Targeting TRIP13 for overcoming anticancer drug resistance (Review)

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Abstract. Cancer is one of the greatest dangers to human wellbeing and survival. A key barrier to effective cancer therapy is development of resistance to anti-cancer medications. In cancer cells, the AAA+ ATPase family member thyroid hormone receptor interactor 13 (TRIP13) is key in promoting treatment resistance. Nonetheless, knowledge of the molecular processes underlying TRIP13-based resistance to anticancer therapies is lacking. The present study evaluated the function of TRIP13 expression in anticancer drug resistance and potential methods to overcome this resistance. Additionally, the underlying mechanisms by which TRIP13 promotes resistance to anticancer drugs were explored, including induction of mitotic checkpoint complex surveillance system malfunction, promotion of DNA repair, the enhancement of autophagy and the prevention of immunological clearance. The effects of combination treatment, which include a TRIP13 inhibitor in addition to other inhibitors, were discussed. The present study evaluated the literature on TRIP13 as a possible target and its association with anticancer drug resistance, which may facilitate improvements in current anticancer therapeutic options.

Contents

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1. Introduction

Thyroid hormone receptor interactor 13 (TRIP13) is a member of the AAA+ ATPase family able to generate mechanical stresses through ATP hydrolase activities (1). TRIP13 was initially identified as a protein that interacts with the E1 protein of the human papillomavirus (2). In 1999, TRIP13 was found to be required for the meiotic checkpoint in yeast (3). Studies have showed involvement of TRIP13 in meiotic recombination and DNA repair in several organisms, including rice (4), yeast (5), *Drosophila melanogaster* (6), *Caenorhabditis elegans* (7) and mice (8-10). Additionally, it has been identified as a constituent of the spindle assembly checkpoint (SAC) pathway (11-13), which is involved in the accurate segregation of chromosomes (14). TRIP13 [and its homolog pachytene checkpoint 2 (PCH2) is an AAA+ ATPase that produces homohexamers and uses ATP as a substrate (3,8,9, 15-19). PCH2 binds to Hop1 and alters its structure, which displaces Hop1 from DNA (20). Hydrolysis of ATP by TRIP13/PCH2 provides energy necessary to undergo conformational changes that exert mechanical force on Hop1 (21). In addition to its role as a kinetochore protein, TRIP13/PCH2 interacts with the $p31^{comet}$ protein, which is responsible for gene silencing (11). TRIP13/PCH2 is linked to various malignancies due to its involvement in ensuring proper biorientation of chromosomes during mitosis; TRIP13 has been shown to be overexpressed in a number of malignancies, including colorectal (22-24), head and neck (25), breast (26,27), lung (28-30), liver (31,32) and prostate cancer (33,34), multiple myeloma (35), bladder cancer (36,37) and human chronic lymphoblastic leukemia (38). Importantly, overexpression of TRIP13 promotes advancement of head and neck squamous cell carcinoma (HNSCC) (25) and lung adenocarcinoma (39). Depletion of TRIP13 or suppression of its activity has been demonstrated to diminish tumor development in head and neck and colon cancer and hepatocellular carcinoma (HCC) (32,40). TRIP13 also serves an essential role in the survival and spread of tumor stem cells

in cutaneous melanoma (41), prostate cancer (33) and lung adenocarcinoma (39). Based on these findings, TRIP13 serves a key role in tumor development.

Effective cancer therapy is hampered significantly by the development of resistance to anticancer medications. Overexpression of TRIP13 has been linked to decreased sensitivity to anticancer medicines (such as bortezomib and cisplatin) (25,42). TRIP13 facilitates development of nedaplatin resistance in esophageal squamous cell carcinoma (43). In addition, synergistic anti-HCC efficacy is achieved by mixing TRIP13 inhibitor DCZ0415 with the PARP1 inhibitor olaparib (44). Therefore, TRIP13 is involved in drug resistance in cancer cells. The present study evaluated the function of TRIP13 expression in anticancer drug resistance and potential methods to overcome this resistance. Furthermore, the present study explored the underlying mechanism of targeting TRIP13 to overcome anticancer drug resistance and summarized the roles TRIP13 plays in cancer treatment. The present study also reviewed the effects of combination treatment, which include a TRIP13 inhibitor in addition to other inhibitors.

2. Structure and biological functions of TRIP13

The structure of human TRIP13, ATP-bound form (45) is shown in Fig. 1. Additionally, TRIP13/PCH2 exhibits kinetochore protein activity by interacting with the silencing protein $p31^{comet}$ (11).

TRIP13/PCH2 has been shown to have a role in mitosis, namely in the transition from metaphase to anaphase, as well as the SAC (19). It also releases anaphase-promoting complex (APC) from checkpoint inhibition (19). Before anaphase, the cell must make sure its chromosomes are appropriately organized and bioriented for separation of sister chromatids. Numerous proteins such as spindle checkpoint, securin and cyclin B, are needed for this process to maintain accurate timing and reliable separation. The activation of the APC is required for mitosis. Protein CDC20, which is typically suppressed by the mitotic checkpoint complex (MCC), activates the APC. The TRIP13-related gene Mad2 exists in two isoforms, the open (O-) form and the closed (C-) form (19). O-Mad2 changes into C-Mad2 when kinetochores detach and C-Mad2 may then hook onto CDC20 and sequester it, blocking mitotic progression (46). MCC must be disassembled, and this process is mediated by $p31^{comet}$ (47). This is hypothesized to take place in part via structural mimicry as $p31^{comet}$ has structural similarities to C-Mad2 (48). Nevertheless, ATP is needed for this step. TRIP13 uses $p31^{comet}$ as an adaptor protein to convert C-Mad2 into O-Mad2, then induces activation of the SAC and the formation of the MCC. To conclude, TRIP13/PCH2 is key for SAC activation and MCC formation.

Similarly, TRIP13/PCH2 is also involved in the G2/prophase stage of meiosis (3). TRIP13 affects the frequency of double-strand breaks (DSBs) promoting homology-directed repair, while suppressing non-homologous end joining and translesion synthesis. Homologous recombination following these breaks needs a protein complex to shape and direct the correct pairing of chromosomes. PCH2 gene in budding yeast is necessary for the meiotic checkpoint that inhibits chromosomal segregation when recombination and chromosome synapsis are impaired (3). TRIP13 is necessary for the creation of the synaptonemal complex (SC), which that builds chromosome pairs. In meiocytes lacking TRIP13, pericentric synaptic forks are more common, crossovers are reduced and chiasma (the site of contact between homologous chromosomes) distribution is disrupted (9). SC synthesis necessitates the elimination of HORMA domain family proteins (HORMADs) during meiosis. PCH2 is required for SC formation to remove Hop1 from chromosomes (49). In mouse spermatocytes, TRIP13 facilitates depletion of other HORMADs, including HORMAD1 and HORMAD2 (10). These findings demonstrate a key dynamic function for TRIP13/PCH2 in removal of several proteins during SC formation and subsequent meiosis.

3. Implications of TRIP13 in cancer

HNSCC exhibits TRIP13 overexpression, which promotes proliferation and invasion (25). Overexpression of both TRIP13 and Mad2 are associated with various types of cancer, including multiple myeloma (42), head and neck cancer (25), colorectal cancer (22-24), chronic lymphocytic leukemia (50), lung adenocarcinoma (39) and prostate cancer (33). Overexpression of TRIP13 attenuates the mitotic delay caused by Mad2 overexpression, but downregulation of TRIP13 compounds the effects of Mad2 overexpression. In addition, downregulating TRIP13 and overexpressing Mad2 suppresses proliferation in cells and tumor xenografts, suggesting therapeutic potential for inhibition of TRIP13 (47). Mad2 promotes drug resistance in ovarian cancer (51). The expression of TRIP13 is markedly increased in epithelial ovarian cancer (EOC) cell lines (SKOV-3, HEY and OVCAR-3) compared with normal ovarian cell lines (52). Additionally, knockdown of TRIP13 in EOC cells inhibits cell proliferation, decreases cell invasion and migration and stimulates apoptosis (52). This demonstrates that TRIP13 promotes the development of tumor cells and may be a potential target for tumor therapy.

4. TRIP13 and anticancer drug resistance

Anticancer regimens have the potential to kill most cancer cells at first, but some malignant cells survive because they have either already developed mechanisms of drug resistance (intrinsic resistance) or have acquired them through random mutation and genetic alteration (acquired resistance). Resistance mechanisms include: Decreased expression or dysfunction of influx drug transporters, increased activity of multidrug-resistant (MDR) efflux pumps of the ATP-binding cassette (ABC) superfamily, such as P-glycoprotein, multidrug resistance associated protein 1 (MRP1) and breast cancer resistance protein (ABCG2) (53), qualitative and quantitative changes in the drug target and drug sequestration within intracellular compartments. MDR efflux pumps remove numerous anticancer medications from cancer cells or store them in organelles such as lysosomes, where they are inaccessible to the cell target sites (54). The emergence of resistance to anticancer drugs is associated with genomic instability, which may include mutations, amplifications, deletion and/or translocations (55). MDR is caused by a combination of variables, including genetics (gene mutations, amplification and epigenetic modifications), growth hormones and higher DNA repair ability (56). According to Vasan *et al* (57), the primary factors

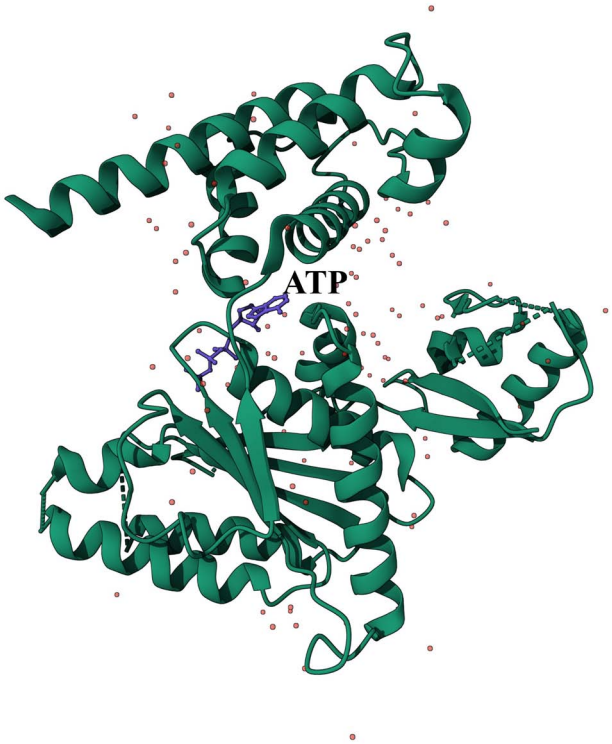

Figure 1. Structure of human TRIP13/ATP bound form. The 3D structures of TRIP13 protein (PDB: 5VQA) bound with ATP.

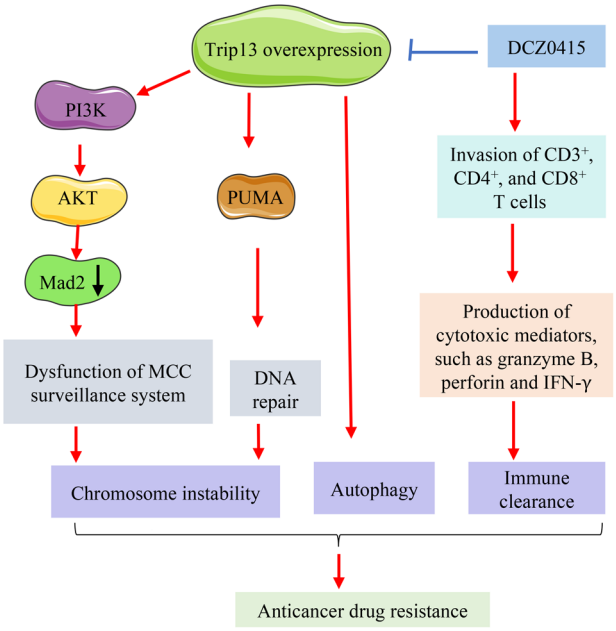

Figure 2. The underlying mechanism of TRIP13 mediated anticancer drug. There are primarily three molecular mechanisms involved in TRIP13-mediated drug resistance. These mechanisms include promoting chromosomal instability, enhancing autophagy, and modulating the tumor microenvironment resistance. MCC, mitotic checkpoint complex, PUMA: p53 upregulated modulator of apoptosis.

that determine treatment resistance include: Tumor burden and growth dynamics; tumor heterogeneity; physical barriers; the immune system and the tumor microenvironment. All of these factors contribute to the diminished effectiveness of the medications used to treat the tumor.

TRIP13 expression is shown to be higher in samples from patients with multiple myeloma compared with control samples (42,58). Overexpression of TRIP13 is linked to decreased sensitivity to bortezomib and cisplatin (25,42,59). TRIP13 is shown to be responsible for the development of nedaplatin resistance in esophageal squamous cell carcinoma (43). Furthermore, considering the role of cisplatin (60-62) and PARP (63-65) inhibitors in the treatment of ovarian cancer, further study is needed to elucidate the role of TRIP13 in treatment-induced drug resistance caused by cisplatin and PARP therapy. These aforementioned results suggest a connection between elevated TRIP13 levels and drug resistance.

5. Targeting TRIP13 for overcoming anticancer drug resistance

Targeting TRIP13 is a potential strategy for overcoming drug resistance. Inhibiting TRIP13 makes HNSCC cells more sensitive to effects of radiation and chemotherapy (25). Recent research found that TRIP13$^{-/-}$ HCC cells are more vulnerable to the effects of chemotherapy than normal HCC cells (44). DCZ0415 may stimulate antimyeloma activity in primary cells generated from individuals with myeloma who are resistant to several drugs (35). Inhibition or depletion of TRIP13 may thus constitute a viable approach to circumventing resistance that anticancer drugs cause.

6. Underlying mechanism of TRIP13-mediated anticancer drug resistance

There are primarily three molecular mechanisms involved in TRIP13-mediated drug resistance. These mechanisms include promoting chromosomal instability, enhancing autophagy and modulating the tumor microenvironment (Fig. 2).

TRIP13 promotes drug resistance by causing chromosome instability. Previous studies have suggested that SAC is a universal safeguard that guarantees the integrity of chromosomal separation in cell division (66-68). Multiple malignancies exhibit overexpression of SAC proteins, which is linked to chromosome instability (CIN) in tumors (69-71). Additionally, telomere dysfunction (72-74) and faulty DNA repair mechanism response (75) contribute significantly to CIN in cancer. Not only does CIN serve a role in the origin, maintenance and growth of tumors, but it also stimulates the development of treatment resistance in cancer cells. TRIP13 is associated with CIN in human malignancies such as multiple myeloma (12,76,77) and treatment resistance. Previous studies have documented that TRIP13 plays a role in the induction of CIN and drug resistance via SAC signaling and modulating DNA damage repair (25,42,43,58,78).

TRIP13 induces drug resistance via inducing the dysfunction of MCC surveillance system. MCC, also known as SAC effector (79), is made of the proteins Mad2, BubR1/Mad3 and Bub3, in addition to CDC20 (68,80,81). Mis-segregation of chromosomes and failure to stop in mitosis may result from malfunctions in the MCC monitoring system. Both of these contribute to the formation of human tumors as well as

medication resistance in cancer (82). Subcellular localization research demonstrates that TRIP13 co-localizes with Mad2 at kinetochores and interacts with $p31^{comet}$, a Mad2-binding HORMA-domain protein that negatively controls SAC localization to kinetochores in prometaphase. When TRIP13 is overexpressed, Mad2 protein levels are reduced (42). Mad2 forms a compound with APC/cyclosome (APC/C) when the MCC monitoring system is activated. This prevents degradation of securin and cyclin B1, which ultimately leads to arrest of the cells in the prometaphase phase of the cell cycle (83). Resistance to paclitaxel is associated with a weaker spindle checkpoint in conjunction with lower expression of Mad2 (84). Through activation of the Akt signaling cascade, TRIP13 ubiquitinates and degrades the checkpoint surveillance protein Mad2, which further results in damaged checkpoint surveillance and subsequent drug resistance (42). Inhibition of PI3k/Akt may partially rescue TRIP13-induced drug resistance to bortezomib (42). The aforementioned studies indicate that TRIP13/Mad2 axis, via activating PI3K-Akt signaling pathway, leads to damage to the checkpoint surveillance system and subsequent anticancer drug resistance. Hence, TRIP13-induced anti-apoptosis action and dysfunction in MCC surveillance system contribute to chromosome instability, leading to drug resistance in cancer cells.

TRIP13 induces drug resistance by promoting DNA repair. To prevent genomic instability in the host, DNA damage response and repair mechanisms have been conserved throughout evolution (85) of both prokaryotes and eukaryotes. In mammalian cells, dysregulation of proteins involved in these processes may increase genomic changes, which lead to genomic instability, a well-established hallmark of cancer (86,87). There has been emergence of new and promising techniques for targeting the DNA damage response and repair pathways to increase cancer cell sensitivity to existing therapeutic drugs (88). Targeting DNA damage is signaling and repair may interrupt the compensatory activation of DNA repair pathways that may function as a drug resistance mechanism. For example, targeting DNA repair has become a legitimate therapeutic approach. This method uses PARP inhibitors to treat breast, ovarian, pancreatic and prostate cancers that have DNA repair deficiencies (89-95). Clinical research and development of small compounds that target key components of the DNA damage response and repair pathways, including DNA-dependent protein kinase (DNA-PK), ataxia telangiectasia mutated (ATM) and Rad3-related kinase (ATR), ATM and checkpoint kinase 1 (CHK1), have been accelerated (96). In addition, accurate targeting of these key molecules offers the possibility of using biomarkers of DNA repair deficiency to choose the most effective therapy for each individual patient to achieve the highest possible therapeutic index (96).

Recent research has provided support for the hypothesis that TRIP13-induced anti-apoptosis may contribute to drug resistance in cancer cells (97). This is because one of the primary strategies anticancer medications utilize to trigger cell death is induction of apoptosis. When TRIP13 is overexpressed, cancer cells are less sensitive to bortezomib and cisplatin (25,42). When multiple myeloma cells transfected with TRIP13 are treated with bortezomib and etoposide, cell viability experiment indicates that the number of viable tumor cells is greater in the TRIP13-transfected cells compared with control cells (42). Comparatively, HNSCC cells that overexpress TRIP13 display a decreased sensitivity to cisplatin when compared with control cells (25). Therefore, TRIP13 plays a role in the development of drug resistance in cancer cells. When treated with increasing doses of bortezomib, TRIP13-overexpressing ARP1 and OCIMy5 multiple myeloma cell lines are less likely to undergo apoptosis and better able to withstand the cytotoxic effects compared with cells transfected with empty vectors. In TRIP13-overexpressing ARP1 multiple myeloma cell line, the G2/M cell cycle arrest induced by bortezomib is consistently suppressed compared with control cells (42). In addition, TRIP13 small interfering (si)RNA knockdown in multiple myeloma cells eliminates doxycycline treatment resistance and triggers apoptosis both *in vitro* and in a mouse model of xenograft myeloma (35,42). In ARP1 and OCIMy5 multiple myeloma cells, downregulation of TRIP13 leads to an increase in levels of cleaved PARP and activation of caspase 3, both of which indicate a potential role for knockdown of TRIP13 in inhibiting the apoptotic pathway (42). Similarly, in human chronic lymphocytic leukemia, microarray data evaluated using the 'canonical pathway' module of Ingenuity route analysis reveal that TRIP13 participates in numerous apoptosis-associated pathways, including 'induction of apoptosis by HIV1', 'p53 signaling' and 'PPAR signaling' (50). In addition, knocking down TRIP13 causes a notable increase in the activity of caspase 3/7 in Granta-519 and JVM-2 B cell lymphocytic leukemia cell lines (50). The modulation of the c-Myc/TRIP13/p53 upregulated modulator of apoptosis (PUMA) axis is the mechanism by which TRIP13 serves a role in the development of chronic lymphocytic leukemia (50). In HNSCC, suppression of TRIP13 also induces cell cycle arrest (25). In cells transfected with TRIP13 siRNA, there is a greater accumulation of phosphorylated histone H2A histone family member X (the marker of DSBs) (25). According to western blot analysis, DSBs caused by TRIP13 siRNA occur prior to apoptosis (25). These results provided compelling evidence that TRIP13 increase DNA repair, which in turn leads to treatment resistance.

TRIP13 induces drug resistance by enhancing autophagy. Autophagy is a natural method of cell survival that is effectively employed by tumor cells to prevent cell death and generate drug resistance (98-100). Both of these may be accomplished by tumor cells via autophagy, a macromolecular process in which cells break down and recycle intracellular substrates and damaged organelles to reduce cell stress caused by factors such as nutritional deficiency, hypoxia, irradiation and cytotoxic chemicals. When cancer is in the early stages, autophagy has been shown to protect against malignant disease; nevertheless, transformed cells exhibit increased autophagy to promote survival, proliferation and metastasis (101-103). Although the precise function of autophagy in cell death and survival remains unclear, autophagy is enhanced in cancer cells exposed to stressful situations, such as anticancer treatment, which may result in anticancer drug resistance (104-106). Previous research examined TRIP13 role in autophagy by treating cells with DMSO (control), gefitinib (an autophagy agonist) and 3-methyladenine (3-MA; an autophagy inhibitor) (107); TRIP13 induces autophagy in non-small cell lung cancer

(NSCLC) cells, shown by an increase in the number of LC3B (autophagy marker)-positive puncta seen by immunofluorescence examination (107). Overexpression of TRIP13 in NSCLC cells leads to an increase in LC3B and decrease in autophagy marker P62 expression (107). The opposite effects are seen in tumor cells when TRIP13 expression is suppressed (107). All of the aforementioned effects are mitigated by the gefitinib therapy, but 3-MA has the opposite effect (107). Therefore, TRIP13 may be responsible for inducing gefitinib resistance in NSCLC cells via increasing autophagy (107). Therefore, TRIP13 can be used as a biomarker and therapeutic target autophagy for overcoming drug resistance.

TRIP13 induces drug resistance by preventing immune clearance. The tumor microenvironment, which comprises immune cells, stroma and vasculature, may promote drug resistance via numerous methods, including inhibiting immune clearance of tumor cells, preventing drug absorption and increasing paracrine growth factors, to promote cancer cell development (108). DCZ0415 prevents proliferation inhibition of multiple myeloma cells even in the presence of bone marrow stromal cells and the cytokines IL6 and IGF1 in a cellular experiment that mimics multiple myeloma in its microenvironment (35). In addition to cytotoxicity against multiple myeloma cells, DCZ0415 also targets the bone marrow microenvironment and overcomes the proliferative effects on bone marrow stromal cells (35).

Additionally, suppression of TRIP13 stimulates an anticancer immune response by increasing production of cytotoxic mediators. Recent studies show that TRIP13 inhibition promotes the invasion of $CD3^+$, $CD4^+$ and $CD8^+$ T cells (35). DCZ0415 considerably increases the production of cytotoxic mediators such as granzyme B, perforin and IFN-γ, which may contribute to the cytotoxic effect against murine MC38 cells. In addition, blocking immunological checkpoints, such as PD-1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA4), in tumors treated with DCZ0415 has the potential to increase cytotoxicity and regression of the tumor (109). Hence, decreased expression of TRIP13 stimulates immune responses in the microenvironment of the tumor, which may help overcome drug resistance to anticancer medications.

7. Combination therapy for overcoming anticancer drug resistance

DNA DSBs and DNA damage responses induced by certain anticancer drugs, such as example, β-emitter iodine-131, O-6-methylguanine-DNA methyltransferases and cisplatin, make cancer cells more vulnerable to further treatment (110). DNA damage response followed by effective repair of DSBs is key to maintain genomic integrity. On the other hand, in cancer, the repair of anticancer agent-induced DSBs via the non-homologous end joining (NHEJ) or homologous recombination (HR) repair pathways enhances treatment resistance and recurrence in patients (111). According to recent research, TRIP13 improves NHEJ repair and generates treatment resistance in head and neck cancer via binding to NHEJ proteins Ku protein with molecular weight of 70 KDa (KU70, encoded by the X-ray repair cross-complementing protein 6 gene located on chromosome 22), Ku protein with molecular weight of 80 KDa, (KU80,encoded by the X-ray repair cross-complementing protein 5 gene on chromosome 2) and DNA-dependent protein kinase catalytic subunit (DNA-PKcs) (25). Additionally, GFP-based reporter experiment demonstrates that DCZ0415 inhibits DNA repair by the NHEJ repair pathway (35). Hence, combining TRIP13 inhibitor with other inhibitors may be an option to overcome anticancer drug resistance (Table I).

In addition, the upregulation of the TRIP13-mediated NHEJ repair pathway is the cause of the resistance to anticancer drugs (such as bortezomib and cisplatin). Therefore, cancer cells that have high levels of TRIP13 expression will be more susceptible to DNA-PKcs inhibitor than cancer cells with low levels of TRIP13 expression (25). Banerjee *et al* (25) showed that tumor cells that overexpress TRIP13 are more sensitive to the DNA-PKcs inhibitor Nu7026 (25). Hence, combining the TRIP13 inhibitor with DNA-PKcs inhibitor may be an effective treatment approach for TRIP13-mediated drug resistance.

Synergistic effects of DCZ0415 and PARP1 inhibitors. Anticancer drug resistance is partly attributed to TRIP13-induced DNA damage (25). Therefore, combining TRIP13 inhibitor with inhibitors against DNA repair proteins may overcome drug resistance (25). Synergistic effects of DCZ0415 and olaparib on increasing anticancer activity have been demonstrated in HCC cells (44). Specifically, in HCC cell lines, combination groups treated with DCZ0415 and olaparib show greater growth suppression compared with single-treatment groups, suggesting that this strategy may represent a viable therapeutic option for HCC (44). Furthermore, Clairmont *et al* (78) and Sarangi *et al* (112) demostrate that $BRCA1^{-/-}$ cells overexpressing TRIP13 or $p31^{comet}$ develop resistance to the PARP inhibitor Olaparib, and this resistance results from the reactivation of homologous recombination (HR)-mediated DNA repair owing to decreased Shieldin complex levels (113).Therefore, for individuals with BRCA1-deficient malignancies who acquire resistance to PARP medicines, blocking TRIP13/$p31^{comet}$-mediated Shieldin disassembly may be a viable therapy option.

Synergistic effects of TRIP13 depletion and aurora kinase inhibitors. Ghosh *et al* (97) show low Rb levels drive sensitivity to aurora kinase inhibitors in human papillomavirus (HPV)-positive cancers (97).Mitotic kinases, in particular, aurora B (114) and A (114), are essential for maintenance of tumors that have loss-of-function RB1 mutations. Inhibition of Rb pathway activity upregulates MCC gene expression, which may lead to chromosomal instability and prolonged mitotic phase of the cell cycle (77,116). In patients with HNSCC, the expression of Bub1B and mitotic arrest deficient 2-like 1 (MAD2L1) is greater in HPV-positive tumors than in HPV-negative tumors. Depletion of Bub1B, as revealed by Gong *et al* (113), partly protects Rb-deficient SCLC cells from apoptosis produced by aurora kinase A inhibition. In a similar manner, knockdown of MAD2L1 and Bub1B significantly decreases the sensitivity to aurora kinase inhibitors in treatment of HPV-positive squamous carcinoma (97), while MAD2L1 regulator TRIP13 is depleted, which leads to an increase in the sensitivity to aurora kinase inhibitors for the treatment of HPV-positive cancers. If mitotic checkpoint gene

Table I. Combination of TRIP13 and TRIP13 depletion inhibitors and other drugs.

Treatment	TRIP13 effect	Pharmacological interaction	Tumor	First author (year)	(Refs.)
DCZ0415 with PARP1 inhibitor Olaparib	Impaired DNA repair gene regulation and expression	Synergistic	Hepatocellular Carcinoma	Xu *et al* (2022)	[44] J Cancer (2022) 13 (7): 2226-2237.
Combining Aurora kinase inhibition with TRIP13 depletion	Led to extensive apoptosis	Synergistic	HPV-negative cancer cells	Soma Ghosh *et al* (2022)	[97] Clin Cancer Res (2022) 28 (20): 4479-4493.
DCZ0415 with the multiple myeloma chemotherapeutic melphalan	Impaired nonhomologous end joining repair and inhibited NF-κB activity	Synergistic	Multiple Myeloma	Yingcong Wang *et al* (2020)	[35] Cancer Res (2020) 80 (3): 536–548.
DCZ0415 with the HDAC inhibitor Panobinostat	Impaired nonhomologous end joining repair and inhibited NF-κB activity	Synergistic	Multiple Myeloma	Yingcong Wang *et al* (2020)	[35] Cancer Res (2020) 80 (3): 536–548.
Combining the DNA-PKcs inhibitor Nu7026 with TRIP13 depletion	TRIP13 provides the energy needed for assembly of the DNA-PKcs complex	Synergistic	Head and neck cancer	Rajat Banerjee *et al* (2014)	[25] Nat Commun. 2014; 5: 4527.

TRIP13, thyroid hormone receptor interactor 13; DCZ0415, a small-molecule inhibitor targeting TRIP13; PARP1, poly(ADP-ribose) polymerase 1; Olaparib, an inhibitor of the enzyme poly ADP ribose polymerase (PARP); DNA, deoxyribonucleic acid; HPV, Human papillomavirus; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; HDAC, Histone deacetylases; DNA-PKcs, DNA-dependent protein kinase, catalytic subunit; Nu7026, a potent DNA-PK inhibitor

MAD2L1 is overexpressed in HPV-positive cells and these cells need TRIP13 and aurora kinase activity to maintain mitotic fidelity, combined suppression of TRIP13 and aurora kinase activity may cause cancer cells to undergo irreversible mitotic arrest, DNA damage and death. According to previous research, the combination of TRIP13 depletion and aurora kinase inhibition leads to increased apoptosis compared with specific inhibition of a single route in HPV-positive tumors (97). Therefore, overexpression of TRIP13 makes cancer cells resistant to aurora kinase inhibitors, which are used in the treatment of HPV-positive squamous carcinoma. This resistance is induced by cancer cell ability to retain their mitotic fidelity. The combined therapeutic benefits of inhibiting TRIP13 and aurora kinase may be a potential technique for treating individuals with malignancies caused by Rb pathway abnormalities.

8. Discussion

TRIP13/PCH2 is associated with a number of malignancies as it ensures proper alignment of chromosomes during mitosis. As a result, TRIP13 may be a target for the development of an anticancer medication. In addition, overexpression of TRIP13 is associated with decreased susceptibility to bortezomib and cisplatin (25,42). In esophageal squamous cell carcinoma, TRIP13 causes nedaplatin resistance (43). In addition, combination of DCZ0415 with olaparib results in a synergistic effect on the activity of HCC (44). Thus, TRIP13 serves a role in cancer cell drug resistance.

To determine how TRIP13 contributes to the development of anticancer drug resistance, it is vital to research the mechanism that controls the regulation of TRIP13 expression. In perihilar cholangiocarcinoma cells, c-Myc stimulates the transcription of TRIP13 (117). In addition, transcription factor specificity protein 1 (SP1) serves a role in controlling the amount of TRIP13 that is expressed (44). TRIP13 expression is drastically reduced by SP1 inhibition or knockdown, whereas overexpression of SP1 notably increases TRIP13 expression (44). However, it is unclear whether c-Myc or SP1 are involved in development of TRIP13-mediated drug resistance. Because of this, identifying the transcription factors that govern expression of TRIP13 is required, as well as genes controlled by TRIP13, which may to act as targets for the development of cancer treatment.

Numerous studies (34,118-120) have shown that microRNAs (miRNAs) directed against TRIP13 suppress or increase proliferation of cancer cells. Cancer may be treated using miRNA mimics or inhibitors, which can also circumvent resistance to anticancer medications (121). To facilitate development of new treatment regimens, for example, the combination of TRIP13 and immune check point inhibitors, it is necessary to have a better understanding of the effects of miRNAs and TRIP13-mediated drug resistance on immune responses in the tumor microenvironment.

To create anticancer treatments that are effective for people with cancer with high levels of TRIP13, it is necessary to identify new TRIP13-binding proteins and the TRIP13 binding domain. There is a possibility that peptides with a structure identical to the binding domain of TRIP13 may facilitate overcoming resistance to anti-cancer medications. For example,

TRIP13 binds to ubiquitin-specific protase-7 (USP7), then TRIP13-induced resistance to proteasome inhibition can be overcome by a USP7 inhibitor (25,42,59).

Additionally, the microenvironment of a tumor comprises innate and adaptive immune cells (B and T, dendritic and myeloid-derived suppressor cells and M1/2 macrophages), as well as cancer cells and endothelial cells and cancer-associated fibroblasts. The tumor microenvironment is essential for the development and progression of cancer. There is evidence that interactions between cancer cells and immune cells may enhance the growth of cancer cells (108). Depletion of TRIP13 facilitates activation of immune responses in the tumor microenvironment (35), which improves anticancer treatment resistance. In immune cells, it is important to discover the genes controlled by the TRIP13 protein to develop potential immunotherapeutic targets.

TRIP13 inhibitor resistance may develop in future. Because of this, it will be required to identify genes that confer resistance to TRIP13 inhibitors as well as genes controlled by TRIP13 inhibitors. It is possible that immune evasion, drug efflux, the overexpression of oncogenes and the downregulation of tumor suppressor genes mediate resistance to TRIP13 inhibitors.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

LZ, NJ and SY wrote the manuscript. TH and YJG performed the literature review and edited the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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