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REVIEW

Targeting epigenetics using synthetic lethality in precision medicine

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Abstract
Technological breakthroughs in genomics have had a significant impact on clinical therapy for human diseases, allowing us to use patient genetic differences to guide medical care. The "synthetic lethal approach" leverages on cancer-specific genetic rewiring to deliver a therapeutic regimen that preferentially targets malignant cells while sparing normal cells. The utility of this system is evident in several recent studies, particularly in poor prognosis cancers with loss-of-function mutations that become "treatable" when two otherwise discrete and unrelated genes are targeted simultaneously. This review focuses on the chemotherapeutic targeting of epigenetic alterations in cancer cells and consolidates a network that outlines the interplay between epigenetic and genetic regulators in DNA damage repair. This network consists of numerous synergistically acting relationships that are druggable, even in recalcitrant triple-negative breast cancer. This collective knowledge points to the dawn of a new era of personalized medicine.

Keywords Synthetic lethality · Epigenetics · Precision medicine · Cancers · Gene network

Abbreviations

HR	Homologous recombination
NHEJ	Non-homologous end joining
MMEJ	Microhomology-mediated end joining
HDAC	Histone deacetylase
HDAC	Histone deacetylase inhibitor
DSB	Double-stranded DNA break
PARP	Poly (ADP-ribose) polymerase
PARPi	Poly (ADP-ribose) polymerase inhibitor
PRC	Polycomb repressive complex
miRNA	Micro-RNA
siRNA	Small interference-RNA
LncRNA	Long non-coding RNA
RNAi	RNA interference
H3K4	Histone H3 lysine 4
H3K4me	Methylated histone H3 lysine 4
H3K27me	Methylated histone H3 lysine 27
H3K36me	Methylated histone H3 lysine 36
SAHA	Suberoylanilide hydroxamic acid
PARylation	Poly ADP ribosylation

Introduction

Anti-cancer chemotherapy reached a critical juncture in recent years, with the realization that subtle genetic variations could be leveraged to create better and more targeted therapies, with improved patient care and fewer adverse effects. The advent of powerful genetic tools, such as next-generation sequencing, allowed for correlations between chemotherapeutic responses and specific genetic backgrounds. Chemotherapeutic agents to this point—developed more than 50 years ago—were first-generation drugs that preferentially targeted actively proliferating cells, which were presumed to be cancerous. This presumption was based on the knowledge that most normal somatic cells are predominantly quiescent, with the exception of progenitor cells at sites subjected to constant abrasion, such as cells in the skin, hair follicles, bone marrow, and digestive tracts, which require continual replacement. Consequently, these normal, highly proliferative regions are also targeted by anti-cancer drugs, leading to significant side effects for the patient.

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This awareness, along with the knowledge that the "one-size-fits-all" approach to cancer treatment was not universally beneficial [1, 2], led to more recent objectives toward personalized or precision medicine. This coincided with the advent of powerful genetic tools, such as next-generation sequencing, which provided opportunities to correlate chemotherapeutic responses with specific patient genetic backgrounds. Indeed, the identification of specific genetic polymorphisms in cancers were proposed to serve as not only prognostic or diagnostic markers, but as targets for cancer treatment regimens [3, 4]. Recognizing the power of this approach, various medical establishments initiated consorted efforts to streamline genomic acquisition toward precision medicine for chemotherapeutic success [5, 6].

One of the most significant discoveries in personalized medicine arose from the findings of oncogenic addiction. First proposed almost two decades ago [7], oncogenic addiction describes how tumors rely on cancer-specific, oncogenic proteins that arise from genetic instability events for their survival and growth. For example, in most patients with chronic myelogenous leukemia (CML; [8]), chromosomal translocation between chromosomes 9 and 22 leads to the formation of a new chromosome 22 (Philadelphia chromosome), which contains the BCR-ABL fusion gene [9]. Chromosomal translocations occur in response to numerous DNA double strand breaks (DSBs) that are misjoined rather than repaired, resulting in the formation of aberrant chromosomes. The later development of the Imatinib tyrosine kinase inhibitor against the BCR-ABL fusion product revolutionized the field, with significant improvement in patient responses and survival rates, raising the hope that protein kinase inhibitors would also act as "magic bullets" for other cancer types. However, aberrations deriving from chromosomal changes account for only a small fraction of malignancies [10–12], and alternative approaches are required for most patients.

The synthetic lethality approach in personalized medicine

About 100 years ago, the study of gene–gene interactions in budding yeasts and fruit flies revealed a phenomenon referred to as "synthetic lethality" [13], which described a loss of cell viability following the concurrent disruption of synergistically acting genes, but not either gene alone [13, 14]. The concept of synthetic lethality has since found applications in cancer therapy, taking advantage of the changes in cellular rewiring that occur in response to altered or mutated gene expression to invoke new vulnerabilities. Conceptually, the same addiction/dependency unique to cancer cells that presents through genetic rewiring can be leveraged to kill the cancer cells, posing minimal side effects to the normal cells that lack these rewired networks or mutations. This is best exemplified in BRCA1/BRCA2-deficient cells in ovarian and breast cancers. These BRCA-deficient cells are defective in homologous recombination (HR) and must rely on the less-stringent non-homologous end joining (NHEJ) for the repair of DNA DSBs. This dependency renders the cells susceptible to inhibitors against poly (ADP-ribose) polymerase (PARP), a nuclear enzyme that aids in the detection of DNA damage and is involved in end-joining, including NHEJ [15, 16]. The loss of both genes results in an accumulation of replication defects and causes cell death. The successes that ensued from PARPi in BRCA-deficient cancer cells led to the search for other targeted approaches against a range of gain-of-function and loss-of-function mutations hitherto considered to be undruggable [14].

There are three key scenarios where the synthetic lethal approach can be leveraged (Fig. 1): (1) where two genes are exclusive, key members of an essential protein complex. For example, BRG1 and BRM are two mutually exclusive catalytic subunits of the chromatin remodeling switch/sucrose non-fermentable (SWI/SNF) complex, which is increasingly implicated in cell survival in several cancer types [17, 18]. BRM and BRG1 are frequently inactivated in kidney, ovarian, and lung cancers, and a recent study shows that targeting BRG1 in BRM-deficient cells in lung cancer is synthetic lethal, reminiscent of the BRCA/PARP scenario in breast and ovarian cancers (Fig. 1a). (2) Where there is a dependency on a specific pathway for survival following an inactivating mutation that occurs in a parallel regulatory mechanism (Fig. 1b). For example, ataxia telangiectasia (ATM) and ataxia telangiectasia and Rad3-related (ATR) both transmit DNA damage signals to activate a checkpoint kinase [19, 20]. Loss-of-function mutations in ATM are commonly found in cancers, and predispose cells to uncontrolled growth [21]. Treatment of ATM-deficient cells with ATR inhibitors can lead to synthetic lethality in lung adenocarcinoma, gastric cancer and mantel cell lymphoma [22–24]. (3) Finally, where a repressor protein keeps an anti-survival pathway in check. For example, BAG1 keeps in check the route to MYC-induced apoptosis. Thus, its downregulation in conjunction with MYC overexpression would induce apoptosis (Fig. 1c) [25].

Yet, identifying which targets can be used in synthetic lethal combinations is not straightforward. There has been much effort invested into performing synthetic lethal screens using siRNA libraries to search for targetable factors. One example is TAK1/MAP3K7 kinase, which was identified through a siRNA-mediated screen for factors that, when downregulated, enhanced the potency of the topoisomerase I inhibitor, camptothecin. The downregulation of TAK1 resulted in breast cancer cell death in conjunction with the LMP-400 Top1 inhibitor [26]. However, screens are costly and can be technically challenging. Model organisms such

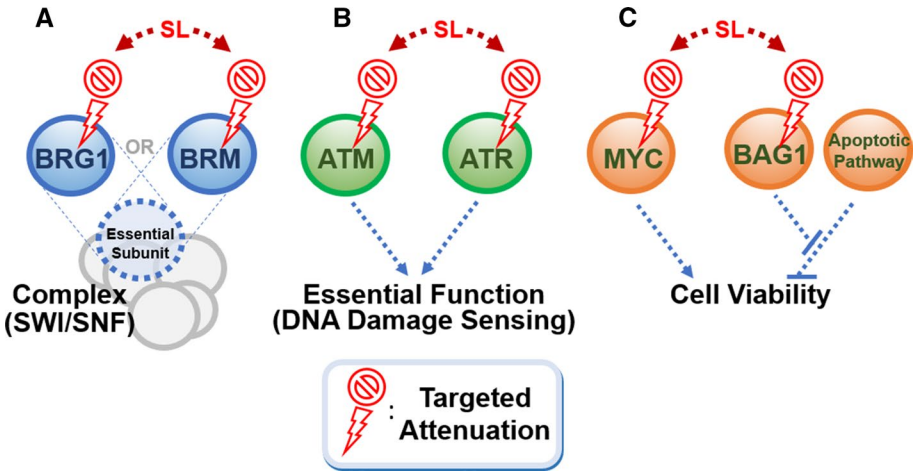

Fig. 1 Genetic interactions that can contribute to a synthetic lethal relationship. The concurrent inactivation of two factors in the genetic relationship can result in cumulative functional inactivation or cell death. **a** BRG1 and BRM are mutually exclusive subunits of a complex. **b** ATR and ATM act synergistically to sense DNA damage, an important process that maintains genomic stability in the cell. **c** The repressor protein BAG1 inhibits an anti-proliferative apoptotic mechanism that counteracts proliferation induced by the Myc oncoprotein

as yeast are also used as an alternative first-line screening option [27, 28]. Indeed, using the fission yeast model organism, we previously showed that vacuolar ATPase acts alongside the ABC drug-transporter multidrug resistance protein 1 (MDR1; also known as p-glycoprotein) to sensitize cells to doxorubicin, a topoisomerase II inhibitor [29, 30]. Doxorubicin also induces cell death when delivered with a histone deacetylase inhibitor in fission yeast [28]. Although DNA damage response pathways remain one of the most—if not the most—useful pathways for inducing synthetic lethality in cancer cells, recent findings point to leveraging the cooperation between epigenetic regulators of chromatin architecture and canonical cancer-related signaling mechanisms to induce cell death.

Epigenetic dysregulation in cancer

Epigenetic regulation involves genomic alterations that are independent of changes in DNA sequences [31, 32]. The genome can be epigenetically regulated through chemical modifications to the scaffolding histone proteins [33] and DNA nucleotide bases [34]; through altered nucleosomal spacing [35, 36]; and via post-translational regulation of transcribed templates, mediated by RNA interference (RNAi) mechanisms with non-coding small RNAs (e.g., microRNAs [miRNAs] or small interference-RNA [siRNA]) [37, 38]. Long non-coding RNA (LncRNA) can also affect the localization and activity of chromatin enzymatic complexes in conjunction with histone and DNA modifications [39–41]. These epigenetic regulations, in turn, affect DNA metabolic pathways such as gene transcription, chromosomal segregation mechanisms, and DNA replication, recombination, and the damage detection/repair [31, 33, 35].

Except when mutated, DNA sequences remain unchanged. In contrast, the epigenetic status can be remodeled in accordance with environmental cues and growth signals [42, 43], which are stably and faithfully maintained across cell generations [44–46]. This level of plasticity makes epigenetic regulation ideal to maintain developmental fate, as observed in dosage compensation, X-inactivation, and genomic imprinting [31]. Epigenetic dysregulation is thus often associated with or drives the development of human disease, particularly cancer, with different stages of oncogenesis liable to epigenetic control [47, 48]. Epigenetic abnormalities may, therefore, underlie cancer-specific phenotypes and represent targetable, molecular vulnerabilities for cancer therapy using the synthetic lethality approach.

Epigenetic aberrations caused by gene fusion (chromosomal translocation) can give rise to tumor-specific fusion products and resemble cancers with gain-of-function mutations that lead to oncogenic addiction. For instance, fusion between the transcriptional activation domain of NUP98 with the methylated histone H3 lysine 4 (H3K4)-binding domain of the H3K4 demethylase JARID1 underlies a subset of acute myeloid leukemia [49, 50], causing aberrant transcription of the homeobox genes that maintain stemness in bone marrow cells. Like many other fusion products and gain-of-function mutations, fusion events between epigenetic regulators are rare, and this has discouraged the pursuit of inhibitors for therapies against such aberrations. Yet, recurrent loss-of-function mutations in epigenetic regulators, particularly in histone modifiers and chromatin remodeling factors [51–57], have been useful in the stratification of tumors [58, 59] and employed in synthetic lethality

approaches to target cancer cell viability. Below, we will explore how chromatin remodeling and histone modification pathways have been targeted in the treatment of cancer using the synthetic lethality approach.

Epigenetic dysregulation as a basis for synthetic lethality

Chromatin remodeling

The chromatin structure—repeating nucleosome units of DNA wound around histone proteins—represents the first-line of defense against agents that threaten to undermine the integrity of DNA. Indeed, the loss of nucleosomal integrity leads to a substantial increase in chromosomal breaks [60, 61]. Yet, DNA sequences must be readily accessible to interact with protein machineries during replication, repair and recombination.

DNA damage can be caused by a range of exogenous (UV exposure, ionizing radiation, chemical exposure and cytotoxic drugs) and endogenous (errors in replication, spontaneous deamination, oxidation and methylation changes) factors, and the cell employs various processes to circumvent or repair damage. Chromatin remodeling complexes, for example, hydrolyze ATP to overcome the energy barrier to slide, reposition via disassembly, and replace histone octamers on the DNA template [35, 36]. The SWI/SNF complex is one of several conserved chromatin-modifying complexes that uses ATP hydrolysis to mobilize nucleosomes and remodel chromatin. Mutations in the SWI/SNF complex have been found in genomic studies in multiple cancers [62, 63]. First identified in budding yeast and subsequently shown to be conserved in human cells, the SWI/SNF complex hosts two mutually exclusive DNA-dependent ATPases: BRG1/SMARCA4 and Brahma/BRM/SMARCA2 [35, 36]. The loss of BRM or BRG1 is commonly found in kidney, ovarian, and lung cancers [63–66]. Recent ChIP-seq efforts revealed colocalization of BRM and BRG1 on overlapping set of genes in the TNFα–NFκB pathway. These genes are transcriptionally co-regulated by SWI/SNF factors [67], and are targeted by hypoxia-induced transcription factor [68] and growth factors [69]. BRM and BRG1 can also differentially interact with RB and p53, checkpoint proteins that regulate progression within the cell cycle [70, 71].

A recent unbiased shRNA screen in > 50 cancer cell lines showed that BRG1/SMARCA4-mutant cancer cells are highly sensitive to BRM/SMARCA2 depletion [18]. Indeed, in BRG1-deficient non-small cell lung cancer (NSCLC) cells, BRM depletion can attenuate cell growth [17]. BRG1 and BRM thus likely constitute mutually exclusive catalytic subunits of different sub-populations of the SWI/SNF complex required for essential cellular processes, such as transcription [67, 72] (Fig. 2).

The SWI/SNF complex also contains the AT-rich interactive domain 1A and 1B (ARID1A and ARID1B) subunit pair, which are also implicated in cancer. Like BRM and BRG1, ARID1A and ARID1B also seem to be alternatively expressed and mutually exclusive [73]. ARID1A is frequently mutated in cancers, with ~ 57% of ovarian clear cell carcinomas (OCCC) associated with ARID1A mutations [63, 74–76]. ARID1B, on the other hand, is associated with only minor perturbations to chromatin accessibility following its knockdown in colorectal cancer cells [77], and mutations have been detected in liver cancer, neuroblastoma, and melanoma [55, 78, 79]. There is also a report of the co-occurrence of ARID1A and ARID1B mutations in ovarian cancer [80]. Although ARID1B plays a less significant role in the SWI/SNF complex, it compensates for the absence of ARID1A function, and thus presents a specific vulnerability in cancers with ARID1A mutations [81]. Knocking down ARID1B in ARID1A-deficient cells increases chromatin

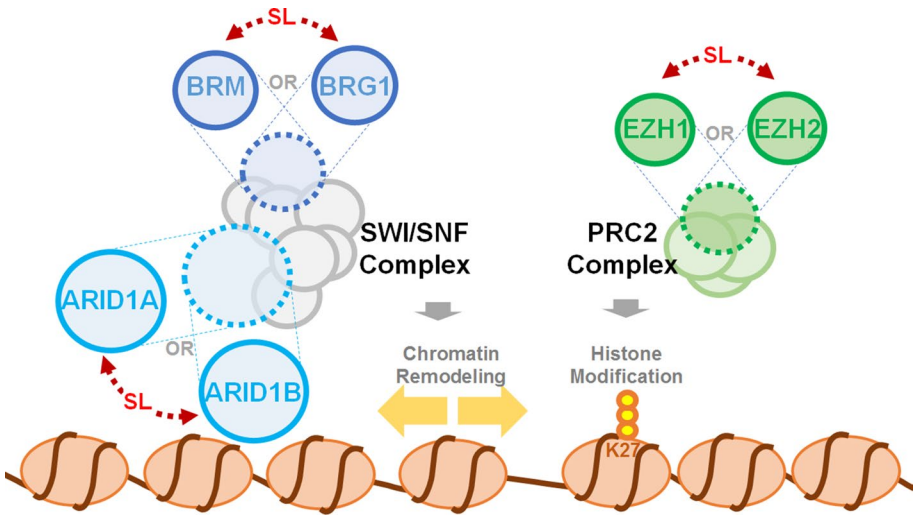

Fig. 2 Mutually exclusive 'sibling' subunits; for example, within SWI/SNF chromatin remodeling and polycomb repressive complex, PRC2. **a** SWI/SNF complex contains either one of the ATPase counterparts BRG1 or BRM; or **b** ARID1A or ARID1B. **c** PRC2 complex contains either one of the two enhancer of zeste homologues EZH1 or EZH2 catalytic subunits. Concurrent downregulation of both 'sibling' factors renders the complex inactive and results in synthetic lethality (SL)

accessibility, especially at enhancer sequences, to control the binding of transacting factors [77]. The mutually exclusive occurrence of ARID1A and ARID1B, therefore, results in specific "subtypes" of the SWI/SNF complex that control nucleosomal spacing, which is essential for the control of cellular events, such as the transcription of important genes; these subtypes of SWI/SNF complexes (containing different ARID1 subunits) could, therefore, be leveraged for synthetic lethal targeting (Fig. 2).

Modifying enzymes of histones

Histone H3 lysine 27 methylation

Enhancer of zeste homolog 2 (EZH2) is the catalytic subunit of the polycomb repressive complex 2 (PRC2), a histone-lysine *N*-methyl transferase that primarily trimethylates histone H3 at lysine 27 (H3 K27me) to silence developmental genes in metazoans [82]. Mutations in EZH2 have been detected in multiple cancers and are associated with poor prognosis, whereas mutations in the core components of the PRC2 (EED and SUZ12) are found in nerve sheath tumors [83–92]. Previous work has shown that inhibition of EZH2 activity and downregulation of EED and SUZ12 can counter tumor growth; this strongly suggests an oncogenic driver role for the PRC2 complex [93, 94], and EZH2 as a potential therapeutic target [93, 95–98]. Furthermore, the dual inhibition of EZH1 and EZH2—as mutually exclusive catalytic subunits of PRC2—offers greater anti-tumorigenicity than inhibiting EZH2 alone [99] (Fig. 2).

OCCC is an aggressive form of ovarian cancer that shows poor prognosis and is refractive to the canonical cisplatin-based chemotherapeutic regimens [100, 101]. Sequencing of OCCC revealed that up to 57% of tumors bear ARID1A mutations, and a shRNA-based screen further showed that inhibition of EZH2 can destabilize ARID1A-deficient OCCC by suppressing the PI3K-AKT pathway to reduce cell growth and induce apoptosis [76]. This synthetic lethal strategy advances the therapeutic hope surrounding this largely incurable cancer. The same approach of targeting EZH2 can be used in cancers that are deficient in other subunits of the SWI/SNF complex [102] (Fig. 2). For example, EZH2 inhibition can significantly increase the susceptibility of BRG1-deficient lung cancer cells to a topoisomerase II inhibitor [103].

H3K27me recruits a PRC1 complex comprising BMI1 (B cell specific, Moloney murine leukemia virus integration site 1). This subunit is implicated in stem cell renewal and may act as a cancer-initiating factor because of its telomerase-activating and senescence-suppressing activities. Recent work [104, 105] notes that the concurrent downregulation of BMI1 and EZH2 can be used against glioblastoma tumors, suggesting that PRC1 and PRC2 may not simply act sequentially in the same epistatic pathway, but are involved in some non-overlapping roles as part of a much more complicated network.

Histone H3 lysine 36 methylation

Histone H3 lysine 36 methylation (H3K36me) facilitates a wide range of cellular processes, including transcription and splicing, and recent studies have focused on the connection between this histone modification and the detection and repair of DNA damage [106, 107]. The histone methyltransferase SETD2, which trimethylates H3K36, is commonly mutated in cancer [57, 108–110], suggesting a tumor suppressor role for the protein [107]. It also has potential prognostic value in cancers like gastric cancer, renal cancer, and leukemia [111–113]. Targeting other loss-of-function mutations in association with a SETD2 mutation, while challenging, could be approached using synthetic lethality. Pfister et al. reported that H3K36me-deficient cancer cells and SETD2-attenuated xenografts show preferential susceptibility toward an inhibitor of the Wee1 kinase, which suppresses cyclin-dependent kinase (CDK). SETD2 disruption downregulates the RRM2 ribonucleotide reductase (RNR) subunit, which, when combined with Wee1 inhibition (activating CDK and repressing RRM2), causes cells to enter into and arrest in S-phase. Cells that linger in S-phase are induced to undergo apoptosis [114] (Fig. 3).

SETD2 also methylates other targets that affect cancer development; for example, the oncogenic signaling factor STAT1 [115] and tubulin for cytoskeleton remodeling [116, 117]. These findings add more complexity—but also opportunities—to exploit SETD2 inhibition in the synthetic lethal targeting of cancers.

Histone H2AX phosphorylation and other chromatin modulations in DNA damage response—PARP and BRCA at center stage

The formation of DNA DSBs is the most detrimental type of DNA damage that can threaten genomic stability and cell viability. Upon detection of a break, cells activate signal transduction via the phosphorylation of histone H2AX (γH2AX) primarily by two DNA damage checkpoint signaling kinases—ATM and ATR. γH2AX is detectable over a long stretch of chromatin encompassing the break site, and this is thought to amplify the damage signal and recruit DNA damage repair factors [118]. ATM and ATR exist synergistically, and their relationship can be exploited to induce synthetic lethality when following attenuation of other DNA damage repair pathway regulators, such as topoisomerase I and DNA polymerase δ [119–121].

Through chemical screens for γH2AX-interacting factors, several studies have identified that both 53BP1, a DSB repair

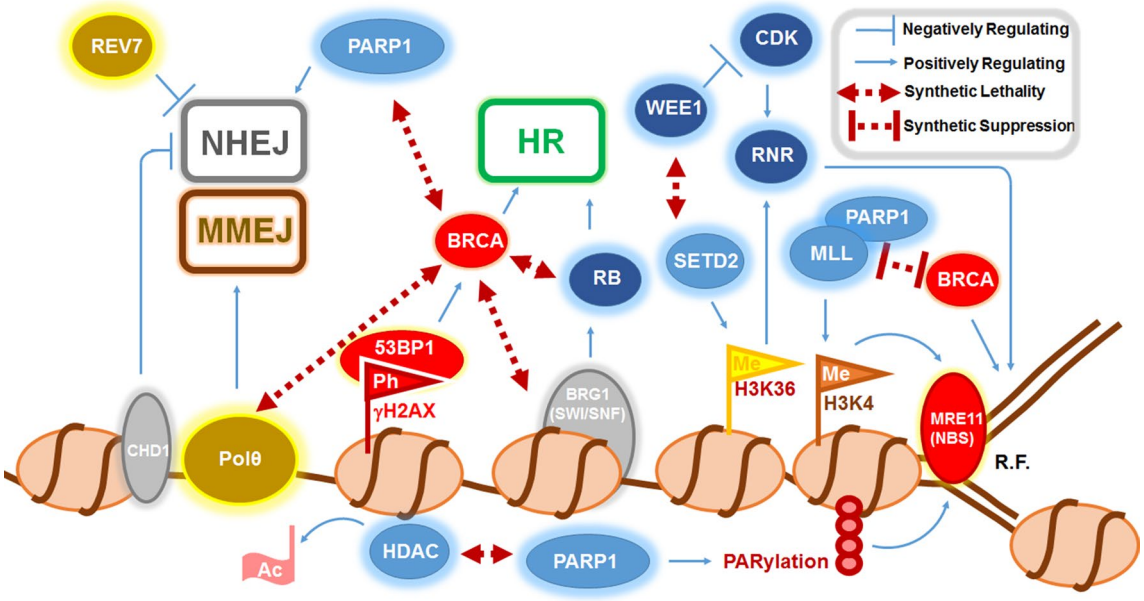

Fig. 3 The genetic–epigenetic interplay involved in cell cycle regulation and DNA damage repair. Cell cycle regulators are in dark blue (WEE1, CDK, RNR, RB), DNA repair factors in red (BRCA, 53BP1, MRE11, NBS); chromatin remodeling factors in grey (CHD1, BRG1), DNA polymerase-linked factors in yellow (Polθ and REV7), nucleosomes in beige, and chromatin-modifying proteins in light blue (HDAC, PARP1, SETD2, MLL) Flags indicate histone modifications that include phosphorylation (Ph) of histone H2AX (γH2AX), methylation (Me) of histone H3 lysine 4 (H3K4) and histone H3 lysine 36 (H3K36). Many regulators of homologous recombination repair (HR) and non-homologous end joining (NHEJ) and microhomology end joining (MMEJ) show synthetic lethal relationship with BRCA proteins. Abbreviations: *R.F.* replication fork; *Ac* acetyl group; *RNR* ribonucleotide reductase; *CDK* cyclin-dependent kinase; *RB* retinoblastoma protein; *HDAC* histone deacetylase; *PARP1* poly (ADP) ribose polymerase 1; *MLL* mixed lineage leukemia; *NBS* Nijmegen Breakage Syndrome; *Polθ* polymerase θ. Double-headed maroon lines indicate interconnecting factors that showed synthetic lethality or suppression upon downregulation. Blue lines represent an induction (positively regulating) and repression (negatively regulating)

factor, and MDC1, a signaling kinase substrate of ATM, interact with γH2AX via their BRCT domains [122–124]. These factors direct the recruitment of downstream DNA repair factors—BRCA1, Rad51 and the NBS component, Mre11—to regulate HR repair [125–128]. 53BP1, however, is also associated with NHEJ at specific chromosomal loci, and it appears that stabilization of 53BP1 is associated with an increase in NHEJ, which is observed when the chromatin remodeler CHD1 is downregulated in prostate cancer cells [129, 130] (Fig. 3).

Even though direct targeting of γH2AX is not commonly employed in cancer strategies, the loss of its downstream effector, BRCA, predisposes cells to become susceptible to PARPi, and this understanding exposes the prominent "Achilles' heel" in ovarian and breast cancers that could similarly be exploited for other cancers. Indeed, a similar synergistic relationship is apparent for Rad51C with PARPi [15, 16, 131]. Thus, the use of PARPi in situations with HR attenuation is currently actively translated for clinical treatments in combination with conventional DNA damaging chemotherapeutics [132–134].

Unfortunately, despite the success of PARPi in BRCA-deficient cells, numerous parallel signaling pathways in cancer cells can confer chemoresistance toward PARPi. For example, activation of a backup DNA end resection pathway can bypass the early step of Rad51 recruitment coordinated by BRCA proteins [135, 136]. One of these is the repression of Rad51 accumulation by REV7, a translesion synthesis (TLS) polymerase ζ component, which is recruited by γH2AX independently of polζ, but requires a physical interaction with 53BP1. Enhancing the role of REV7 downplays HR and, in combination with PARPi, results in synthetic lethality thus proposing the usefulness of an agonist of REV7 to effect synthetic lethal targeting in cancer cells [137, 138] (Fig. 3).

HR repair also acts in parallel with the error-prone microhomology-mediated end joining (MMEJ) or alternative NHEJ (alt-NHEJ, or alternative end joining [alt-EJ]) catalyzed by polymerase θ (Polθ), which is encoded by the POLQ gene [134, 139–144]. Polθ downregulation results in a heavier reliance on HR activity through the release of RAD51 protein, which can be sequestered upon physical binding to a RAD51-binding motif on Polθ [142]. Consistently, the loss of Polθ function in HR-deficient epithelial ovarian cancer cells and BRCA$^{-/-}$ mouse embryonic fibroblasts results in synthetic lethality [141, 142]. Translocation

of Polθ on chromatin can also facilitate the removal of single-stranded DNA-stabilizing Replication Protein A (RPA) complex from resected DSBs to expose stretches of homology for annealing and subsequent joining by MMEJ [145]. Thus, in cells with altered HR activity, MMEJ can overcome the effect of PARPi. However, the additional use of a Polθ inhibitor could potentially prevent this route of chemoresistance (Fig. 3).

Unexpectedly, the simultaneous loss of PARP and BRCA function can lead to synergistic viability [146, 147]. A considerable proportion of the damage found in BRCA-deficient cells is due to disrupted replication fork stability, which can be strengthened by preventing the recruitment of MRE11 to degrade nascent DNA at the fork. This is sufficient to restore viability to BRCA-deficient cells even in the presence of PARPi and platinum-based agents. However, MRE11 recruitment relies on several histone modifications at the replication fork, including H3K4me and poly ADP-ribosylation (PARylation) [148, 149]. Therefore, the downregulation of MLL3/4 H3K4 methyltransferase complex combined with PARPi treatment can suppress the growth defect in BRCA-deficient cells [146, 147] (Fig. 3). As a result, the sequence of inactivation of PARP and BRCA function is important, rendering either a synthetic lethal (BRCA inactivation before PARP inactivation) or rescue phenotype [147]. This observation profoundly impacts the chemotherapeutic application of PARPi. Although the inhibitor would be efficacious in a total loss-of-function $BRCA^{-/-}$ background, most BRCA mutations do not result in total loss of function. Thus, the pharmacokinetics of PARPi and the administration sequence must be carefully considered for the efficacy of this approach and, in some cases, BRCA function must be downregulated before that of PARP. Furthermore, the extent of functional impairment to BRCA genes is conceptually important, as a deletion that removes the bulk of its BRCT and DNA binding domains still retains HR competency. Thus, the type of BRCA mutation in patients may reliably predict the efficacy of PAPRi-based regimens [150].

Histone acetylation will also affect the efficacy of PARPi. In vitro experiments have shown that PARylation can occur preferentially on acetylated histones [149]. Histone acetyltransferases (HAT) and deacetylases (HDAC) play essential roles not only in gene transcription (e.g., in the transcription of the chief oncogene, MYC [151]), but also in DNA damage repair, and inhibitors of these enzymes can induce cancer cell death. HDAC inhibitors (HDACi), such as suberoylanilide hydroxamic acid (SAHA), are approved for chemotherapy against cutaneous lymphoma [152–154]. HDACi sensitize cancer cells toward many DNA damaging chemotherapeutic drugs, presumably by inducing an opened chromatin conformation to facilitate DNA access or by impeding cell cycle progression by disrupting DNA replication integrity. Thus, HDACi can act in a synthetic lethal manner with other DNA aberrations (drug-induced or otherwise) to induce apoptosis [28, 152, 155, 156]. Unexpectedly, HDACs were recently shown to positively regulate several key HR genes, and HDAC inhibition was found to dampen HR and enhance the susceptibility of triple-negative breast cancer cells towards PARPi [157] (Fig. 3). This insight and others highlight the need to fine-tune therapeutic applications of HDACi for specific patients and in other types of cancers.

There is a pressing need for a more comprehensive understanding of the interactive network between PARPi and BRCA genes and their role in anti-cancer therapy [158]. The links between epigenetic and genetic factors in governing pathway choices is complex and likely enriched by synergistically acting factors (Fig. 3). Collectively, these studies have highlighted the options for targeted therapy and offer potential treatment regimens for cancers, including triple-negative breast cancers, which have been problematic to treat up to now.

Concluding remarks

Technology that permits whole-genome interrogation brings forth the dawn of precision medicine, allowing links to be made between previously disconnected factors within the global gene network. This also excites the possibility of targeting the epigenetic mechanisms that affect the entire genome. First-generation epigenetic drugs tend to be toxic and associated with significant side effects. However, a better understanding of the networks involved should help in the selection of more applicable drugs and sidestep the off-target effects seen with drugs that targets cells based on proliferation. Furthermore, experimental successes in cultured cells or animal models must be further scrutinized in primary human normal and cancerous cells; these largely intractable models await further gene-editing breakthroughs. However, with the success of the synthetic lethality approach in targeting once-intractable cancers, there is a high hope of customized and personalized treatment strategies for patients, and it will be exciting to see the development in this field in the coming years.

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Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

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