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## REVIEW ARTICLE

# Role of EMT in the DNA damage response, double-strand break repair pathway choice and its implications in cancer treatment

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## Abstract

Numerous epithelial–mesenchymal transition (EMT) characteristics have now been demonstrated to participate in tumor development. Indeed, EMT is involved in invasion, acquisition of stem cell properties, and therapy-associated resistance of cancer cells. Together, these mechanisms offer advantages in adapting to changes in the tumor microenvironment. However, recent findings have shown that EMT-associated transcription factors (EMT-TFs) may also be involved in DNA repair. A better understanding of the coordination between the DNA repair pathways and the role played by some EMT-TFs in the DNA damage response (DDR) should pave the way for new treatments targeting tumor-specific molecular vulnerabilities, which result in selective destruction of cancer cells. Here we review recent advances, providing novel insights into the role of EMT in the DDR and repair pathways, with a particular focus on the influence of EMT on cellular sensitivity to damage, as well as the implications of these relationships for improving the efficacy of cancer treatments.

## KEYWORDS

DNA damage response, DNA repair, epithelial–mesenchymal transition, synthetic lethality, ZEB1

Caroline Moyret-Lalle and Mélanie K Prodhomme contributed equally.

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## 1 | INTRODUCTION

Epithelial to mesenchymal transition (EMT) is a physiologically reversible process essential for key embryonic steps. In adults, this conversion is activated during physiological processes, such as wound healing, and may be involved in pathological aspects of fibrosis and cancer. EMT is a major driver of cellular plasticity allowing cells to remodel, reshape, and acquire enhanced motility and stemness properties without genetic modification. This transition is orchestrated by multiple signaling pathways, transcription factors, and chromatin-remodelers. Key EMT-associated transcription factors (EMT-TFs) are divided into three main families: the zinc-finger E-box binding protein, including ZEB1 and ZEB2, the SNAIL family, encompassing SNAIL and SLUG, and the TWIST family, containing TWIST1. Nevertheless, the switch from one transcriptional state to another is sustained by chromatin remodeling, also known as chromatin plasticity. In such events, the ZEB1 promoter status may be crucial as it maintains a bivalent chromatin configuration that enables the cell to respond readily to extracellular signals.<sup>1</sup> A major aspect of chromatin plasticity is its impact on DNA damage signaling and DNA repair. In this review, we will concentrate on double-strand break (DSB) repair as a major cause of cancer-related genomic instability.

The proper coordination of DNA synthesis with other aspects of chromatin structure regulation are important for efficient DNA replication and repair. Defects in this coordination can trigger replication stress and further chromosome rearrangements. To maintain genome integrity, cancer cells depend heavily on the modulation of both the chromatin environment and the DNA damage response (DDR) (please refer to [Section 2](#)). Then, to ensure DSB repair, cells rely on four mechanisms, two dominant, mainly faithful repair mechanisms, and two error-prone processes (please refer to [Section 3.1](#)). Modulation of the choice of DSB pathway is presented depending on chromatin topology, cell type, cell cycle commitment, transcription (please refer to [Section 3.2](#)), and EMT (please refer to [Section 3.3](#)). This strategy is hijacked during resistance to cancer treatment, as it was shown that DNA damage signaling and repair pathways contributed significantly to intrinsic or acquired drug resistance,<sup>2</sup> providing key target mechanisms in cancer. Indeed, some tumors harbor defects in one of the DSB repair processes, thereby rendering them dependent on backup pathways to repair broken DNA. This vulnerability can be targeted by synthetic lethality approaches (please refer to [Section 4](#)). Here, we discuss recent findings on the coordination of multiple DNA repair pathways and synthetic lethality approaches with a focus on EMT.

## 2 | EPITHELIAL TO MESENCHYMAL TRANSITION AND REGULATION OF DDR/ DNA DAMAGE SIGNALING

The DDR is a complex signaling pathway that senses DNA damage and mobilizes the subsequent cascade of DNA repair pathways.<sup>3</sup> The apical sensor kinase for DSBs is Ataxia-telangiectasia-mutated

(ATM). ATM acts as a very first sensor by interacting with the DSB-binding complex MRN (MRE11, RAD50, and NBS1). ATM also promotes the recruitment of the poly(ADP-ribose)polymerase 1 (PARP1) to produce poly(ADP-ribose) (PAR) polymers and extend DNA damage signaling.<sup>4</sup> ATM instantly autophosphorylates and rapidly triggers a phosphorylation cascade, targeting downstream effectors such as the histone H2A variant H2AX that, upon phosphorylation at Serine 139, forms the  $\gamma$ H2AX mark of damaged chromatin that acts as a platform to recruit DNA repair proteins.<sup>5</sup> It has been shown that heterochromatic DSBs require ATM kinase signaling to be repaired and this ATM dependency is correlated with increased chromatin complexity rather than the damage itself.<sup>6</sup>

Recent investigations have highlighted the implication of some EMT-TFs in DDR regulation through their physical interaction with large chromatin protein remodeling complexes, advocating for a broader range of functions for EMT-TFs compared with those specifically restricted to orchestrating the expression of epithelial/mesenchymal genes. Zhang et al.<sup>7</sup> identified ZEB1 as a target of ATM in response to DNA damage. The phosphorylated ZEB1 was shown to directly interact with the USP7 deubiquitylating enzyme, surprisingly triggering the stabilization of CHK1 to promote homologous recombination (HR)-dependent DNA repair. Indeed, knocking-down ZEB1 decreased CHK1 protein abundance, but had no effect on CHK2. This pioneering work established a link between EMT and DDR, and unveiled an association between ZEB1 and radioresistance. Additionally, ZEB1 forms a complex with p300/pCAF to activate the ATM promoter, therefore participating in a positive feedback loop with ATM and increasing the DNA repair capacity in response to radio or chemotherapy.<sup>8</sup> Radiation was found to stabilize the ZEB1 protein, but had no effect on SNAIL, SLUG, or TWIST proteins.<sup>7,9</sup> An interplay between miRNAs, ZEB1 and DNA damage signaling pathways was identified, in which phosphorylated ZEB1 following irradiation could repress the transcription of its own negative regulator, miR-205, but not miR-200c.<sup>10</sup>

Aside from the strong implication of ZEB1, other EMT-TFs are also involved in the DDR. The E3 ubiquitin ligase RNF8 ubiquitinates TWIST1, which promotes its nuclear translocation and then modulates DDR pathways, leading to increased expression of HR genes.<sup>11</sup> In turn, it has been shown that RNF8 is a key player in DDR by modulating ATM activation and the DNA damage response.<sup>12</sup> In addition, impairing PARP1 induced EMT, in particular by triggering ZEB1 expression.<sup>13</sup>

## 3 | EPITHELIAL TO MESENCHYMAL TRANSITION AND DSB REPAIR PATHWAY CHOICE

### 3.1 | Double-strand break repair pathways

Double-strand breaks are mainly repaired by canonical nonhomologous end joining (c-NHEJ) and HR, but single-strand annealing (SSA) and the more recently characterized Alternative-End Joining pathways (Alt-EJ)<sup>14</sup> also contribute ([Figure 1](#)).

The c-NHEJ is a rapid and high-capacity pathway that joins two DNA ends with no complementary base pairing. HR, SSA, or Alt-EJ enable DSB repair after DNA resection initiated by the MRN complex.<sup>15</sup> In recent years, the notion of Alt-EJ has emerged. The most extensively described idea is called microhomology-mediated end joining (MMEJ) or theta-mediated end joining (TMEJ), an error-prone repair pathway in which DNA polymerase theta uses microhomologies to perform end joining repair. Several proteins have been described in human models to execute TMEJ, such as DNA polymerase  $\theta$  (coded by *POLQ* gene),<sup>16</sup> PARP1, XRCC1, and DNA ligase III $\alpha$  (LIG3).<sup>17–19</sup> *POLQ* depletion increases micronuclei,<sup>20,21</sup> suggesting the reliance on TMEJ for repair of certain types of lesions. Nevertheless, the protective effect of *POLQ* on genomic integrity is associated with an enhanced genomic instability<sup>22</sup> in cancer cells, highlighted recently in the work by Prodhomme and colleagues,<sup>23</sup> even if TMEJ is associated with a protective role in noncancer models.<sup>21</sup>

### 3.2 | Modulating the choice of DNA repair pathway

It has long been accepted that the nature of the DSB is the first determinant to influence the choice of the DNA repair pathway.<sup>24</sup> The choice of repair pathway also depends on the environment of the break, chromatin status and nuclear position (heterochromatin, euchromatin, centrosome, telomere, etc.)<sup>25</sup> and the phase of the cell cycle.<sup>26–28</sup>

In human cells, a blunt DNA-end DSB is preferentially repaired by c-NHEJ. However, DSBs arising from a fork collapse or DNA-end are not directly manageable by ligation, and initially require a resection step making DNA ends available for HR, SSA, or TMEJ.<sup>29</sup> While the HR mechanism is active in S/G2, TMEJ appears to be used more in the S phase, although theoretically TMEJ is used during the whole cell cycle, as for c-NHEJ.<sup>27,28</sup> Key factors of DNA DSB repair also regulate the choice of DNA repair pathway. The switch from c-NHEJ to HR and vice versa has been largely studied. For example, 53BP1 promotes c-NHEJ by blocking CtIP-dependent DNA resection.<sup>30</sup> Inversely, BRCA1 promotes HR by 53BP1 dephosphorylation and RIF1 release.<sup>31</sup>

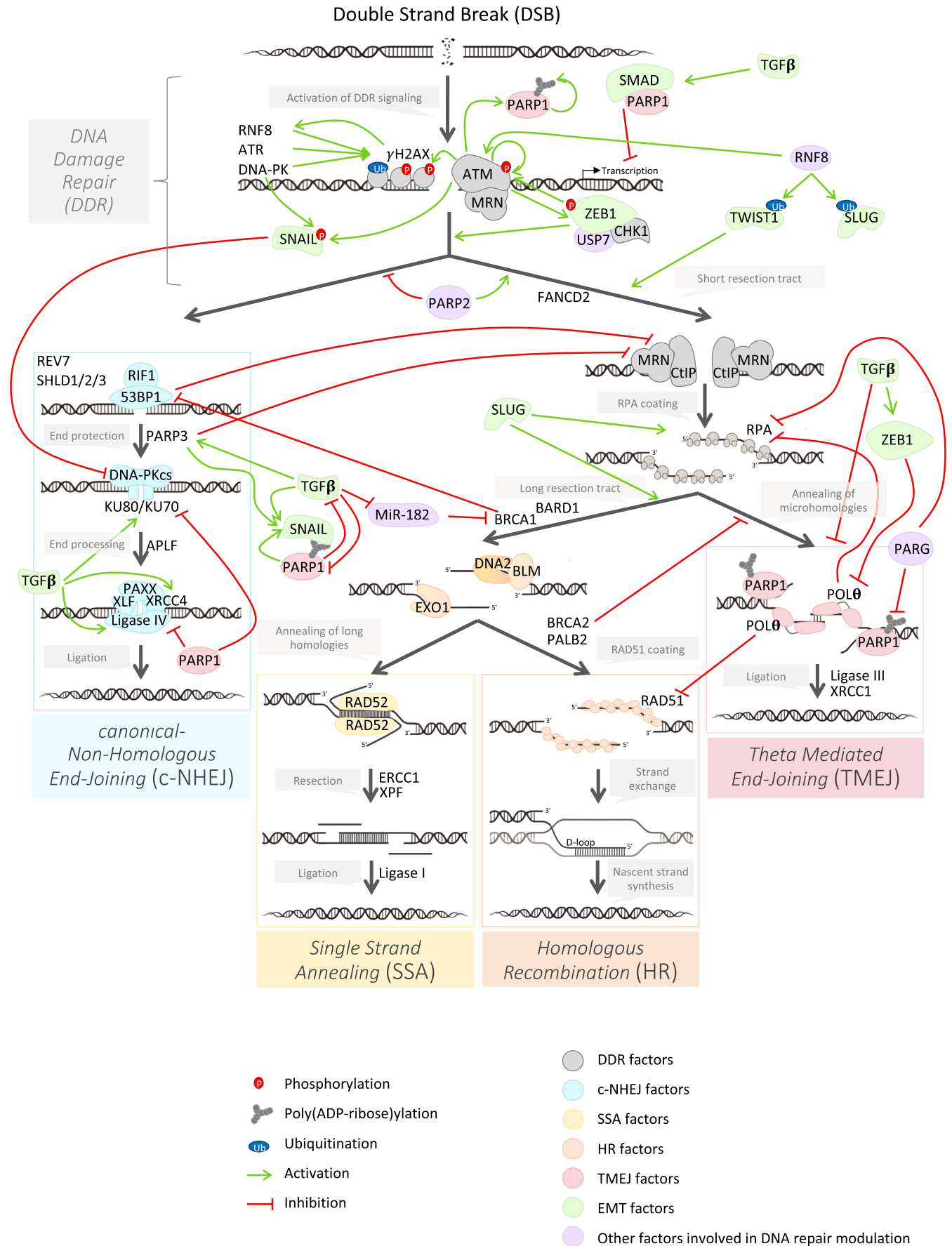
The continual identification of novel players completes this initial binary model. Indeed, BRCA2, main actor of HR, can stabilize replication protein A (RPA) proteins to inhibit TMEJ activity.<sup>29,32</sup> Conversely, *POLQ*, a key factor in TMEJ, also modulates HR activity.<sup>33</sup> Indeed, *POLQ* interacts directly with RAD51, limits RAD51–ssDNA nucleofilament assembly, and therefore suppresses the HR pathway in favor of TMEJ.<sup>34</sup> Moreover, the helicase domain of *POLQ* has the ability to remove the loading of RPA and stimulates annealing of ssDNA, an essential step to switch from the HR to the TMEJ pathway.<sup>33,35</sup> In addition, FANCD2, required for fork protection and fork restart in BRCA1/2-deficient tumors, promotes *POLQ* recruitment to lesions and promotes TMEJ repair.<sup>36</sup> Finally, in the G1 phase of the cell cycle, loss of 53BP1 or RIF1 enhances the recruitment of BRCA1, CtIP/MRE11-dependent end resection and RPA, but not

of RAD51, therefore promoting TMEJ activity but not that of HR.<sup>37</sup> Taken together, these findings highlight a close link between HR and TMEJ pathways and the loss of HR activity to encourage the cell to rely on the TMEJ pathway.

Finally, the synthesis of PAR polymers, catalyzed by PARPs, is a powerful regulator of several DSB repair pathways and, of note, PARP1 is the major producer of cellular PAR.<sup>38</sup> PARP1, PARP2, and PARP3 activities increase in response to DSBs.<sup>39–42</sup> PARP1 is a player in the TMEJ pathway<sup>17</sup> and seems to be a platform regulating the balance between HR and TMEJ. For example, PARP1 seems to promote mutagenic TMEJ repair by inhibiting c-NHEJ repair mediated by the inhibitory action of PARP1-Ku70 and PARP1-Lig4 on the BRCT domain of PARP1.<sup>43,44</sup> PARP2 plays an important role in the regulation of DSB repair pathway choice.<sup>39</sup> PARP2 limits 53BP1 accumulation onto DNA lesions, facilitating the CtIP-dependent DNA-end resection and thereby limiting c-NHEJ activity.<sup>39</sup> Finally, PARP3 limits DNA-end resection and promotes c-NHEJ activity by its direct interaction with PARylated Ku70/Ku80 and induces an imbalance between the specific pathways of BRCA1 and 53BP1.<sup>38,41,45</sup> Last, PAR glycohydrolase (PARG), a strong regulator of PARP activity due to its ability to degrade PAR from PARylated proteins, limits c-NHEJ pathway DNAPK-cs dependent activity.<sup>46</sup> Moreover, the loss of PARG, in particular PARG-2 in *Caenorhabditis elegans*, was reported to increase TMEJ activity.<sup>47</sup>

### 3.3 | Epithelial to mesenchymal transition and DNA repair

Over the last few years, many studies have shown that EMT, particularly EMT-TFs, are involved in the choice of DNA DSB repair pathways (Figure 1). EMT is associated with chemoresistance and radioresistance, among others, through the acquisition of stem cell properties. As previously mentioned, ZEB1 promotes DDR, but also the DNA repair choice itself. This function of ZEB1, initiated by phosphorylation and stabilization of ZEB1 by ATM, leads to increased HR pathway activity.<sup>7</sup> Along the same lines, transforming growth factor- $\beta$  (TGF- $\beta$ ) signaling, known to induce EMT and to activate EMT-TF expression,<sup>48</sup> such as that of ZEB, SNAI and TWIST families,<sup>49,50</sup> supports HR activity.<sup>51</sup> Indeed, TGF- $\beta$  signaling inhibits miR-182, which represses both BRCA1, necessary for HR, and FOXO3, required for ATM kinase activity. Consistently, compromised TGF- $\beta$  signaling impairs HR proficiency.<sup>52</sup> Finally, more recently, the EMT-TF ZEB1 was revealed as a direct regulator of DSB repair. Indeed, ZEB1 is a negative regulator of TMEJ, which may explain why some tumors with stem cell properties display low genomic instability.<sup>53,54</sup> *POLQ* expression, mainly associated with genomic instability and TMEJ activity, is lower in ZEB1-expressing claudin-low tumors characterized by a subnormal genomic landscape. ZEB1 represses the *POLQ* promoter, which consequently limits TMEJ activity<sup>23</sup> and therefore most probably favors HR and/or c-NHEJ. These results were confirmed by recent work from the Barcellos-Hoff team. Indeed, in this article, the authors show that



**FIGURE 1** Influence of epithelial to mesenchymal transition (EMT) on the modulation of the DNA repair pathway choice. This schematic representation describes the strong complexity of the modulation of the DNA damage response (DDR) signaling (in gray) as well as the four major DNA double-strand break repair pathways: c-NHEJ (in blue), SSA (in yellow), HR (in orange) and TMEJ (in red). This regulation occurs from the DDR signaling, to orientate the repair toward one of these four pathways. Other factors external to the DNA repair pathways (in purple) influence this choice, notably by post-translational modification (phosphorylation, PARylation, ubiquitination). As shown in this figure, EMT factors (in green) are key modulators of pathways choice

not only that TGF- $\beta$  is able to limit the activity of TMEJ by inhibiting POLQ expression, but also by inhibiting PARP1 and LIG1.<sup>55</sup> TGF- $\beta$  also enhances c-NHEJ activity, as demonstrated by Kim and colleagues,<sup>56</sup> who showed that TGF- $\beta$  treatment increased the levels of LIG4, XRCC4 and KU70/KU80. In conclusion, ZEB1 and possibly other EMT-TFs, seem to inhibit error-prone repair and encourage faithful DNA repair.

Additionally, repair factors have been shown to both induce or prevent EMT. First, the PARP family plays an important role in the modulation of EMT. Indeed, PARP1 deficiency results in the acquisition of an EMT phenotype during tumorigenesis.<sup>57</sup> Conversely, impairing PARP1 upregulates TGF- $\beta$  and SMAD pathways, which induce EMT and increase the levels of ZEB1 and SNAIL. In 2011, Rodriguez et al. revealed a new regulatory mechanism of SNAIL by PARP1, involving its post-translational stabilization by PARylation.<sup>58</sup> This functional interaction highlights the importance of PARP1 activity in the control of SNAIL activation with major consequences on malignant transformation through EMT. Moreover, Kumar et al. recently showed that PARP1 facilitates EMT in non-small-cell lung cancer through the induction of ZEB1 and the SMAD pathway.<sup>59</sup> PARP3, another actor of the PARP family, also promotes EMT by TGF- $\beta$  induction, cell motility, and chemoresistance in mammary epithelial cells.<sup>60</sup> Finally, the kinase DNA-PKcs, a key actor in c-NHEJ, is responsible for SNAIL stabilization by phosphorylation at Ser100. Consequently, the kinase activity of DNA-PKcs is inhibited by phospho-SNAIL, resulting in the inhibition of c-NHEJ.<sup>61</sup> Downstream of ATM activation, SLUG is essential for the activation of RPA32 (subunit of RPA with RPA70 and RPA14), resulting in efficient HR-mediated DSB repair.<sup>62</sup> In conclusion, a strong interconnection exists between EMT and DNA DSB repair.

#### 4 | EPITHELIAL TO MESENCHYMAL TRANSITION AND SYNTHETIC LETHALITY APPROACHES BASED ON DSB REPAIR PATHWAYS TARGETING

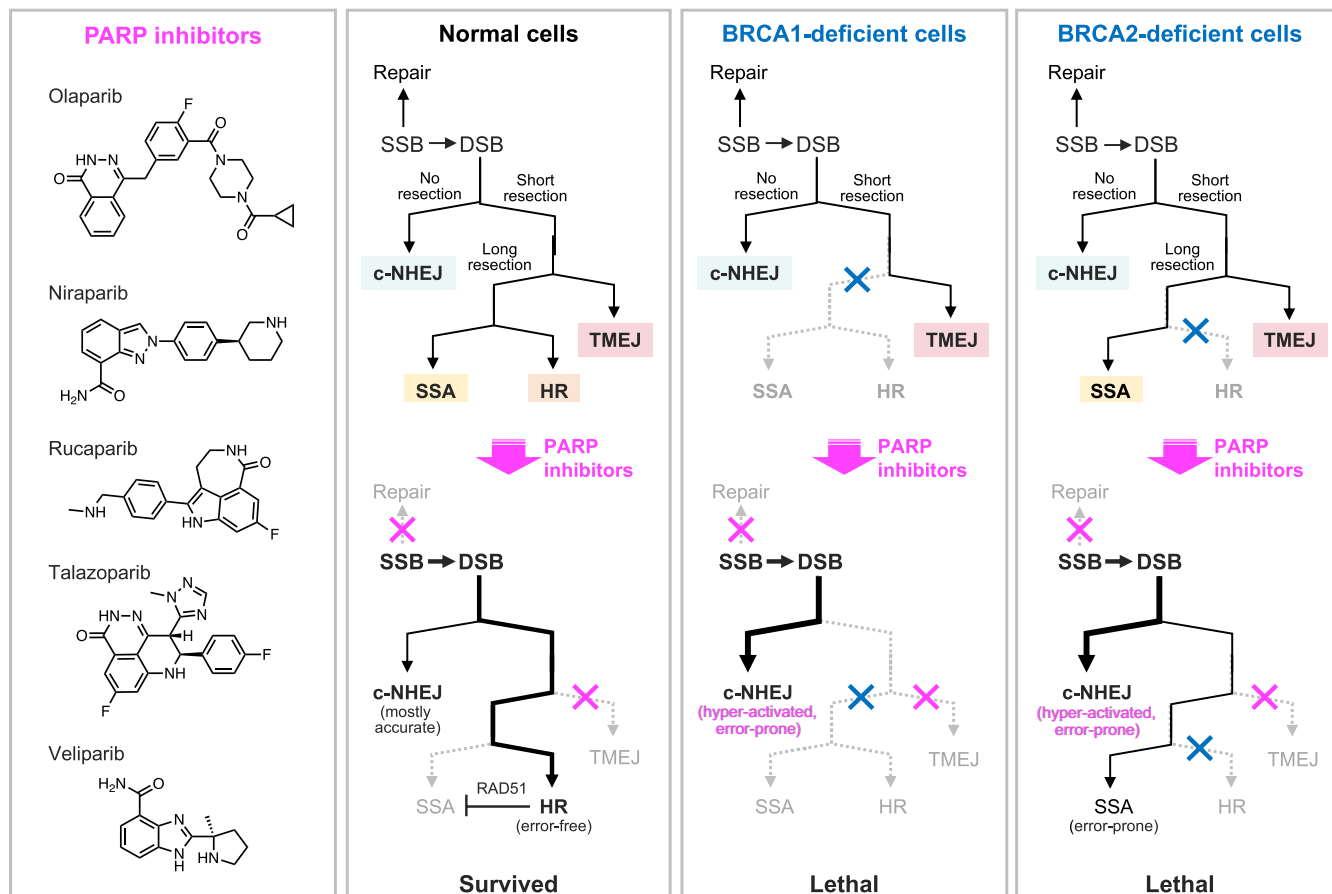
As described above, when a specific DDR pathway is inactivated, cancer cells become dependent on other DDR pathways to overcome the deleterious effects of DNA damage. This is a rationale for using a synthetic lethality approach in the context of a genetic deficiency in a DDR pathway and a drug that targets the fallback repair pathway. Theoretically, synthetic lethality-based drugs should exhibit a high therapeutic index and have been proposed as promising anticancer treatments. The most successful examples are PARP inhibitors (PARPi; Figure 2). PARP inhibition causes synthetic lethality

with deficiency in tumor suppressor *BRCA1* or *BRCA2* genes.<sup>63,64</sup> PARPi repress the repair of single-strand breaks (SSB), which results in DSBs when the cell enters S phase of the cell cycle. Because DSBs in S/G2 phases are repaired by HR, cells with intact HR survive upon PARP inhibition. In contrast, *BRCA1/2*-deficient cancer cells cannot repair DSBs by HR and progress to cell death (Figure 2). Following approval of olaparib, several PARPi, such as niraparib, rucaparib, and talazoparib, have also been approved by the Food and Drug Administration in the USA. The United States indications for the first-in-class PARPi, olaparib, include breast, ovarian, pancreatic and prostate cancers with HR deficiency (referred to as HRD) and platinum-sensitive ovarian cancer. As companion diagnostics, Myriad HRD assay and Foundation Medicine loss of heterozygosity (LOH) assay predict HRD. PARPi also have the so-named PARP trapping activities, which stabilize the SSB-PARP complex and cause catastrophic DNA damage. Among PARPi, talazoparib exhibits the most potent PARP trapping activity, whereas that of veliparib, still under clinical tests, is at the lowest level.

PARPi resistance emerges in patients within a year of treatment. Mechanisms for resistance to PARPi include restoration of HR by frame-revertant mutations in *BRCA1/2*<sup>65</sup> or inactivation of c-NHEJ factors (53BP1 and shieldin components, such as REV7),<sup>66,67</sup> PARP1 loss-of-function mutations<sup>68</sup> enhanced the drug efflux by P-glycoprotein/ABC1 overexpression<sup>69</sup> and replication fork stabilization by SLFN11 downregulation.<sup>70</sup> The role of EMT in the occurrence of drug resistance has been widely described.<sup>71</sup> PARPi treatments are no exception, and EMT appears as a new PARPi resistance mechanism.<sup>72</sup> It has been recently shown that the combination of niraparib, cisplatin, and downregulation of TWIST1 re-sensitized ovarian cells to niraparib.<sup>73</sup>

Because PARPi induce replicative stress, PARPi-resistant cancer cells often acquire a high dependency on the ATR/CHK1/WEE1 pathway. This suggests that this pathway may be a promising target to overcome PARPi resistance.

Currently, an ATR inhibitor, VE-821, and a CHK1 inhibitor, prexasertib, have shown these types of results in ovarian cancer cells.<sup>74,75</sup> VE-821 disrupts both RAD51 loading to DSBs and fork protection in PARPi-resistant *BRCA1*-deficient cancer cells. ATR inhibitors are also effective in ATM-mutated gastric cancer and chronic lymphocytic leukemia, as ATR and ATM pathways bear a synthetic lethal relationship.<sup>76,77</sup> Furthermore, the combination with gemcitabine and an ATR inhibitor, berzosertib, extended the progression-free survival of platinum-resistant high-grade serous ovarian cancer patients compared with gemcitabine treatment alone in a phase 2 clinical trial.<sup>78</sup> Mechanistically, gemcitabine causes replicative stress, whereas inhibition of the ATR/CHK1/WEE1 pathway prevents the replicative stress response, leading to cytotoxicity.



**FIGURE 2** Poly(ADP-ribose)polymerase (PARP) inhibitor-driven synthetic lethality in the contexts of DNA damage repair deficiencies. PARP inhibitors repress single-strand break (SSB) repair and base excision repair, as well as TMEJ. While normal cells can repair the resulting double-strand breaks (DSBs) via the error-free HR pathway, HR-deficient cells (e.g., BRCA1/2-deficient cells) cannot escape from these deleterious effects. In BRCA2-deficient cells, high dependency on SSA is lethal because this repair system is error prone and causes cell catastrophe. The PARP trapping activity, which is the most marked for talazoparib and the weakest for veliparib, also leads to DNA damage and yields therapeutic efficacies

Recently, some studies have investigated the role of EMT in response to ATR inhibitors, including VE-821. Rapidly after treatment with VE-821, treated pancreatic cancer cell lines have increased migratory ability, decreased protein level of E-cadherin, and increased protein levels of vimentin and ZEB1, suggesting an increase in EMT upon loss of ATR.<sup>79–81</sup> The combined loss of ATR and ZEB1 then significantly reduces cell survival.<sup>80</sup> This latest study also shows that ZEB1 inhibition promotes CHK1 phosphorylation, suggesting that the dual inhibition of ZEB1 and CHK1 may be an essential treatment strategy in the treatment of ZEB1-expressing tumors. Another study has already shown, previously, the close link between CHK1 and ZEB1. In 2014, Peijing Zhang et al.<sup>7</sup> conversely showed that the loss of ZEB1 in mouse embryonic fibroblasts (MEFs) led to a decrease in protein levels of CHK1, but that the simultaneous loss of ZEB1 and CHK1 led to sensitization of cells to radiotherapy.

HR deficiency provides additional opportunities for synthetic lethality-based therapies. As described above, the DSB repair mechanisms involving end resection include HR, SSA, and Alt-EJ or TMEJ. Accordingly, HRD cancer cells often gain a hyperdependence on SSA and TMEJ pathways. As TMEJ requires POL $\theta$ , POL $\theta$  inhibition

induces synthetic lethality in HRD epithelial ovarian cancers.<sup>34</sup> From a diagnostic perspective, POL $\theta$  upregulation is one of the hallmarks of HRD and TMEJ dependency, which could be used as a predictive biomarker for response to PARP and POL $\theta$  inhibitors. EMT can lead to inefficiency of POL $\theta$  inhibitors as we have shown that ZEB1 expression leads to TMEJ repression.<sup>23</sup> RAD52 binding to ssDNA is required for the SSA repair mechanism. A small-compound, AICAR, which disrupts the RAD52/ssDNA interaction and SSA, preferentially inhibits the growth of BRCA1/2-deficient cancer cells.<sup>82</sup> Therefore, protein–protein interactions (PPIs) and protein–DNA interactions (PDIs) may also constitute promising therapeutic targets in DSB repair pathways. However, unlike the design of enzyme inhibitors, the development of PPI/PDI modifiers remains challenging due to the difficulty in blocking specific macromolecular interactions using small compounds. Recent technologies, such as proteolysis-targeting chimera (PROTAC), may offer the opportunity to target these nonenzymatic molecules.

Accumulating evidence indicates that DSB repair pathways are affected by oncogenic alterations of epigenetic regulators. For example, gain-of-function mutations of isocitrate dehydrogenase-1

and -2 (IDH1/2) foster enzymes to produce an oncometabolite, 2-hydroxyglutarate (2-HG), instead of  $\alpha$ -ketoglutarate ( $\alpha$ -KG). This metabolic alteration represses the  $\alpha$ -KG-dependent histone lysine demethylases KDM4A and KDM4B, which are required for DSB repair. Therefore, IDH1/2 mutations cause HRD, providing a therapeutic opportunity for PARPi-mediated synthetic lethality.<sup>83</sup> IDH1/2 mutants also induce EMT with high levels of ZEB1 and knockdown of IDH1 mutant form is sufficient to reverse many characteristics of EMT.<sup>84,85</sup> Targeted inhibitors of IDH1 are currently under trials for glioma cancer.<sup>86</sup>

Overexpression of CARM1, an arginine methyltransferase, in ovarian cancer induces the epigenetic silencing of the shieldin component MAD2L2/REV7 in a histone lysine methyltransferase EZH2-dependent manner. In this cellular context, EZH2 inhibition derepresses MAD2L2/REV7 expression and switches the DSB repair pathway from HR to c-NHEJ. EZH2 and PARPi, GSK126, and olaparib, and therefore respectively exhibit a synergetic antitumor effect in orthotopic and patient-derived xenograft models.<sup>87</sup>

However, EZH2 knockdown by GSK126 induced EMT-like changes in ovarian cancer cells. The EMT-TF ZEB2 was upregulated in cells treated with this EZH2 inhibitor. Furthermore, TGF- $\beta$  enhanced the expression of ZEB2 in EZH2 siRNA- or GSK126-treated cells.<sup>88</sup>

These observations indicate that transcriptional reprogramming EMT may affect cell vulnerability to DDR-directed drugs and be worth monitoring to predict and even enhance the therapeutic impact of DDR-directed drugs.

## 5 | CONCLUSION

To conclude, in addition to the direct competition for access to a given DNA damage locus, many complex mechanisms influence the use of one repair pathway over another, such as the nature of the DNA lesion (single-strand or DSB, intercrosslink, mismatch, G-quadruplex, etc.), the location of the lesion (heterochromatin, euchromatin, centrosome, telomere, etc.), the cell cycle, the environment (hypoxia, the immune system, etc.).<sup>24</sup> More recently, EMT has also been described as a potent regulator of DDR signaling and DSB repair pathways, as presented in this review.

Epithelial to mesenchymal transition-TFs, such as ZEB1, may influence DNA repair pathway choice directly, by regulating POLQ expression for instance, but also indirectly in response to environmental stress during tumorigenesis. For example, even if the role of hypoxia as a modulator of DNA repair pathways via ZEB1, or via EMT, has yet to be demonstrated, hypoxia-inducible factor 1 alpha (HIF-1 $\alpha$ ), the main hypoxia-induced factor, is known to induce ZEB1 and EMT.<sup>89</sup> We propose that part of the role of hypoxia in modulating DNA repair choice may be regulated by ZEB1.

Overall, we proposed that the role of EMT is to limit the establishment of high genomic instability<sup>23,53</sup> by the non-use of a mutagenic repair pathway. Therefore, some DNA damage cannot be dealt with and a loss of genomic integrity is observed, as evidenced by

the high level of micronuclei in EMT-TF-expressing cells.<sup>23</sup> These conclusions can be extended to other EMT-TFs and EMT or DNA damage other than DSBs. ZEB2 increases the nucleotide excision repair (NER) pathway activity. In colorectal cancer, ZEB2 enhances resistance of cancer cells to oxaliplatin-induced DNA damage, by increasing NER capacity by upregulation of the *ERCC1* gene.<sup>90</sup> Again, in this case, ZEB2-mediated EMT is instrumental in increasing genomic stability and cell survival.

Through all these roles, EMT, and more precisely ZEB1, induces a strong resistance to conventional treatments in cancer patients. Indeed, ZEB1 has frequently been associated with the mechanisms of resistance to radiotherapy or chemotherapy.<sup>7</sup> EMT inhibitors, such as ZEB1 inhibitors, could therefore be promising treatment options for blocking tumor initiation, reducing the occurrence of metastases, but also for modulating DNA repair and therefore sensitizing tumors to radiotherapy or chemotherapy.

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