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Review Article

Methyltransferases in cancer drug resistance: Unlocking the potential of targeting SMYD3 to sensitize cancer cells

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ABSTRACT

Drug resistance is a significant challenge in oncology and is driven by various mechanisms, among which a crucial role is played by enhanced DNA repair. Thus, targeting DNA damage response (DDR) factors with specific inhibitors is emerging as a promising therapeutic strategy. An important process involved in the modulation of DNA repair pathways, and hence in drug resistance, is post-translational modification (PTM). PTMs such as methylation affect protein function and are critical in cancer biology. Methylation is catalyzed by specific enzymes called protein methyltransferases. In recent years, the SET domain-containing N-lysine methyltransferase SMYD3 has emerged as a significant oncogenic driver. It is overexpressed in several tumor types and plays a signal-dependent role in promoting gastrointestinal cancer formation and development. Recent evidence indicates that SMYD3 is involved in the maintenance of cancer genome integrity and contributes to drug resistance in response to genotoxic stress by regulating DDR mechanisms. Several potential SMYD3 interactors implicated in DNA repair, especially in the homologous recombination and non-homologous end-joining pathways, have been identified by *in silico* analyses and confirmed by experimental validation, showing that SMYD3 promotes DDR protein interactions and enzymatic activity, thereby sustaining cancer cell survival. Targeting SMYD3, in combination with standard or targeted therapy, shows promise in overcoming drug resistance in colorectal, gastric, pancreatic, breast, endometrial, and lung cancer models, supporting the integration of SMYD3 inhibition into cancer treatment regimens. In this review, we describe the role played by SMYD3 in drug resistance and analyze its potential as a molecular target to sensitize cancer cells to treatment.

1. Introduction

Drug resistance followed by disease recurrence is a common clinical problem in many cancers. The molecular mechanisms underlying the development of drug resistance can be classified into a number of different categories, defined as the hallmarks of anticancer drug resistance, which often occur together [1]. In particular, one of the strategies adopted by cancer cells to overcome drug sensitivity is the increased ability to repair DNA damage [2]. As suggested by growing evidence, targeting DNA damage response (DDR) factors may thus be a promising approach for therapeutic intervention [3]. As a result, various inhibitors of DDR factors are being tested in preclinical and clinical investigations [3].

Post-translational modifications (PTMs) are chemical alterations that occur after protein synthesis. They involve the enzyme-mediated covalent addition of functional groups to proteins and include phosphorylation, ubiquitination, acetylation, SUMOylation, PARylation, and methylation [4]. As such, they expand the diversity of the proteome by altering protein structure, localization, and interactions, thereby affecting their functions [5]. PTMs are implicated in all aspects of normal cell biology and pathogenesis and have been shown to regulate several human cancer hallmarks [4]. In particular, they play a major role in the modulation of DNA repair processes [4,6], which suggests their involvement in the development of cancer drug resistance [7].

Based on the PTM status of human proteins retrieved from the UniProt Database, protein methylation ranks fourth among all PTMs in terms of number of modified proteins [7]. Interestingly, extensive crosstalk has been described between methylation and other types of

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PTMs and between adjacent methylation sites [8]. The methylation of lysine and arginine residues on non-histone proteins has been shown to significantly impact cell fate, as it plays a key role in signaling pathways governing cell proliferation and differentiation, whose dysregulation is associated with cancer [8]. Indeed, aberrant protein methylation mediates most of the important pathway abnormalities occurring in cancer and affects cellular processes such as chromatin remodeling, gene transcription, protein synthesis, signal transduction, and DNA repair [8,9]. Methylation is catalyzed by methyltransferases, whose overexpression has been observed in a variety of cancers and is associated with poor clinical outcomes [10]. Based on these findings, both preclinical and clinical trials of methyltransferase inhibitors are currently underway in cancer settings [11].

Several methyltransferases have been found implicated in chemoresistance, and recent studies indicated that their inhibition can reverse this process [12]. In particular, the lysine methyltransferase SMYD3 has been shown to be associated with several cancers [13].

SMYD3 belongs to the SMYD (SET and MYND Domain) lysine methyltransferase family, which consists of five members (SMYD1–5) [14]. A SET domain combined with adjacent cysteine-rich regions, the pre-SET (N-terminal) and post-SET (C-terminal) domains, is required for their methyltransferase activity and substrate recognition [15,16]. The MYND domain is involved in the interaction with partner proteins *via* PXLXP motifs [15]. The *SMYD3* gene was first described in a pioneering study that identified its encoded protein as a 428-amino acid histone methyltransferase with oncogenic functions in hepatocellular carcinoma (HCC) and colorectal cancer (CRC) [17]. The gene consists of 12 exons and spans 757.8 kb on chromosome 1q44. A variable number of tandem repeats polymorphism located in the E2F-1 binding site within the promoter region of *SMYD3* has been strongly linked to an increased risk of CRC, HCC, and breast cancer (BC) [18]. *SMYD3* was shown to be transcriptionally enhanced by E2F-1 through interaction at these E2F-1–binding elements, with the number of tandem repeats affecting its basal expression in some types of cancer cells [18]. The N-terminal region of SMYD3 has a composite structure consisting of α helices (α1–α7), β-strands (β1–β12), and long extended loops and contains the SET, MYND, and post-SET domains, while the C-terminal region includes mainly α helices (α8–α15) and has a tetratricopeptide repeat (TPR)-like domain that influences its interaction with other proteins and nuclear localization [19].

SMYD3 acts both in the nucleus and in the cytoplasm, methylating both histone and non-histone proteins. It shows ubiquitous tissue expression and has been found overexpressed in several cancers [20]. Importantly, it was identified as a direct player in cancer progression *in vivo* by using SMYD3-deficient mouse models of lung adenocarcinoma and pancreatic ductal adenocarcinoma [21]. Sarris et al. further generated SMYD3-knockout (KO) mice and a mouse model where SMYD3 is specifically overexpressed in the liver in order to demonstrate its oncogenic function in CRC and HCC *in vivo* models [22]. The authors showed that SMYD3 is required for chemically-induced CRC and HCC formation, suggesting that it may play a signal-dependent role in promoting cancer formation and development in response to genotoxic stress [22]. Besides its role as an activator of multiple oncogenic mechanisms that promote cancer cell growth, emerging pieces of evidence revealed that SMYD3 is involved in the regulation of DDR mechanisms in cancer cells exposed to genotoxic stress, reducing sensitivity to chemotherapeutics (CHTs) and supporting cell survival [20,23–26].

In light of the above, after providing a brief overview of the involvement of methyltransferases in cancer chemoresistance, here we focus on the molecular functions of SMYD3 that play a role in resistance to anticancer drugs and discuss the potential of targeting SMYD3 as a therapeutic strategy to promote cancer cell chemosensitization.

2. Methyltransferases in cancer drug resistance

Protein methyltransferases modify their substrates by transferring a methyl group from the methyl donor S-adenosylmethionine (SAM) to the target, *i.e.*, histones and non-histone proteins. Methylation changes the physicochemical properties of the substrate, affecting its stability and affinity for binding partners, and is a dynamic process, as methyl marks can be removed by demethylases [27]. Proteins that are targeted by methyltransferases can be classified into histones and non-histone proteins. Histone methylation is an epigenetic modification that alters chromatin structure and therefore regulates gene expression without changing the DNA sequence. Non-histone methylation also plays a crucial role in cell biology, as it affects protein function by modifying protein-protein interactions, protein stability, subcellular localization, and enzymatic activity. Aberrant histone and non-histone methylation due to methyltransferase dysregulation has been shown to contribute to tumor drug resistance [7,28,29], and these enzymes are now considered to be potential therapeutic targets [12]. Several methyltransferase inhibitors have been developed to date, some of which have been tested in clinical trials for different cancers and in some cases even approved for specific indications (Fig. 1) [30,31].

EZH2 is one of the most studied methyltransferases in cancer research, and various EZH2 inhibitors have been developed in the last decade [32]. EZH2 plays a role in drug resistance and has been found overexpressed in drug-resistant cancer cell lines. Specifically, its ablation has been shown to reverse cisplatin-resistance in human non-small-cell lung (NSCLC) and gastric (GC) cancer cells [33] and sensitize pancreatic cancer (PC) cells to doxorubicin and gemcitabine [34], suggesting that combining EZH2 inhibitors with standard chemotherapy may be an effective approach for these cancers. Moreover, curcumin has been reported to sensitize gemcitabine-resistant PC stem cells by inhibiting the EZH2-PVT1-c-myc axis. In particular, curcumin reduced the expression of the EZH2 subunit PRC2 and, consequently, of the long non-coding RNA PVT1, through which EZH2 modulates epithelial-mesenchymal transition and cancer stemness, two processes that are commonly associated with drug resistance [35]. In another study, it was shown that blocking EZH2 activity can overcome docetaxel resistance in prostate cancer cells. The authors found that EZH2 activity was essential for the increased population of cancer stem cells in docetaxel-resistant cell lines since it was required for the induction of NANOG, SOX2, and CD44 expression upon docetaxel treatment [36]. Additional reports indicated that EZH2 upregulation promotes cisplatin resistance in ovarian cancer (OvCa) cells. Specifically, increased EZH2 expression was due to c-myc-mediated suppression of the microRNA miR-137, which targets EZH2 mRNA, and clinical evidence of c-myc-miR-137-EZH2 pathway activation was observed in platinum drug-resistant OvCa patients [37]. EZH2 was also shown to activate the PI3K/AKT pathway in NSCLC, thereby promoting resistance to gefitinib [38], and its inhibition was reported to rescue the expression of SLFN11, a protein implicated in DNA repair, and sensitize cells to chemotherapy-induced DNA damage [39]. In addition, pharmacological inhibition of EZH2 was found to enhance apoptosis induced by DNA-damaging agents in multiple myeloma cells by reducing the increase in H3K27me3 levels caused by these agents and further intensified DNA damage [40].

EZH2 inhibitors have been tested in several clinical trials in recent years, also in combination with DNA-damaging agents [41]. The first FDA-approved EZH2 inhibitor, called tazemetostat, is now indicated for selected patients with epithelioid sarcoma or follicular lymphoma and is currently being evaluated in a phase III clinical trial in combination with doxorubicin for the treatment of advanced epithelioid sarcoma (NCT04204941) [42]. In addition, tazemetostat has been administrated together with the R–CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) without increased toxicity (NCT02889523) [43,44]. Further investigations are needed to confirm the encouraging preliminary data obtained with this approach. Another EZH2 inhibitor, called CPI-0209, is also being studied in a phase I/II

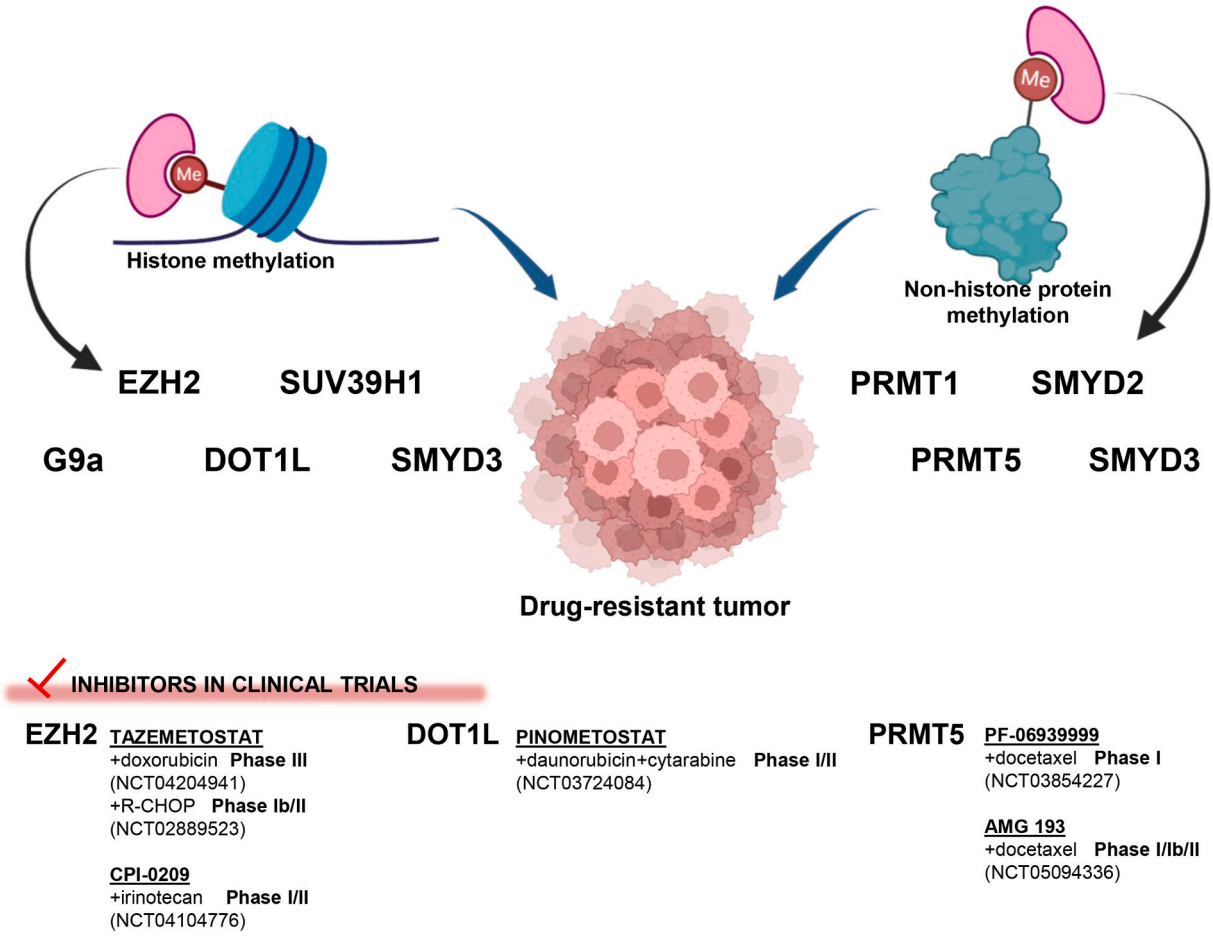

Fig. 1. Overview of the protein methyltransferases that have been found involved in cancer drug resistance. These enzymes act by methylating histones and/or non-histone proteins. Inhibitors of these methyltransferases that have been tested in clinical trials in combination with chemotherapeutics are also depicted. Created with BioRender.com.

clinical trial as a monotherapy and in combination with irinotecan in patients with advanced tumors (NCT04104776) [45].

G9a and SUV39H1 are H3K9 methyltransferases that have been found overexpressed in drug-resistant cancer cells and whose inhibition enhances cancer chemosensitivity [46]. While G9a has been shown to play a role in head and neck squamous cell carcinoma (HNSCC) cisplatin resistance [47], SUV39H1 has been reported to be responsible for CRC resistance to 5-fluorouracil, and its inhibition with the specific compound F5446 impaired the expression of genes involved in DNA replication and cell cycle [48]. It has been recently found that G9a and EZH2 interact and cooperate to promote NSCLC drug resistance, and targeting both methyltransferases with the dual inhibitor SU08 overcame resistance to therapeutic drugs by modulating the SMAD4/ERK/c-myc signaling axis [49].

The methyltransferase DOT1L has also been shown to be linked to chemoresistance. Targeting DOT1L by miR-133b reduced CRC chemoresistance and stemness by suppressing of H3K79 di-methylation of stemness genes [50]. Moreover, Liu et al. found that DOT1L is co-recruited with the transcription factor C/EBPβ to multiple drug-resistance genes in OvCa cells, where it enables chromatin accessibility by methylating H3K79 [51]. The use of the DOT1L inhibitor pinometostat with standard chemotherapy in patients with newly diagnosed acute myeloid leukemia and *MLL* gene rearrangement is currently being evaluated in a phase I/II clinical trial (NCT03724084) [52].

In addition to the above-mentioned methyltransferases, which are linked to epigenetic dynamics, other methyltransferases have been shown to be responsible for the methylation of proteins involved in DDR and therefore in drug resistance mechanisms (Fig. 1). Protein arginine methyltransferases (PRMTs) have been found to directly methylate DDR factors to regulate their functions [53]. Overexpression of these enzymes has been observed in several types of cancers, and growing evidence highlighted the potential clinical implications of PRMT inhibitors in decreasing cancer drug resistance [54]. PRMT1 plays an important role as a DDR regulator by methylating several proteins, including MRE11, BRCA1, 53BP1, DNA polymerase β, FEN1, APE1, and hnRNPUL1 [55–61]. Interestingly, PRMT1-dependent BRCA1 methylation has been shown to trigger BRCA1 activity and promote efficient DNA repair and apoptosis inhibition, resulting in radioresistance [62]. Furthermore, PRMT1 targets both MRE11 and 53BP1, which are critical for the choice of the DNA repair pathway: MRE11 promotes homologous recombination (HR) by initiating DNA end resection, while 53BP1 favors the non-homologous end-joining (NHEJ) pathway by inhibiting resection of DNA breaks [63]. This suggests that targeting PRMT1 may be an effective approach to enhance cancer cell chemosensitivity. PRMT5 also acts by methylating several DDR proteins, including 53BP1, FEN1, RAD9, RUVBL1, and TDP1 [53]. A phase I study of the PRMT5 inhibitor PF-06939999 together with docetaxel in NSCLC patients showed a tolerable safety profile and clinical response, confirming the potential of inhibiting this methyltransferase for combination therapy strategies (NCT03854227) [64]. A first-in-human study of another PRMT5 inhibitor, AMG 193, in combination with docetaxel, is currently ongoing (NCT05094336) [65].

Among SMYD methyltransferases, SMYD2 has been shown to

contribute to cancer drug resistance. It catalyzes the methylation of p53, a crucial protein involved in DDR [66]. Indeed, SMYD2 inhibition with the specific inhibitor BAY-598 enhanced cell sensitivity to cisplatin in NSCLC through apoptosis induction mediated by the activation of the p53 pathway [67]. Furthermore, blocking SMYD2 was recently shown to sensitize NSCLC cells to doxorubicin by inhibiting the NFκB and JAK-STAT signaling pathway [68]. In recent years, compelling evidence has also been gathered on the major role played by the methyltransferase SMYD3 in maintaining genome integrity in gastrointestinal (GI) cancer, BC, and endometrial cancer (EC) cells [20,23–26]. SMYD3 has been described as a cell cycle regulator that enables cancer cells to bypass signals of cell cycle arrest, thus promoting unlimited proliferation [20]. Recent findings further elucidated its oncogenic role, revealing that SMYD3 actively participates in the repair of damaged DNA in cancer cells, thereby facilitating uninterrupted cell division and contributing to drug resistance (Fig. 1) [23–26].

3. A computational approach to cluster potential SMYD3 interactors involved in DNA repair

Given the wealth of data supporting the involvement of SMYD3 in cancer development, an *in silico* analysis was recently performed by our group to identify potential SMYD3 interactors. Our approach involved screening the human proteome with a library of rare tripeptides (named P-tripeptides) that had been previously tested for their binding affinity to SMYD3. These potential SMYD3-interacting proteins (named P-proteins) were clustered based on their involvement in cancer hallmarks by selecting pertinent pathways in the Reactome database [69]. This analysis revealed a significant enrichment of P-proteins implicated in the "genome instability & mutation" cancer hallmark and included in the "DNA repair" Reactome cluster (Reactome ID: R-HSA-73894.5), which was one of the pathways with the highest percentage of identified P-proteins (46.8 %, 147/314) [69]. This Reactome cluster includes human DNA repair genes that were first reviewed and classified by Wood et al. in 2001 [70] and is being continuously updated [71–73]. These genes are grouped into seven main DNA repair mechanisms, *i.e.*, DNA damage bypass (Reactome ID: R-HSA-73893.3), DNA damage reversal (Reactome ID: R-HSA-73942.4), base excision repair (BER) (Reactome ID: R-HSA-73884.4), nucleotide excision repair (NER) (Reactome ID: R-HSA-5696398.4), mismatch repair (MMR) (Reactome ID: R-HSA-5358508.3), DNA double-strand break (DSB) repair (Reactome ID: R-HSA-5693532.5), and interstrand crosslink (ICL) repair *via* the Fanconi anemia (FA) pathway (Reactome ID: R-HSA-6783310.6) [74].

DNA damage bypass is a mechanism that does not remove the damage but allows translesion DNA synthesis (TLS) using a damaged template strand, thereby enabling cells to complete DNA replication and postpone repair until after cell division. The DNA polymerases involved in TLS are error-prone, often causing base substitutions and/or small insertions and deletions [75]. DNA damage reversal targets a narrow range of base modifications, removing modifying groups to restore DNA bases to their original state [76]. BER is an error-free pathway that corrects DNA damage resulting from oxidation, deamination, and alkylation, which cause minimal distortion to the DNA helix structure. It involves DNA glycosylases that cleave a wide array of damaged bases, producing an abasic site, which is then processed by DNA endonucleases, polymerases, and ligases, depending on the cell cycle stage, the specific DNA glycosylase involved, and the presence of additional damage [77]. The NER pathway removes bulky lesions that distort the DNA double helix. NER proteins promote the excision of the oligonucleotide containing the lesion, followed by gap-filling DNA synthesis and ligation of the repaired DNA [78]. MMR proteins identify mismatched base pairs or small insertion/deletion loops during DNA replication. They correct these errors by excising the mismatched nucleotides from the newly synthesized DNA strand, ensuring that the template strand remains intact [79]. DSB repair is involved in the restoration of breaks that affect both strands of the DNA helix and can occur by two major mechanisms in mammalian cells, the highly accurate HR repair and the error-prone NHEJ pathway [80]. ICL repair enables the formation of covalent bonds between DNA strands, hindering replication fork progression. FA proteins repair ICLs by unhooking them from one strand, thereby allowing TLS to bypass the unhooked ICL. This results in two replicated DNA molecules: one with a DSB, which triggers DSB repair, and another with a bulky unhooked ICL, which is removed *via* NER [81]. Most of these mechanisms share proteins that can play a role in the activation of different pathways for various types of DNA damage.

Based on the above, the P-proteins identified by our group can be subclustered into specific DNA repair pathways, revealing that the DNA damage bypass, FA, NER, and DSB repair pathway subclusters include the highest percentage of P-proteins (52.08 %, 50 %, 46.36 %, and 46.05 % respectively), followed by the MMR (40 %), BER (27.39 %), and DNA damage reversal (25 %) pathways (Table 1). Another interesting aspect of this analysis is the number of P-proteins that contain various different P-tripeptides in each Reactome subcluster: 6 P-proteins with at least four different P-tripeptides are included in the DSB repair pathway, 4 in the NER pathway, 2 in the DNA damage bypass and FA pathways, and 1 in the DNA damage reversal and BER pathways, while the MMR pathway only comprises P-proteins with less than 4 P-tripeptides (Fig. 2) [69]. As indicated above, the DSB subcluster includes the HR and NHEJ mechanisms, which share several proteins that are key determinants of the DSB repair pathway choice. A detailed analysis of these two pathways shows that they are both enriched in P-proteins (41.80 % for HR and 41.18 % for NHEJ) (Table 2), 4 of which contain at least 4 P-tripeptides in each pathway (Fig. 3) [69]. These findings suggest that the interactions between SMYD3 and the identified P-proteins involved in the NHEJ and HR pathways warrant further investigation, together with an in-depth characterization of their activity and function in these processes.

4. Understanding the role played by SMYD3 in DNA repair pathways and cancer cell drug response

In the past decade, various reports investigated the effects of SMYD3 overexpression in cancer cells to get insights into the involvement of this methyltransferase in cancer development, with emerging evidence in GI tumors suggesting that SMYD3 may play a signal-dependent role in promoting cancer formation and development in response to genotoxic stress [22,82]. Based on the findings gathered from the *in silico* peptide screening described above, our group explored the function of SMYD3 in the maintenance of genome integrity by analyzing the cluster of potential SMYD3 interactors involved in DNA repair pathways [23]. The

Table 1
Quantitative analysis of the potential SMYD3 interactors (P-proteins) included in the "DNA repair" Reactome subclusters. P-proteins were originally identified *via* an *in silico* screening approach [69].

Reactome ID	Name	Total proteins	Total P-proteins	% of P-proteins on total proteins
R-HSA-73893.3	DNA Damage Bypass	48	25	52.08
R-HSA-6783310.6	Fanconi Anemia Pathway	38	19	50
R-HSA-5696398.4	Nucleotide Excision Repair	110	51	46.36
R-HSA-5693532.5	DNA Double-Strand Break Repair	152	70	46.05
R-HSA-73884.4	Base Excision Repair	73	20	27.39
R-HSA-73942.4	DNA Damage Reversal	8	2	25

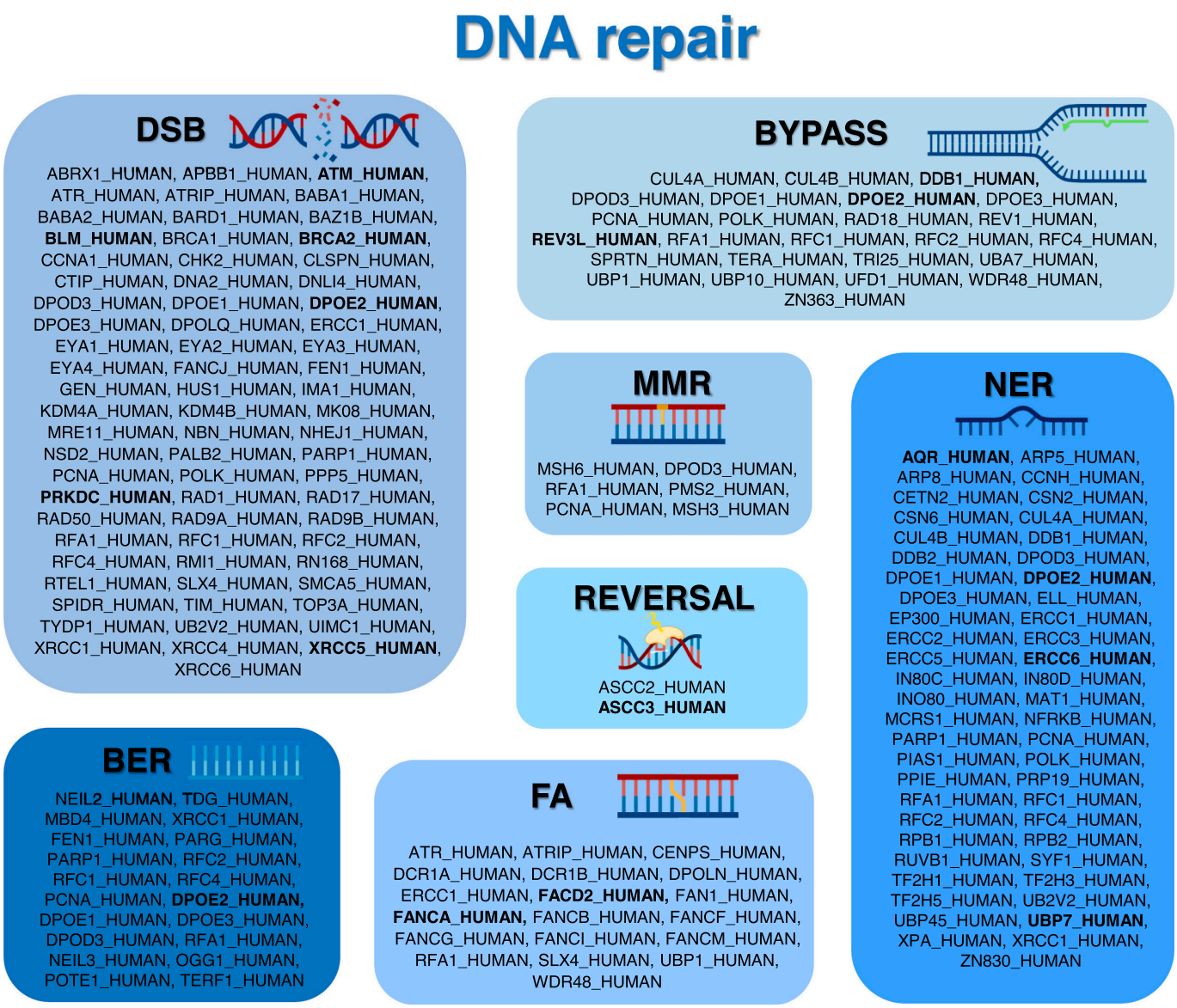

Fig. 2. Lists of the P-proteins identified in each DNA repair pathway (see Table 1). P-proteins with at least 4 P-tripeptides are reported in bold. Created with BioRender.com.

Table 2
Quantitative analysis of the P-proteins included in the "DSB repair" Reactome subclusters. P-proteins were originally identified *via* an *in silico* screening approach [69].

Reactome ID	Name	Total proteins	Total P-proteins	% of P-proteins on total proteins
R-HSA-5693538.4	Homology Directed Repair	122	51	41.80
R-HSA-5693571.3	Nonhomologous End-Joining	51	21	41.18

best candidates identified in this cluster were BRCA2 and ATM, with 6 P-tripeptides each. The interaction of SMYD3 with ATM, BRCA2, and CHK2 (another P-protein acting downstream of ATM), which are all crucial sensors and effectors of HR, was validated and characterized both *in vitro* and *in cellulo* by pull-down and co-immunoprecipitation assays [23]. Moreover, *in vitro* competition assays performed by using purified tripeptides confirmed the direct involvement of the tripeptide motifs in the identified binding patterns, since they interfered with the interaction in a dose-dependent manner [23]. Further investigations also showed that SMYD3 phosphorylation by ATM facilitates the formation of ATM-CHK2-BRCA2 complexes during DDR, and this interaction propagates the HR cascade, promoting the recruitment of RAD51 to DSBs. Moreover, its enzymatic activity enables DSB resolution in cancer cells, thereby supporting cancer genome integrity (Fig. 4) [23]. These findings validated our *in silico* screening approach and highlighted the crucial function played by SMYD3 in HR repair in cancer cells.

Several studies support a major role for SMYD3 in promoting the propagation of cancer-related pathways by orchestrating protein interactions and functions [13,16,20]. A previous report demonstrated the involvement of SMYD3 in HR through its action as a transcriptional activator. In particular, Chen and colleagues showed that SMYD3 ablation made cancer cells more vulnerable to ionizing radiation (IR) stress and increased DNA damage. Indeed, silencing SMYD3 impaired HR repair and caused genomic instability at longer recovery times [83]. To get insight into the molecular mechanism by which SMYD3 mediates HR

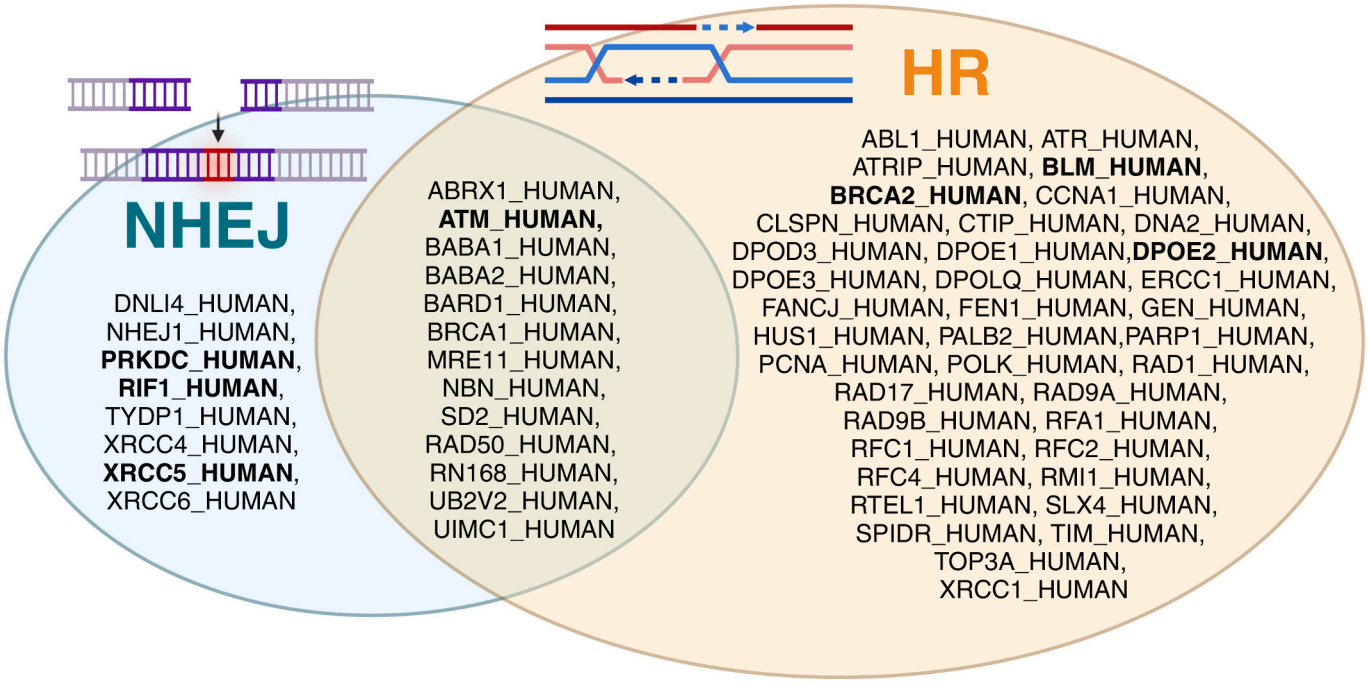

Fig. 3. Lists of the P-proteins identified in the "DSB repair" Reactome subclusters (HR and NHEJ pathways) (see Table 2). P-proteins with at least 4 P-tripeptides are reported in bold. Created with BioRender.com.

repair, the authors investigated SMYD3 epigenetic regulation of HR genes and found that it occurs through histone H3K4 methylation at target gene promoters, thus highlighting a major epigenetic role for SMYD3 (Fig. 4) [83].

In order to get a broader picture of SMYD3 involvement in DNA repair mechanisms, our group characterized its interaction with other players that are implicated in cancer processes by directly or indirectly mediating DNA damage. AMPK and mTOR were identified as novel SMYD3 interactors by the *in silico* screening described above and clustered in the "deregulating cellular energetics" and "avoiding immune destruction" cancer hallmarks, respectively. The interaction of SMYD3 with these two P-proteins was subsequently validated by co-immunoprecipitation assays in several GI cancer cell lines, supporting the involvement of SMYD3 in GI cancer-related metabolism [69]. Intriguingly, the AMPK and mTOR cascades are crucial signaling pathways triggered in response to stress events, and crosstalk between these two pathways upon DNA damage results in a pro-survival response mediated by AMPK activation, which negatively regulates mTOR. This in turn promotes cell cycle progression delay or arrest, allowing cancer cells to undergo DNA repair [84]. Molecular characterization of GI cancer and BC cells recently confirmed that SMYD3 is part of a multi-protein DDR complex that includes AMPK and mTOR. Specifically, upon exposure to the DSB-inducing agent neocarzinostatin, pharmacological inhibition of SMYD3 suppressed AMPK cascade activation and thereby promoted the mTOR pathway. Moreover, SMYD3 was shown to methylate AMPK at the evolutionarily conserved residues K411 and K424. These data revealed that SMYD3 is implicated in the modulation of the balance between AMPK and mTOR signaling during the response of cancer cells to DNA damage (Fig. 4) [24].

The emerging role of the SMYD3 methyltransferase in maintaining cancer cell genomic stability by regulating DDR *via* HR repair suggests that its activity may be involved in drug resistance, as described for other methyltransferases. Our group conducted an in-depth study of SMYD3 activity in cancer response to chemotherapy in resistant and SMYD3-KO CRC models [26]. The analysis of an oxaliplatin-resistant CRC cell line and patients' residual gastric or rectal tumors that were resected after neoadjuvant therapy revealed increased SMYD3 protein levels in resistant samples. Consistently, SMYD3-KO CRC cells and xenograft mice models showed reduced cancer cell resistance to CHTs when SMYD3 was genetically ablated. Exogenous expression of the wild-type protein, but not the catalytically inactive form, restored the resistant phenotype, supporting the hypothesis that SMYD3 activity mediates cancer drug response [26]. Further investigations on the underlying molecular mechanisms revealed that SMYD3 was essential for the resolution of CHT-induced DSBs, which are primarily recognized and repaired by the HR pathway [85]. Specifically, SMYD3 was shown to methylate the upstream sensor ATM and regulate the activation of the CHT-induced ATM-CHK2-p53 cascade, thereby promoting efficient DSB restoration *via* HR and contributing to cancer chemoresistance (Fig. 4) [26].

In parallel, Huang and colleagues investigated the pivotal oncogenic role of SMYD3 in the progression of EC, describing its activity in mediating NHEJ [25]. The authors found that SMYD3 protein levels increased upon IR or CHT and that SMYD3 was recruited to DNA damage sites through a PARP1-dependent mechanism. This study revealed that SMYD3 could interact with the LIG4/XRCC4/XLF complex upon IR/CHT treatment and facilitated NHEJ repair by methylating LIG4, thereby influencing the recruitment of the complex at damaged sites (Fig. 4) [25]. These data contributed to a comprehensive understanding of SMYD3 involvement in DNA repair, which is increasingly being characterized for both DSB repair mechanisms and in various types of cancers. Notably, LIG4, XRCC4, and XLF are all P-proteins as well, as they contain at least one P-tripeptide, and are included in the NHEJ Reactome cluster (Fig. 3, UniProt entry names: DNL14_HUMAN; XRCC4_HUMAN; NHEJ1_HUMAN), which further validates our *in silico* methodology for the identification of SMYD3 interactors.

Furthermore, we recently widened this scenario by exploring the interaction between SMYD3 and specific P-proteins identified in our screening and involved in other cancer hallmark pathways, as these represent pro-survival mechanisms that can promote drug resistance in cancer cells [69]. We confirmed the interaction between SMYD3 and RPB1 (POLR2A), one of the first identified SMYD3 partners [86], in GI cancer cell lines by co-immunoprecipitation assays [69]. RPB1 plays a crucial role in several cancer hallmarks, including "enabling replicative

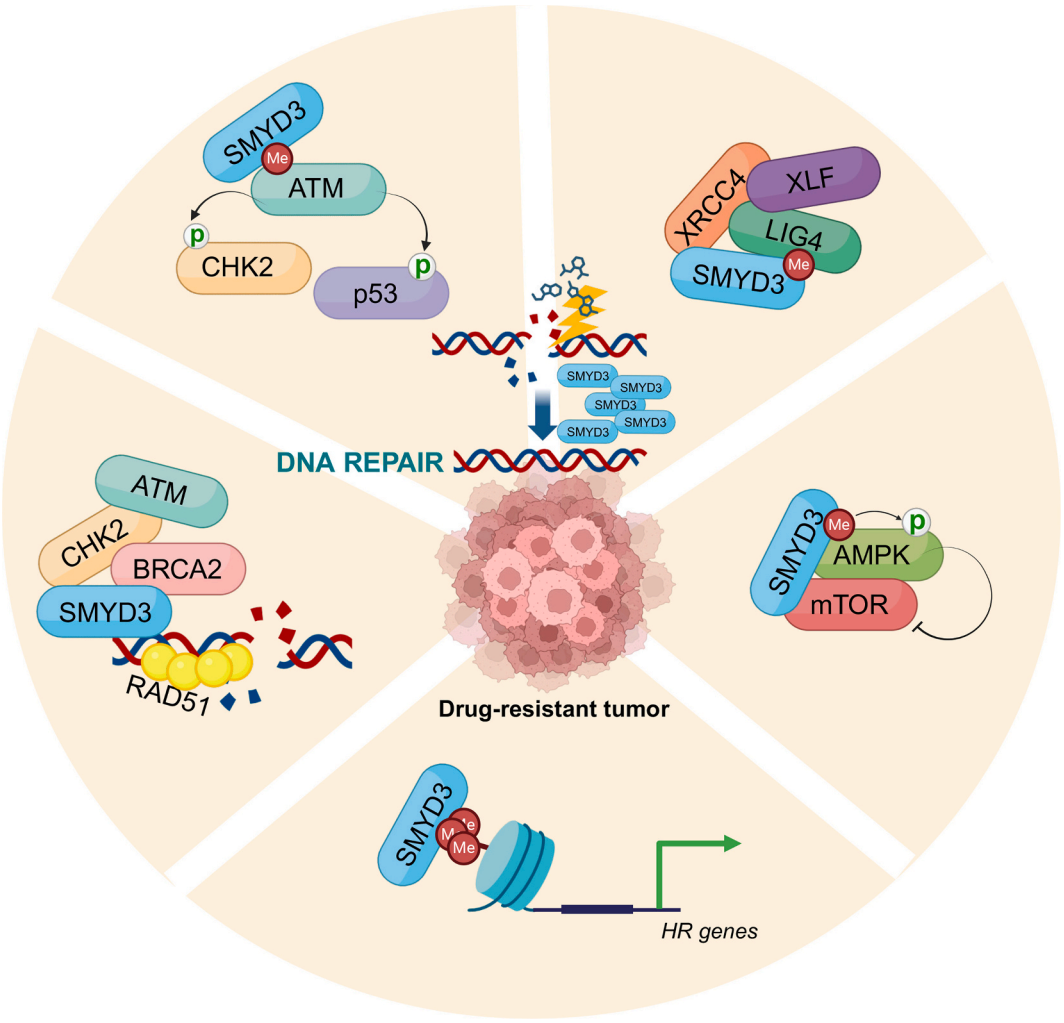

Fig. 4. Overview of the mechanisms by which SMYD3 promotes DNA repair. Cancer cells overexpressing SMYD3 are able to efficiently repair chemotherapy-induced DNA damage, leading to the acquisition of drug resistance. In these cells, SMYD3 supports DNA repair by interacting with and/or methylating both histones and DNA damage response (DDR) proteins. HR = homologous recombination. Created with BioRender.com.

immortality", "genome instability", and "sustaining proliferative signaling". Additionally, AKT1 and HSP90, which have been found to interact with SMYD3 [87,88], are involved in the "tumor-promoting inflammation" and "resisting cell death" cancer hallmarks, respectively [69], while another known SMYD3 interactor, VGFR1, has been implicated in the "inducing angiogenesis" cancer hallmark [89]. Moreover, we validated novel SMYD3 interactors involved in other cancer hallmarks. In particular, co-immunoprecipitation assays revealed that SMYD3 interacts with BLM, MET, and p130, which play a role in the "enabling replicative immortality", "activating invasion and metastasis", and "evading growth suppressors" cancer hallmarks, respectively [69,90]. Each of these identified interactors has been shown to mediate drug resistance in cancer cells [91–93]. This broader picture of cancer-related processes involving SMYD3 suggests that blocking its activity may co-target multiple cancer hallmarks, offering a promising strategy to overcome drug resistance and improve patient outcomes.

5. SMYD3 inhibitors in combined therapies to counteract cancer drug resistance

Altogether, the findings described above provided new insights into the role of SMYD3 in DNA repair in cancer settings, contributing to a comprehensive understanding of its involvement in drug resistance and paving the way for new approaches in cancer therapy. Indeed, they highlighted the potential of targeting SMYD3 to sensitize cancer cells to conventional therapy.

Wang and colleagues first revealed an association between SMYD3 and cancer drug resistance, showing that SMYD3 knockdown with small interfering RNAs increased cisplatin sensitivity in BC cells [94]. Another report detected SMYD3 overexpression in cisplatin-resistant NSCLC tissues and cell lines and confirmed that SMYD3 knockdown in resistant cell lines, both *in vitro* and in a xenograft mice model, increased cisplatin sensitivity, while its overexpression in cancer cells expressing low SMYD3 levels promoted resistance [95].

Consistent with these results, various studies showed that pharmacological interventions targeting SMYD3 enhance the responsiveness of cancer cells to clinically approved anticancer agents. These studies took advantage of some of the various SMYD3 inhibitors (SMYD3is) developed in the last few years as a result of the growing evidence supporting a major role for SMYD3 in oncogenic processes. BCI-121 was the first substrate-competitive SMYD3i described to impair histone methylation and SMYD3 recruitment at promoter sites, thereby inhibiting cancer cell growth by inducing S-phase arrest [96]. It was later shown to prevent epithelial-mesenchymal transition, tumor invasion, and metastasis [97–99]. The benzodiazepine-based SMYD3i BAY-6035 also binds to the substrate-binding pocket of the enzyme, showing specific inhibition of SMYD3-mediated MAP3K2 methylation [100]. GSK2807 is a SAM-competitive inhibitor that exhibited high selectivity for SMYD3.

Neither BAY-6035 nor GSK2870 have been tested so far in cellular models. Three SMYD3is developed by Epizyme (EPZ031686, EPZ030456, and EPZ028862) are potent nanomolar compounds that inhibit both the substrate- and SAM-binding pockets of the enzyme [101,102]. Another substrate-competitive inhibitor with a high binding affinity for SMYD3, named Inhibitor-4, showed the ability to reduce the viability of BC, CRC, and lung carcinoma cells [103,104]. Recently, a novel class of compounds that can inhibit SMYD3 with a covalent mechanism of action has been developed. Specifically, Compound 29 exhibited high inhibition potency and antiproliferative activity in 3D cell cultures [105]. In addition, we identified a novel covalent SMYD3i, named EM127, which forms a stable complex with the enzyme, providing potent inhibition of its enzymatic activity and longer-lasting effects [106].

Our group first described the effect of inhibiting SMYD3 to enhance sensitivity to anticancer therapies by focusing on a synthetic lethality approach involving PARP inhibitors (PARPis) [23]. In general, strategies based on synthetic lethality operate on the premise that a mutation in a cancer gene often introduces a novel vulnerability that can be targeted therapeutically, and that the combination of two genetic defects can be lethal, while each alteration alone is not, due to the compensatory or partially redundant functions of the targeted genes. As a result, the clinical effect of drugs targeting these genes individually is limited, but their impact is significantly enhanced when used in combination [107]. PARPi treatments have been tested in clinical trials for various types of GI cancers, often in combination with radio- and chemotherapy [108,109], and have been approved by the FDA for several cancers harboring *BRCA1/2* pathogenic variants or other markers of HR repair deficiency, including OvCa, BC, PC, and prostate cancer [110].

The molecular mechanism underlying this approach is that PARP1 is a crucial player in the repair of single-strand breaks (SSB) *via* the BER pathway. Upon PARP inhibition, SSBs progress to DSBs, which are most effectively repaired by HR. In HR-deficient cells, the repair process is compromised, thereby causing vulnerable cells to undergo apoptosis.

Our group focused on a subset of tumors that are HR-proficient and overexpress SMYD3, which we considered appropriate candidates for a new therapeutic strategy combining a SMYD3i and a PARPi. This approach was based on the hypothesis that the SMYD3is BCI-121 and EPZ031686 would inhibit HR repair and their combination with a PARPi would completely impair the ability of cancer cells to repair DNA damage, leading to cell death. As hypothesized, the combined treatment caused a cytotoxic effect in CRC, BC, and PC cells, showing that SMYD3 inhibition sensitized HR-proficient cancer cells to the PARPi, thereby extending the potential of using PARPis to a fraction of human tumors determined to be eligible for this therapeutic approach [23]. Furthermore, this combination strategy may be helpful to overcome PARPi resistance, which is experienced by most patients due to the restoration of HR repair, resulting in a stronger and more durable therapeutic effect.

The potential use of SMYD3is to enhance tumor sensitivity and overcome acquired resistance to various CHTs is also supported by other reports. Based on the observation that SMYD3 can methylate RNF113A, a protein associated with alkylation damage repair, Lukinovic and colleagues focused on alkylation-based therapies in small-cell lung cancer (SCLC) [111]. Since methylation by SMYD3 was found to regulate RNF113A phosphorylation levels, thereby modulating its activity, and abnormal regulation of RNF113A was shown to lead to the development of therapeutic resistance, the authors examined the effect of SMYD3 ablation on cancer response to alkylation-based treatments. Based on their findings, SMYD3 depletion or inhibition with EPZ031686 had a synergistic effect with cyclophosphamide in SCLC mouse models and patient-derived SCLC xenografts [111].

In the aforementioned work by Huang and colleagues, pharmacological inhibition of SMYD3 was found to enhance the response of EC cells to radiotherapy. Specifically, the combination of the SMYD3i BCI-121 with radiation was evaluated both *in vitro* and in a xenograft model, showing a significant synergistic effect and a marked reduction in tumor size. However, as discussed by the authors, BCI-121 requires high concentrations that may induce off-target effects, highlighting the need for novel and more efficient SMYD3is [25].

In this regard, our group recently investigated the effect of SMYD3 pharmacological inhibition on cancer chemoresistance. Based on our data, SMYD3 inhibition with EM127 reversed GI cancer and BC chemoresistance more effectively than BCI-121 with a 20-fold lower dosage [26]. Pre-treatment with EM127 showed a significant synergistic effect with CHTs and induced apoptosis in cancer cells cultured as monolayers or spheroids and in CRC preclinical models [26]. These findings further support that targeting SMYD3 may be an effective therapeutic strategy to overcome chemoresistance.

6. Dual role of DDR in healthy and tumor cells: harnessing the potential of targeting SMYD3 in cancer therapy

To better define the potential of inhibiting DDR-regulating factors, such as SMYD3 and other methyltransferases, for cancer treatment, it is essential to examine the opposite but interconnected roles of DNA repair in healthy and cancer cells. DNA damage occurs as a result of intrinsic or extrinsic agents. Healthy cells initiate DDR to prevent accumulated DNA lesions from causing irreversible harm, thereby protecting DNA integrity and fidelity [112]. Unrepaired or improperly repaired DNA can lead to genomic instability and mutations, which are hallmarks of cancer [112]. To prevent cancer, tumor suppression mechanisms involve DDR proteins known as caretakers and gatekeepers. Caretakers safeguard the genome from mutations, while gatekeepers trigger cell death or halt the cell cycle in precancerous cells [113]. Defects or mutations in DDR genes compromise this protective role, making cells more sensitive to DNA-damaging agents and promoting tumor development.

Likewise, DDR has a protective function also in cancer cells; however, in this pathological setting, it acquires an oncogenic role. On the one hand, it maintains cancer genome integrity and prevents the accumulation of endogenous DNA lesions caused by cellular metabolic processes and polymerase incorporation errors due to unlimited replication, thus supporting uncontrolled proliferation and disease progression. On the other hand, as described in this review, DDR pathways help cancer cells escape apoptosis and survive under exogenous stress, contributing to drug resistance. This dual role of DDR in healthy and cancer cells entails the need for a therapeutic approach that specifically targets cancer cells. Thus, an in-depth knowledge of the DDR pathways and the involved proteins is crucial for targeting cancer-specific DDR dependencies to preferentially kill cancer cells. In this context, methyltransferases, and specifically SMYD3, are promising candidates, because cancer cells often overexpress these enzymes, which increase the activity of the oncogenic-related pathways they regulate, including DDR.

Analyses of publicly available human cancer data from The Cancer Genome Atlas (TCGA), cBioPortal, and Catalogue of Somatic Mutations in Cancer (COSMIC) datasets showed that missense and loss-of-function *SMYD3* genetic variants were present in less than 2 % of tumor tissues from patients with BC, GC, CRC, PC, as well as uterine, prostate, and lung cancers [23,114]. Additionally, copy number amplifications were observed more frequently (approximately 10–19 %) in BC tissues, while a small fraction of other tumors exhibited copy number alterations [23,114]. Consistent with other studies, these analyses revealed increased SMYD3 mRNA levels in these cancer cohorts [23,114], indicating that in a wide range of tumor tissues, the primary alteration involving the *SMYD3* gene is mRNA overexpression [20,23]. This further supports the potential of SMYD3 inhibition in these settings. Another important observation is that SMYD3 homozygous KO mice do not exhibit significant phenotypic alterations [21,22,115,116], suggesting that pharmacological inhibition of SMYD3 as an anticancer strategy may be associated with limited off-target toxicity. In addition, specific testing to detect SMYD3 protein expression on patient biopsies could be integrated into histopathologic analysis to obtain insights for predicting outcomes and guiding personalized treatments. Indeed, using

SMYD3is to treat patients with SMYD3-overexpressing tumors would allow therapies to selectively target tumor cells while causing minimal damage to healthy cells that express basal SMYD3 levels. This strategy might also help to reduce CHT dose and timing, thereby limiting their toxicity, which is due to their ability to kill rapidly dividing cells without differentiating between malignant and healthy cells. Moreover, combining two DDR inhibitors (*e.g.*, a SMYD3i and a PARPi, as discussed above) in a synthetic lethality approach would further select target tumor cells and may achieve greater efficacy.

7. Conclusions

Drug resistance poses significant challenges to public health. This is particularly relevant in the context of cancer. It is thus crucial to understand the molecular mechanisms through which cancer develops resistance and identify the main players involved. Importantly, these may also be used as biomarkers, thereby helping to tailor treatments more effectively. Based on available data, combining drugs that target different pathways may provide more efficient therapeutic options to prevent chemoresistance. This will require in-depth studies to find the best combinations and dosing regimens, together with the major challenge of developing novel drugs that improve efficacy while reducing side effects.

In this scenario, the findings summarized in this review highlight the potential of introducing SMYD3is in combined therapies aimed at overcoming cancer cell chemoresistance, suggesting that future strategies to mitigate DDR-based adaptive feedback resistance in cancer patients may benefit from the use of these compounds. Specifically, combining a SMYD3i with anticancer agents, including drugs that are already approved for clinical use, may represent an effective personalized approach for resistant cancers and reduce the required therapeutic dose and administration frequency, significantly improving patient health outcomes. This strategy may also expand the cohort of eligible patients to include those who are not currently considered for existing therapies due to their genetic and molecular profiles, thus allowing clinicians to target a broader range of cancer types. Additionally, administering SMYD3is during initial tumor response to treatment might prevent tumor evolution and resistance, thereby increasing patient survival.

The next step in the journey of these compounds from the laboratory to the clinic is a thorough investigation of their safety and efficacy in preclinical and clinical trials, while another important aspect to be explored in future studies involves the still unclear upstream molecular events that govern SMYD3 overexpression and activation in drug-resistant cancers. The elucidation of these mechanisms may further aid in the development of combined strategies to enhance chemosensitivity.

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Author statement

Paola Sanese: Conceptualization, Methodology, Writing- Original draft preparation, Writing- review and editing, investigation, funding acquisition. **Candida Fasano**: methodology, funding acquisition. **Martina Lepore Signorile**: investigation, visualization. **Katia De Marco**: investigation, visualization. **Giovanna Forte**: methodology, visualization. **Vittoria Disciglio**: visualization, funding acquisition. **Valentina Grossi**: visualization, validation, funding acquisition. **Cristiano Simone**: supervision, project administration, funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests

Cristiano Simone: Inventor of international patent, application n. PCT/IB2023/060121. Filing date 13.10.2022. Publication date 18/04/2024, n. WO2024/079603. Patent applicant: Istituto di Ricovero e Cura a Carattere Scientifico "Saverio De Bellis". Title: “Pharmaceutical formulations with activity inhibiting histone methyltransferases for the treatment of neoplastic diseases”. All other authors declare no competing interests.

Data availability

I have shared the file with my raw data

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Appendix A. Supplementary data

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