Double-Strand break. *Trends Cell Biol.* **2015**, *26*, 52–64. [CrossRef] [PubMed]
51. Clairmont, C.S.; Sarangi, P.; Ponnienselvan, K.; Galli, L.D.; Csete, I.; Moreau, L.; Adelmant, G.; Chowdhury, D.; Marto, J.A.; D'Andrea, A.D. TRIP13 regulates DNA repair pathway choice through REV7 conformational change. *Nat. Cell Biol.* **2020**, *22*, 87–96. [CrossRef] [PubMed]

52. Joshi, N.; Brown, M.S.; Bishop, D.K.; Börner, G.V. Gradual Implementation of the Meiotic Recombination Program via Checkpoint Pathways Controlled by Global DSB Levels. *Mol. Cell* **2015**, *57*, 797–811. [CrossRef]
53. Mizushima, N. The pleiotropic role of autophagy: From protein metabolism to bactericide. *Cell Death Differ.* **2005**, *12*, 1535–1541. [CrossRef] [PubMed]
54. Zhang, D.; Tang, B.; Xie, X.; Xiao, Y.-F.; Yang, S.-M.; Zhang, J.-W. The interplay between DNA repair and autophagy in cancer therapy. *Cancer Biol. Ther.* **2015**, *16*, 1005–1013. [CrossRef] [PubMed]
55. Liu, D.; Shaukat, Z.; Xu, T.; Denton, D.; Saint, R.; Gregory, S. Autophagy regulates the survival of cells with chromosomal instability. *Oncotarget* **2016**, *7*, 63913–63923. [CrossRef] [PubMed]
56. Xiao, Z.; Li, M.; Zhang, X.; Rong, X.; Xu, H. TRIP13 overexpression promotes gefitinib resistance in non-small cell lung cancer via regulating autophagy and phosphorylation of the EGFR signaling pathway. *Oncol. Rep.* **2023**, *49*, 1–13. [CrossRef] [PubMed]
57. Nguyen, A.; Lugarini, F.; David, C.; Hosnani, P.; Alagöz, Ç.; Friedrich, A.; Schlütermann, D.; Knotkova, B.; Patel, A.; Parfentev, I.; et al. Metamorphic Proteins at the Basis of Human Autophagy Initiation and Lipid Transfer. *Mol. Cell* **2023**, *83*, 2077–2090.e12. [CrossRef]
58. Nguyen, A.; Faesen, A.C. The Role of the HORMA Domain Proteins ATG13 and ATG101 in Initiating Autophagosome Biogenesis. *FEBS Lett.* **2023**, *598*, 114–126. [CrossRef]
59. Davoli, T.; Uno, H.; Wooten, E.C.; Elledge, S.J. Tumor aneuploidy correlates with markers of immune evasion and with reduced response to immunotherapy. *Science* **2017**, *355*, eaaf8399. [CrossRef] [PubMed]
60. Sheltzer, J.M.; Ko, J.H.; Replogle, J.M.; Burgos, N.C.H.; Chung, E.S.; Meehl, C.M.; Sayles, N.M.; Passerini, V.; Storchova, Z.; Amon, A. Single-chromosome gains commonly function as tumor suppressors. *Cancer Cell* **2017**, *31*, 240–255. [CrossRef]
61. Ben-David, U.; Amon, A. Context is everything: Aneuploidy in cancer. *Nat. Rev. Genet.* **2019**, *21*, 44–62. [CrossRef]
62. Chen, S.-H.; Lin, H.-H.; Li, Y.-F.; Tsai, W.-C.; Hueng, D.-Y. Clinical significance and systematic expression analysis of the thyroid receptor interacting protein 13 (TRIP13) as human Gliomas biomarker. *Cancers* **2021**, *13*, 2338. [CrossRef]
63. Xue, J.; Wu, H.; Shi, Y.; Li, Z. TRIP13 overexpression in hepatocellular carcinoma: Implications for poor prognosis and immune cell infiltration. *Discov. Oncol.* **2023**, *14*, 176. [CrossRef] [PubMed]
64. Lu, S.; Qian, J.; Guo, M.; Gu, C.; Yang, Y. Insights into a Crucial Role of TRIP13 in Human Cancer. *Comput. Struct. Biotechnol. J.* **2019**, *17*, 854–861. [CrossRef] [PubMed]
65. Zhang, G.; Yang, R.; Wang, B.; Yan, Q.; Zhao, P.; Zhang, J.; Su, W.; Yang, L.; Cui, H. TRIP13 Regulates Progression of Gastric Cancer through Stabilising the Expression of DDX21. *Cell Death Dis.* **2024**, *15*, 622. [CrossRef] [PubMed]
66. Chen, Y.; Chen, D.; Qin, Y.; Qiu, C.; Zhou, Y.; Dai, M.; Li, L.; Sun, Q.; Jiang, Y. TRIP13, Identified as a Hub Gene of Tumor Progression, Is the Target of MicroRNA-4693-5p and a Potential Therapeutic Target for Colorectal Cancer. *Cell Death Discov.* **2022**, *8*, 35. [CrossRef]
67. Ni, F.; Liu, X.; Xia, Y.; Zhu, H.; Li, F.; Zhang, N.; Xu, H. TRIP 13-dependent pathways promote the development of gastric cancer. *Funct. Integr. Genom.* **2023**, *23*, 232. [CrossRef] [PubMed]
68. Yan, S.R.; Zhang, Q.; Liu, X.C.; Yuan, J.J.; Zhang, F.; Zhou, K.S. Regulation of TRIP13 on Proliferation and Apoptosis of B-Cell Lymphoma Cells and Its Mechanism. *Zhongguo Shi Yan Xue Ye Xue Za Zhi* **2021**, *29*, 1485–1492. [PubMed]
69. Cai, W.; Ni, W.; Jin, Y.; Li, Y. TRIP13 Promotes Lung Cancer Cell Growth and Metastasis through AKT/MTORC1/C-Myc Signaling. *Cancer Biomark.* **2021**, *30*, 237–248. [CrossRef]
70. Li, C.; Pan, D.; Lin, W.; Deng, D.; Zhou, Y.; Zhao, H.; Pan, F.; Xu, L.; Li, E.; Long, L. RIOK1 Synergizes with TRIP13 by Regulating the E2F–Rb Signaling Pathway to Promote the Proliferation of Esophageal Cancer Cells. *Genes Dis.* **2024**, *11*, 100990. [CrossRef] [PubMed]
71. Singh, S.P.; Goswami, K.; Asch, A.S.; Rao, C.V.; Madka, V. Abstract 506: TRIP13 is a promising therapeutic target for bladder cancer. *Cancer Res.* **2024**, *84*, 506. [CrossRef]
72. Tao, Y.; Yang, G.; Yang, H.; Song, D.; Hu, L.; Xie, B.; Wang, H.; Gao, L.; Gao, M.; Xu, H.; et al. TRIP13 Impairs Mitotic Checkpoint Surveillance and Is Associated with Poor Prognosis in Multiple Myeloma. *Oncotarget* **2017**, *8*, 26718–26731. [CrossRef] [PubMed]
73. Zhu, M.-X.; Wei, C.-Y.; Zhang, P.-F.; Gao, D.-M.; Chen, J.; Zhao, Y.; Dong, S.-S.; Liu, B.-B. Elevated TRIP13 drives the AKT/mTOR pathway to induce the progression of hepatocellular carcinoma via interacting with ACTN4. *J. Exp. Clin. Cancer Res.* **2019**, *38*, 1–15.
74. Liu, X.; Shen, X.; Zhang, J. TRIP13 exerts a cancer-promoting role in cervical cancer by enhancing Wnt/β-catenin signaling via ACTN4. *Environ. Toxicol.* **2021**, *36*, 1829–1840. [CrossRef] [PubMed]
75. Li, Z.-H.; Lei, L.; Fei, L.-R.; Huang, W.-J.; Zheng, Y.-W.; Yang, M.-Q.; Wang, Z.; Liu, C.-C.; Xu, H.-T. TRIP13 Promotes the Proliferation and Invasion of Lung Cancer Cells via the Wnt Signaling Pathway and Epithelial-Mesenchymal Transition. *J. Mol. Histol.* **2021**, *52*, 11–20. [CrossRef]
76. Liu, L.; Zhang, Z.; Xia, X.; Lei, J. KIF18B promotes breast cancer cell proliferation, migration and invasion by targeting TRIP13 and activating the Wnt/β-catenin signaling pathway. *Oncol Lett.* **2022**, *23*, 112. [CrossRef] [PubMed]

77. Zhang, L.-T.; Ke, L.-X.; Wu, X.-Y.; Tian, H.-T.; Deng, H.-Z.; Xu, L.-Y.; Li, E.-M.; Long, L. TRIP13 induces nedaplatin resistance in esophageal squamous cell carcinoma by enhancing repair of DNA damage and inhibiting apoptosis. *BioMed Res. Int.* **2022**, *2022*, 7295458. [CrossRef] [PubMed]
78. Chen, G.; Gao, X.; Jia, X.; Wang, Y.; Xu, L.; Yu, D.; Chang, S.; Deng, H.; Hu, K.; Wang, G.; et al. Ribosomal protein S3 mediates drug resistance of proteasome inhibitor: Potential therapeutic application in multiple myeloma. *Haematologica* **2023**, *109*, 1206. [CrossRef] [PubMed]
79. Banerjee, R.; Liu, M.; Bellile, E.; Schmitd, L.B.; Goto, M.; Hutchinson, M.-K.N.D.; Singh, P.; Zhang, S.; Damodaran, D.P.V.; Nyati, M.K.; et al. Phosphorylation of TRIP13 at Y56 induces radiation resistance but sensitizes head and neck cancer to cetuximab. *Mol. Ther.* **2021**, *30*, 468–484. [CrossRef]
80. Liu, J.; Chen, C.; Wu, G.; Yao, X.; Liu, F.; Liu, S. Knockdown of TRIP13 inhibits gastric cancer stemness and cisplatin resistance by regulating FBXW7/ENO1 axis. *Trop. J. Pharm. Res.* **2024**, *23*, 27–35. [CrossRef]
81. Li, C.; Xia, J.; Franqui-Machin, R.; Chen, F.; He, Y.; Ashby, T.C.; Teng, F.; Xu, H.; Liu, D.; Gai, D.; et al. TRIP13 Modulates Protein Deubiquitination and Accelerates Tumor Development and Progression of B Cell Malignancies. *J. Clin. Investig.* **2021**, *131*, e146893. [CrossRef] [PubMed]
82. Wang, Y.; Huang, J.; Li, B.; Xue, H.; Tricot, G.; Hu, L.; Xu, Z.; Sun, X.; Chang, S.; Gao, L.; et al. A Small-Molecule inhibitor targeting TRIP13 suppresses multiple myeloma progression. *Cancer Res.* **2019**, *80*, 536–548. [CrossRef] [PubMed]
83. Xu, H.; Ma, Z.; Mo, X.; Chen, X.; Xu, F.; Wu, F.; Chen, H.; Zhou, G.; Xia, H.; Zhang, C. Inducing synergistic DNA damage by TRIP13 and PARP1 inhibitors provides a potential treatment for hepatocellular carcinoma. *J. Cancer* **2022**, *13*, 2226–2237. [CrossRef] [PubMed]
84. Chang, S.; Xiao, W.; Xie, Y.; Xu, Z.; Li, B.; Wang, G.; Hu, K.; Zhang, Y.; Zhou, J.; Song, D.; et al. TI17, a Novel Compound, Exerts Anti-MM Activity by Impairing Trip13 Function of DSBs Repair and Enhancing DNA Damage. *Cancer Med.* **2023**, *12*, 21321–21334. [CrossRef] [PubMed]
85. Wang, Y.; Dong, S.; Hu, K.; Xu, L.; Feng, Q.; Li, B.; Wang, G.; Chen, G.; Zhang, B.; Jia, X.; et al. The Novel Norcantharidin Derivative DCZ5417 Suppresses Multiple Myeloma Progression by Targeting the TRIP13–MAPK–YWHAE Signaling Pathway. *J. Transl. Med.* **2023**, *21*, 858. [CrossRef] [PubMed]
86. Dong, S.; Hu, K.; Shi, Y.; Wang, G.; Yu, D.; Zhao, Y.; Zhang, H.; Wang, Y.; Sun, H.; Xu, Z.; et al. Design and synthesis of cantharidin derivative DCZ5418 as a TRIP13 inhibitor with anti-multiple myeloma activity in vitro and in vivo. *Bioorg. Med. Chem. Lett.* **2023**, *98*, 129590. [CrossRef] [PubMed]
87. Liu, L.; Liao, B.; Fan, R.; Liu, Y.; Li, A.; Liu, L.; Li, Y.; Li, J. TRIP13 plays an important role in the sensitivity of leukemia cell response to sulforaphane therapy. *ACS Omega* **2024**, *9*, 26628–26640. [CrossRef] [PubMed]
88. Sun, Y.; Zhang, Q.; Cao, S.; Sun, X.; Zhang, J.; Zhang, B.; Shang, Z.; Zhao, C.; Cao, Z.; Zhang, Q.; et al. Tetrahydrocurcumin Targets TRIP13 Inhibiting the Interaction of TRIP13/USP7/C-FLIP to Mediate C-FLIP Ubiquitination in Triple-Negative Breast Cancer. *J. Adv. Res.* **2024**, *in press*. [CrossRef]
89. Mittal, K.; Cooper, G.W.; Lee, B.P.; Su, Y.; Skinner, K.T.; Shim, J.; Jonus, H.C.; Kim, W.J.; Doshi, M.; Almanza, D.; et al. Targeting TRIP13 in Favorable Histology Wilms Tumor with Nuclear Export Inhibitors Synergizes with Doxorubicin. *Commun. Biol.* **2024**, *7*, 426. [CrossRef] [PubMed]
90. Yao, J.; Zhang, X.; Li, J.; Zhao, D.; Gao, B.; Zhou, H.; Gao, S.; Zhang, L. Silencing TRIP13 Inhibits Cell Growth and Metastasis of Hepatocellular Carcinoma by Activating of TGF-β1/Smad3. *Cancer Cell Int.* **2018**, *18*, 1–13. [CrossRef]
91. Yu, D.-C.; Chen, X.-Y.; Zhou, H.-Y.; Yu, D.-Q.; Yu, X.-L.; Hu, Y.-C.; Zhang, R.-H.; Zhang, X.-B.; Zhang, K.; Lin, M.-Q.; et al. TRIP13 Knockdown Inhibits the Proliferation, Migration, Invasion, and Promotes Apoptosis by Suppressing PI3K/AKT Signaling Pathway in U2OS Cells. *Mol. Biol. Rep.* **2022**, *49*, 3055–3064. [CrossRef] [PubMed]
92. Zhang, Q.; Dong, Y.; Hao, S.; Tong, Y.; Luo, Q.; Aerxiding, P. The Oncogenic Role of TRIP13 in Regulating Proliferation, Invasion, and Cell Cycle Checkpoint in NSCLC Cells. *Int. J. Clin. Exp. Pathol.* **2019**, *12*, 3357. [PubMed]
93. Li, F.; Zhao, C.; Wang, L. Molecular-targeted agents combination therapy for cancer: Developments and potentials. *Int. J. Cancer* **2013**, *134*, 1257–1269. [CrossRef] [PubMed]
94. Lindahl, T.; Barnes, D.E. Repair of endogenous DNA damage. *Cold Spring Harb. Symp. Quant. Biol.* **2000**, *65*, 127–134. [CrossRef]
95. Ghosh, S.; Mazumdar, T.; Xu, W.; Powell, R.T.; Stephan, C.; Shen, L.; Shah, P.A.; Pickering, C.R.; Myers, J.N.; Wang, J.; et al. Combined TRIP13 and aurora kinase inhibition induces apoptosis in human Papillomavirus–Driven cancers. *Clin. Cancer Res.* **2022**, *28*, 4479–4493. [CrossRef] [PubMed]