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Mini-review

DNA damage response and resistance of cancer stem cells

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ABSTRACT

The cancer stem cell (CSC) model defines tumors as hierarchically organized entities, containing a small population of tumorigenic CSC, or tumour-initiating cells, placed at the apex of this hierarchy. These cells may share common qualities with chemo- and radio-resistant cancer cells and contribute to self-renewal activities resulting in tumour formation, maintenance, growth and metastasis. Yet, it remains obscure what self-defense mechanisms are utilized by these cells against the chemotherapeutic drugs or radiotherapy. Recently, attention has been focused on the pivotal role of the DNA damage response (DDR) in tumorigenesis. In line with this note, an increased DDR that prevents CSC and chemoresistant cells from genotoxic pressure of chemotherapeutic drugs or radiation may be responsible for cancer metastasis. In this review, we focus on the current knowledge concerning the role of DDR in CSC and resistant cancer cells and describe the existing opportunities of re-sensitizing such cells to modulate therapeutic treatment effects.

1. Introduction

Chemo- and radioresistant cancer cells are the major cause of tumour recurrence and relapse [1]. Some of the tumor cells possess intrinsic resistance, whereas others are initially sensitive but acquire resistance during the course of chemo- or radiotherapy. Growing evidence supports the notion that resistance of cancer is driven by small population of cancer stem cells (CSC), responsible for tumor initiation, growth and metastasis, and that therapeutic intervention helps to activate and select CSC resulting in resistance, relapse and poor prognosis [2]. Considering many previous observations, it is undeniable that the development of targeted therapies able to eradicate CSC could become a key factor to reduce metastasis occurrence and therefore improve overall survival.

Although still poorly understood, CSC and chemoresistant cancer cells use a series of self-defense mechanisms against the chemotherapeutic drugs or radiotherapy. These mechanisms include but are not limited to amplification of alternative oncogenes or inactivation of alternative survival pathways, increased expression of ATP binding cassette (ABC) membrane transporters, overexpression of anti-apoptotic proteins, and many others [3]. Recent data suggest that CSC are even more resistant to chemo- and radiotherapy than non-stem cells [4]. Of note, both radio- and chemotherapeutic treatment induce DNA damage to kill fast dividing cells [5]. However, in the case of slow-cycling CSC or chemoresistant cancer cells the therapeutic response seems not to be very efficient. Moreover, many recent studies demonstrate that CSC possess a highly efficient DNA damage response (DDR) system, which is considered a contributor to the resistance of these cells from exposures to DNA damaging agents.

In this review, we outline the role of elevated DDR in CSC and chemoresistant cancer cells and provide state-of-the-art molecular approaches aiming to target components of DNA repair machinery in order to eliminate these cellular subsets or make them susceptible to conventional anticancer therapy.

2. CSC and chemoresistance in the context of cancer biology

Resistance to chemo- and radiotherapy continues to be a major problem in oncology affecting the majority of cancer patients. The current concept of cancer resistance suggests that the de novo radio- or chemoresistance is attributed to the existence of CSC, while the epi/genetic alterations in dysregulation of oncogenes or tumor suppressor genes contribute to the acquired chemoresistance [6]. However, in light of new studies demonstrating that chemo- and radioresistant cancer cells possess common properties with CSC, these categories of cells should not be separated. A better understanding of oncogenic networks among these types of cells will likely identify optimal conditions necessary to target these cells and to improve therapeutic strategies.

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2.1. Brief description of CSC

In the last decades, cancer has been progressively recognized as an heterogeneous disease, constituted by distinct cellular populations that contribute to the biology of the tumor [7]. It is well understood that the existence of such intratumoral heterogeneity is an essential contributor to therapeutic failure leading to the progression of the disease [8,9]. Several mechanisms are known that give rise to this heterogeneity, namely, genetic and/or epigenetic heritable changes (clonal evolution), composition and influence from the tumor microenvironment as well as the presence of a subset of CSC with self-renewal and multi-lineage differentiation properties [10–12].

The CSC model defines tumors as hierarchically organized entities, containing a small subset of tumorigenic CSC placed at the apex of this hierarchy [13]. According to this model, CSC possess the sole ability to self-renew and to differentiate in non-tumorigenic cancer cells that will form the bulk of the tumor [12,14,15]. The first experimental evidence of the existence of CSC was provided by Dick and colleagues, who showed that only a small population of human leukemia (AML) stem cells (identified as $CD34^+/CD38^-$) were capable of transferring AML from human patients to NOD/SCID mice, proving that different populations of AML cells have variable clonogenic capacity [16]. Since then, several studies have taken similar approaches to confirm the CSC hypothesis in a wide array of solid tumors, as in breast [17,18], brain [19,20], pancreatic [21,22], colon [23,24] or ovarian cancer [25].

To date, various strategies have been developed to identify and isolate CSCs from tumors. The FACS sorting based on the overexpression in CSC of specific surface markers (i.e. CD44 [26], CD133 [27], CD90 [28] or CD36 [29]) is the most extended method. In addition, certain intracellular markers have also been described as overexpressed in cancer and normal stem cells, such as the enzyme aldehyde dehydrogenase (ALDH) [30–35] or well-known pluripotent transcriptional factors, including Nanog [36,37], Oct4 [38–40] and SOX2 [41]. Other features attributed to CSC include the presence of transmembrane ABC transporters [42], the ability to form tumourspheres in non–-adherent conditions [43] and higher tumorigenic capacity in xenotransplantation studies in contrast with other cell populations (which is known as the current "gold standard" assay to identify CSC) [14,15,44].

Despite the aforesaid advances in the field, the CSC paradigm is still surrounded by skepticism since the identification of this cellular subset is yet not well established and its study still present some challenges. Inter- and intra-tumoral heterogeneity regarding expression of the most commonly used CSC markers has been described [45,46]. Another concern is the use of immunocompromised mice for xenotransplantation studies, thus modifying the microenvironment conditions and therefore possibly underestimating their tumorigenic capacity [47]. In addition, the use of different experimental models and the plasticity of CSC and different tumour cells to acquire stem properties and dedifferentiate via epithelial-mesenchymal transition (EMT) are other obstacles to overcome [11,15].

2.2. CSC and metastasis

The implication of CSC in metastasis is not fully elucidated yet. For metastasis to take place, cells need to dedifferentiate via EMT, detaching from the tumour of origin, travel by blood or lymphatic vessels as circulating tumor cells (CTC) and finally reattach to distant sites where they will de-differentiate again [48]. A compelling body of evidence shows that both CTC and CSC display an EMT phenotype [49–51]. It has also been described that the induction of EMT can in turn co-induce stem properties in non-stem cancer cells [52]. Additionally, CTC have been linked with stem characteristics [53,54].

The EMT program is characterized by a loss of cell-to-cell adhesion molecule E-cadherin and the activation of several transcription factors like SNAI1, SLUG, ZEB-1, N-cadherin and vimentin [55,56]. A study performed with breast and colon cancer cell lines showed that some cells possessed a lower adherence and were enriched in both EMT and stem markers. Remarkably, this cellular subset also showed a higher tumorigenic and metastatic potential *in vivo* [57].

A higher metastatic capacity was also described in a CSC subset derived from colorectal cancer patient samples in Todaro et al. [58]. $CD44v6^+$ CSCs originated metastasis in 80% of the xenoengrafted mice in comparison with the absence of metastasis in $CD44v6^-$ CSC tumors. Moreover, $CD44v6^+$ was mainly detected in metastatic lesions and in the invasion front of aggressive tumors, suggesting the migratory phenotype of CSCs. Interestingly, cytokines produced by tumor associated cells were able to convert $CD44v6^-$ cells in $CD44v6^+$, suggesting that microenvironmental influence may be essential to maintain the CSC population and their aggressive behavior.

Another study evaluated 83 pancreatic tumor samples and revealed that the presence of $CD133^+/BMI\text{-}1^+$ CSC was associated with metastatic stages and a lower median survival time. Moreover, these cells presented a higher invasion capacity and knockdown of BMI-1, a member of the Polycomb repressor complex 1, decreased the invasion and metastatic capacity *in vitro* and *in vivo*, while inhibiting the expression of EMT markers [59].

2.3. Resemblance of CSC to chemo- and radio-resistant cancer cells

Although much controversy remains about the validity of CSC and their connection to chemoresistant tumors, it seems likely that both CSC and chemoresistant cells may share common qualities [60]. For example, residual breast cancer cells after chemo-therapy are enriched in CSC markers [61]. In turn, biopsies from the most aggressive breast cancer, known as chemoresistant triple-negative breast cancers (TNBC), showed an increased expression of genes associated with CSC [62]. We and others demonstrated that chemo- and radioresistant cells share stem cell markers with CSC. For example, our recent findings on isogenically derived CSC and chemoresistant cancer cells demonstrate that both categories of cells have higher expression levels of various stem cell proteins, including NANOG, ALDH1, Klf4, Oct4, etc. In general, using cytotoxic levels of chemotherapeutic drugs can select and enrich a subset of resistant cells with cancer stem cell features [63–65].

The above similarities also can be viewed as the consequences of closely activated pathways. For example, Wnt/β-catenin pathway is active in both CSC and resistant cancer cells, while high Wnt signalling is associated with radioresistance in intestinal CSC [66]. Posttranslational DDR protein UBE2 (RAD6) was found to stabilize β-catenin by promoting expression of stem cell markers in ovarian and breast cancers and by increasing chemoresistance of ovarian cancer [67]. Proliferating cell nuclear antigen (PCNA)-associated factor (PAF)-Wnt signalling axis modulates cell plasticity, which is required for the maintenance of breast cancer cell stemness [68]. The Notch signaling pathway is one of the most important pathways implicated in self-renewal of adult stem cells and in chemoresistant phenotype of cancer cells. All Notch receptors and particularly Notch-2 seem to play an important role in CSC [69] and chemoresistant phenotype of cancer cells [70].

Both CSC and resistant cancer cells are in general slow cycling cells and prone to senescence. The non-lethal levels of DNA damage induce stable changes in gene expression through activating the senescence response program [71]. Several studies suggest that tumor cells spontaneously reverted from drug-induced senescence are more stem-like [63,72]. Another mechanism underlining the dual role of senescence in tumorigenesis has been described in multiple myeloma cancer stem cells - after treatment with therapeutic agents, remaining DNA damage lead to a senescence-associated secretory phenotype which promotes malignancy [73].

Finally, maintaining genomic integrity CSC could be due to activation of DDR pathways or overexpression of DDR proteins. Below, we intend to describe the connection of specific DDR pathways with CSC.

Table 1
Abundance of DDR proteins in connection to CSC and resistant cancers.

DDR proteins		Functions	Abundance in CSC	References
BER	APE1	Apurinic/apyrimidinic endonuclease	oral tongue squamous CSC	[78]
			colon CSC	[79]
	ERCC1	endonuclease	oral tongue squamous CSC	[78]
			esophageal CSC	[80]
	MTH1	hydrolase	CSC-like circulating tumor cells in blood samples of metastatic breast cancer patients	[82]
			Glioblastoma stem cells	[83]
NER	DDB2 (XPE)	recognition of DNA damage	Ovarian CSC	[85]
	RPA1	binding ssDNA	Gastrointestinal CSC	[86]
	RPA2	binding ssDNA	Glioma CSC	[156]
PPR	UBE2 (RAD6)	Ubiquitin-conjugating enzyme	ovarian CSC	[67]
	PAF	PCNA-related protein	breast CSC	[68]
	RAD18	E3 ubiquitin-protein ligase	glioblastoma CSC	[88]
	BMI-1	SUMO conjugation	basal cell carcinoma CSC	[89]
			oral squamous CSC	[90]
NHEJ	RIF1	Replicase	pancreatic CSC	[92]
	SETMAR	Transposase, methylase	colon CSC	[93]
	SETMAR-1200	Transposase	glioblastoma CSC	[94]
	PARP1	NAD + ADP - ribosyl-transferase 1	glioblastoma CSC	[95]
HR	RAD51	Homologous pairing	glioblastoma CSC	[98]
			TNBC CSC	[99]
			pancreatic CSC	[100]
	BRCA1	Recombinase and E3 ubiquitin ligase	oral CSC	[101]
	RAD52	Homologous pairing	oral CSC	[101]
	NBS1	Homologous pairing	glioblastoma CSC	[103]
	RAD50	ATPase	breast CSC	Unpublished
	ATM	Kinase	breast CSC	[106]
	CHK1	Checkpoint kinase	NSCLC CSC	[107]
FA and other	FANCD2	DSB sensor	Biliary tract CSC	[109]
			ovarian CSC	[110]
	BRCA1	Tumour suppressor	breast CSC	[109]

3. Enhanced DDR in CSC and chemo-/radio-resistant cancer cells

Recent findings suggest that activation of DDR pathways can be responsible for the resistance of CSC and radio-/chemo-resistant cancer cells. The DDR is a very complex network that is comprised of several pathways, each of which is involved in much cross-talk both within the network and with other signalling systems [74]. Several recent studies linked stemness of cancer cells with the activation of DDR pathways and chemoresistance. Population of lung cancer cells expressing stemness marker CD133 contained altered expression of DNA repair genes that are inducible upon exposure to chemotherapy [75]. DDR and the expression of various repair proteins are also found to be highly upregulated in $Lin^{-}CD29^{H}CD24^{H}$ tumor-initiating cells isolated from mammary gland tumors, indicating an elevated DDR in these CSC [76]. Here, we summarize involvement of CSC with specific DDR pathways (Table 1).

3.1. Base excision repair

Base excision repair (BER) corrects small base lesions produced by deamination, oxidation, or methylation of DNA without significant distortion the DNA helix structure [77]. BER involves the activity of strand break joining factors, endonucleases, ligases and DNA glycosylases. Apurinic/Apyrimidinic endodeoxyribonuclease APE-1 and DNA ligase factor XRCC-1, both from BER pathway, are upregulated in oral tongue squamous cell carcinoma, and XRCC-1 expression is associated with better clinical staging and nodal status [78]. At the same time, Ape1 signaling plays a role in the regulation of colon CSC growth [79]. CSC-like population in esophageal cancer has elevated level of ERCC1 [80]. Enhanced CSC properties in esophageal squamous cell carcinoma was associated with the expression of ERCC1 [81]. As revealed by analyses of circulating tumor cells in blood samples of metastatic breast cancer patients, the expression of ERCC1 in stem cell-like CTC (positive for ALDH1) was significantly associated with therapy failure [82]. BER-associated hydrolase, MTH1, which degrades oxidized nucleotides, reveals high expression levels in glioblastoma stem cells and correlates with aggressiveness of glioblastomas [83].

3.2. Nucleotide excision repair

Nucleotide excision repair (NER) is responsible for the removal of bulky DNA lesions induced by UV irradiation, environmental mutagens, and certain chemotherapeutic agents. The NER system cuts out damaged DNA bases within a string of nucleotides, and replaces them with DNA as directed by the undamaged template strand eventually causing a significant distortion in the DNA helix [84]. The NER operates though a number of DNA helicases and DNA binding proteins. DNA damage-binding protein 2 (DDB2 or XPE) was abundant in CSC subpopulation of ovarian cancer [85]. NER proteins, RPA1 and RPA2, form subunits of the heterotrimeric Replication Protein A (RPA) complex that binds to single-stranded DNA (ssDNA). RPA1 serves as an oncogene during progression of gastrointestinal cancers progression and is linked to CSC, whereas RPA2 is associated with glioma stem cells and contributes to tumor propagation and relapse [86].

3.3. Post-replication repair

Post replication repair (PRR) is a mechanism specialized in tolerating DNA lesions allowing PRR proteins to “patch” ssDNA gaps in the daughter strand and restore DNA to its double-stranded state for subsequent DNA repair [87]. There are two mechanisms of PRR: translesion synthesis (TLS), which employs TLS polymerases to directly

replicate across the DNA lesion, and template switching (TS), which "borrows" the genetic information from the newly synthesized sister chromatid as a replication template and thus avoids the lesion.

PCNA-related protein PAF is associated with breast CSC [68]. The expression level of PRR protein UBE2 (RAD6) correlates strongly with acquired chemoresistance and expression of ovarian CSC genes and poor clinical prognosis. Its upregulation promotes stem cell-like characteristics and cisplatin resistance in ovarian cancer [67]. Another PRR protein from the same epistasis group, RAD18, was found to be abundant in CSC highly resistant to DNA damaging agents [88]. BMI-1, an early DDR protein, was found to be essential for the increased radiation resistance observed in basal cell carcinoma CSC [89]. BMI-1 expression was also associated with oral squamous cell carcinoma ALDH1-positive cells [90].

3.4. Non-homologous end-joining repair

Classical non-homologous end-joining (NHEJ) repair is the dominant pathway for double strand break (DSB) repair in adult mammalian cells [91]. The two NHEJ pathways involve distinct sets of proteins: classical NHEJ (C-NHEJ) uses Ku, DNA-dependent protein kinase (DNA-PK), 53BP1 and XRCC4/Lig IV, while alternative end joining (Alt-EJ) uses single-strand break repair proteins, such as PARP1 and Lig IIIα/XRCC1. The expression of replication timing regulatory factor 1 (RIF1) which is involved in NHEJ was shown to be several hundred times higher in the pancreatic CSC [92]. DNA damage-associated transposase SETMAR (METNASE) plays a role in maintenance of the stemness phenotype in colon CSC [93]. Its level impact expression of NANOG, OCT3/4, and SOX2. Both SETMAR and its associated protein SETMAR-1200 were able to increase DNA repair by NHEJ and their levels were enriched in glioblastoma CSC [94]. Poly (ADP-ribose) polymerase (PARP) is a family of proteins involved in a number of cellular processes such as DNA repair, genomic stability, and programmed cell death. Glioblastoma-initiating cells exhibit enhanced basal activation of SSB repair due to enhanced activation of PARP1 [95].

3.5. Homologous recombination repair

Homologous recombination (HR) repair enables the cell to access and copy intact DNA sequence to repair DNA damage affecting both strands of the double helix [96]. The central player of HR is the strand-exchange protein, Rad51 [97]. RAD51 is highly expressed in clinical samples and patient-derived glioblastoma stem cells (GSC) [98]. In addition, the resistance of CSC from TNBC is mediated by RAD51 [99]. The HR system also incorporates accessory factors for recombination, MRE11-RAD50-NBS1 (MRN) complex that activates ataxia telangiectasia mutated (ATM) kinase, early checkpoint response kinases and BRCA-related proteins. Not surprisingly, increased expression of BRCA1 and RAD51 has also been observed in pancreatic putative CSC compared with bulk cells [100]. These spheroid cells demonstrated more efficient repair of DNA breaks, than parental cells after treatment with gemcitabine. Oral CSC display radio-resistance due to preferential activation of ATM, BRCA1, elevated levels of RAD52, XLF, and a significantly faster rate of DNA double-strand-breaks clearance [101]. A more efficient HR repair was reported in GSC [102]. In line with this note, CSC from glioblastomas display a preferential activation of DNA damage checkpoint and are relatively resistant to radiation. L1CAM regulates expression of NBS1 (NBN or nibrin), one of the first factors to accumulate at sites of DSBs. Ectopic expression of NBS1 in GSCs rescued the decreased checkpoint activation and radioresistance caused by L1CAM knockdown, demonstrating that L1CAM signals through NBS1 to regulate DNA damage checkpoint responses [103]. RAD50, another component of the MRN, is abundant in both CSC from TNBC and corresponding chemoresistant cells (unpublished data). Biocomputational analyses proposed RAD50 to play a role in CSC [104]. Indeed, the up-regulated level of RAD50 in these cells, as well as in biopsies taken from TNBC patients, was associated with HR and increased chemoresistance to DNA damaging drugs.

The ATM-CHK2 and ATR-CHK1 pathways are activated by DSBs and ssDNA [105]. ATM is required both for ATR-CHK1 activation and to initiate DNA repair via HR. The phenotypic radiation resistance of $CD44^+/CD24^{-/low}$ breast cancer cells is mediated through the enhanced activation of ATM signaling [106]. Activation of CHK1 and cell cycle arrest were observed in patient-derived non-small-cell lung cancer (NSCLC) stem cells compared to their corresponding differentiated cells after exposure to DNA damaging agents [107].

3.6. Fanconi anemia and other pathways

The Fanconi anemia (FA) pathway repairs DNA interstrand cross-links (ICLs) in the genome [108]. FA proteins are involved into multiple genome-surveillance checkpoints, where monoubiquitylation of the FANCD2-FANCI heterodimer signals to recruitment of DNA repair effectors to resolve DNA damage. The $CD24^+/44^+$ population of biliary tract (BT) cancer revealed higher expression of FANCD2 protein representing BRCA/FA pathway. The $CD24^+/44^+$ population was increased in chemoresistant (gemcitabine) BT cancer cells and revealed highly expressed BRCA/FA genes [109]. FA pathway also involves TLS repair and enhanced TLS could be responsible for chemoresistance in various ovarian CSC [110]. Mismatch repair (MMR) pathway removes nucleotides mispaired arising from replication errors. Loss of MMR genes have been associated with cancer chemoresistance [111], while proficient MMR correlated with high levels of CSC [112].

All major mechanisms and key DDR players related to CSC chemo- or radioresistance are summarized on Fig. 1. Up-regulation of genes involved in DDR pathways, including ERCC1, BRCA1 and BRCA2, has

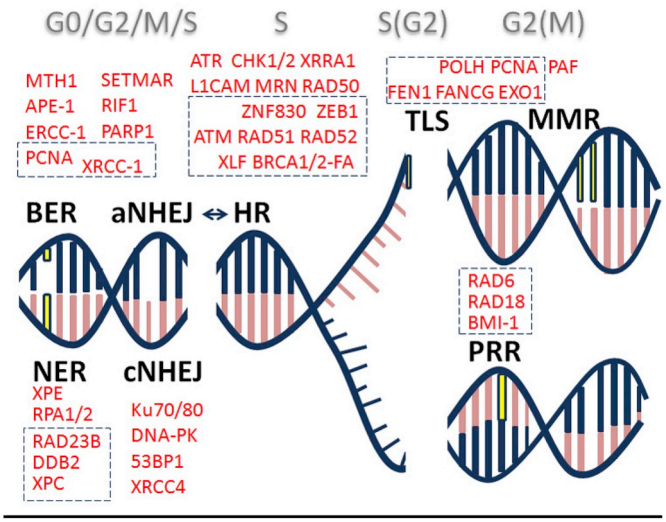

Fig. 1. Enhanced DDR pathways mediate resistance in CSC. Major DNA damage and repair pathways (bold black) are active in CSC. Upregulated proteins related to corresponding DDR are shown in red and those mediating radio- and/or chemoresistance of CSC are dot-framed. Most studies suggest that resistance of CSC manifests during the S phase by HR. This is regulated by MRN complex and activated by ATM/ATR. 53BP1 and receptor-associated protein RAP80 restrict resection and promote NHEJ. The switch from NHEJ to HR is accompanied by 53BP- mediated G2/M arrest and results in increased resistance of CSC to multiple forms of chemotherapy. The importance of S-phase repair also appears for CSC resistance after chemotherapy through enhanced activation of TLS by polymerase (POLH). BER—base excision repair; FA—Fanconi anemia; HR—homologous recombination; NER—nucleotide excision repair; a,cNHEJ—alternative and classical non-homologous end joining; MMR—mismatch repair; PPR—post replication repair; TLS—translesion synthesis. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

been shown to render tumor cells chemoresistant [113]. Enhanced expression of DNA polymerase eta (POLH) contributes to chemoresistance of ovarian CSC [110]. Other genes involved in DNA repair, like FEN1, FANCG, RAD23B, were found to be upregulated in chemoresistant human colon cancer cell lines [114], whereas ovarian cancer DDR is linked with chemoresistance through NF-κB-HOTAIR axis [115]. Malignant melanoma cells acquire chemoresistance by p53-triggered upregulation of DDB2/XPC-mediated DNA repair [116] or by induction of DNA repair gene ERCC1 [117]. HR-mediated zinc proteins ZNF830 [118] and ZEB1 confer chemotherapeutic resistance to breast cancer by activating ATM [119]. XRRA1 is involved in a DNA damage response that drives radio- and chemoresistance by regulating the ATM/CHK1/2 pathway in colorectal cancer [120]. Finally, secondary mutations in the DDR genes can reinstate their functions in DNA repair. For instance, almost half the time chemoresistance in BRCA1-and BRCA2-mutant cancers is due to restored DNA repair through secondary mutations in the BRCA genes [121].

4. Enhanced DNA repair capacity in CSC in comparison with non-stem tumor cells

How do CSC exhibit enhanced DNA repair capacity in comparison with non-stem tumor cells? This increase can be either through elevated DNA repair mechanisms, or through delayed cell-cycle progression. A major sensor of DNA double-strand breaks termed MRN complex is active in both CSC, malignant and normal cells. However, unlike non-stem tumor cells the MRN function is enhanced in CSC through communication with CSC-related molecules Notch1, ALDH1A1, CD44, Sonic Hedgehog and BMI1 [122] or through CD171 that preferentially activates DNA damage checkpoint and augments radioresistance of CSC [103].

It is a generally accepted concept that the cell fate decision following exposure to chemo- or radiotherapy depends on a certain threshold of DNA damage. While the levels of SSBs and DSBs are low, the DDR causes temporal cell cycle arrest to initiate NHEJ pathway and repair majority of radio- or chemotherapeutically-induced lesions [123]. When more significant DNA damage occurs, DDR causes activation of p53 signaling and apoptosis. Similar to normal stem cells, chemo-/radioresistant and CSC populations are slow-proliferating or quiescent cells [124]. On the one hand, this allows cells to wait out therapeutic intervention; on the other hand, these cells lack the efficiency of DNA repair, which can lead to the accumulation of additional DNA damage. However, many CSC seem to activate DNA repair mechanisms in the late S phase of the cell cycle enabling resection and repair by the HR to increase radio- and chemoresistance [125]. 53BP1 and receptor-associated protein RAP80 restrict resection and promote NHEJ. During the switch from NHEJ to HR, 53BP1 mediates G2/M phase arrest with increased resistance to multiple forms of chemotherapy and a propensity to evade apoptosis [126]. Chemo-/radioresistant cancer cells as well as CSC tolerate replication stress by ATR or ATM – activated DDR and choosing HR in the S phase [127]. The repair at S-phase also appears for CSC resistance after chemotherapy through enhanced activation of TLS by polymerase eta [110].

Along with upregulation of DNA repair, the basal activation status of checkpoint kinases may constitute a key mechanism for CSC to resist genotoxic agents. Lung CSC preferentially activate CHK1 in response to the ATM- and ATR-dependent G2-M checkpoint to survive radiotherapy [107]. The radioresistance of nasopharyngeal CSC relies on the transactivation of CHEK1/2, resulting in a proficient DNA damage checkpoint [128]. As aforementioned, ATR-Chk1 and ATM-Chk2 signaling pathways are preferentially activated in CSC-like progenitor cells, but not in non-stem cancer cells in response to genotoxic stress [129]. The EMT-inducing transcription factor ZEB1 participates in an ATM-dependent mechanism that supports the DDR in CSC by stabilizing CHK1 [130].

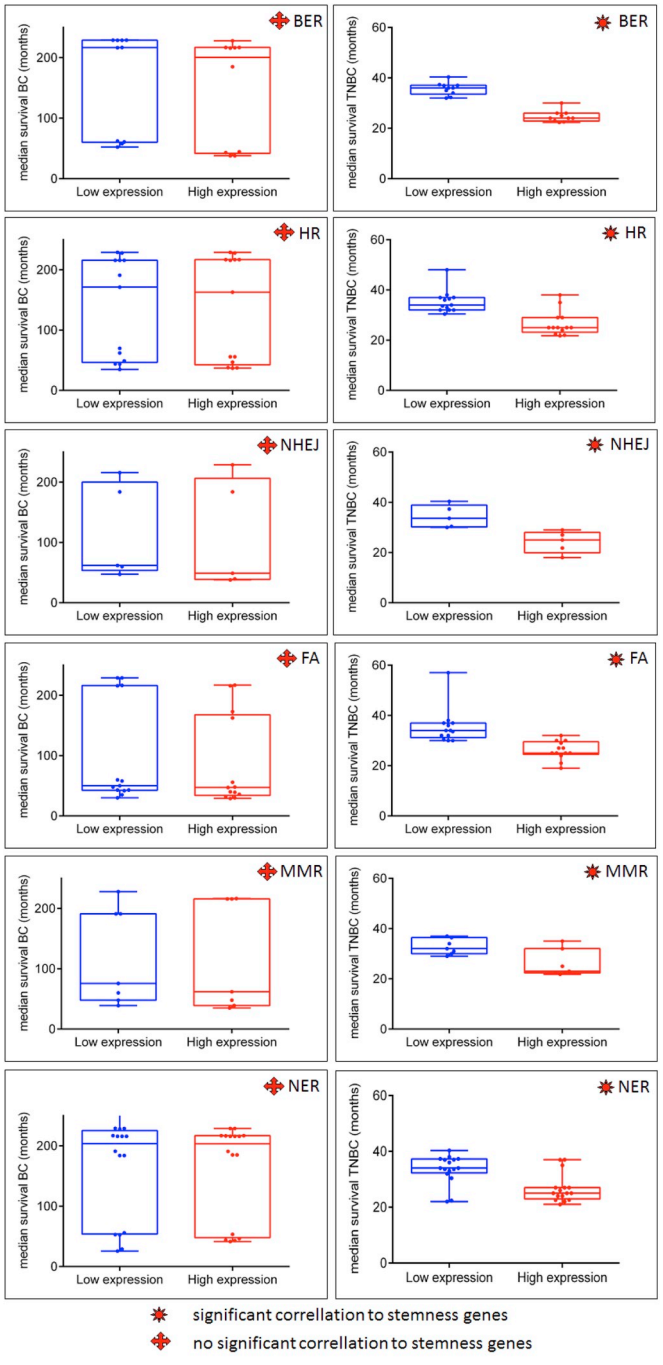

Fig. 2. Higher expression of DDR genes in a cohort of TNBC correlates with co-expression of stemness genes and poor survival rate. Comparison was made between the two patient cohorts in terms of overall survival. Multivariate analysis of breast cancer patients (n = 5143) from 2010 to 2017 databases, including E-MTAB, E-TABM, GSE was performed. Biased and outlier arrays were excluded. Filtering was done for the patients with systemic treatment (n = 3099) from which patients treated with endocrine therapy (n = 1718) were excluded. For TNBC cohorts, filtering was done over ER negative (n = 1214), PR negative (n = 1028), HER2 negative (n = 1456) patients with grade 3 (n = 1090). The hazard ratio with 95% confidence intervals and log-rank P value as output were determined. DDR genes represented groups of mismatch repair (MSH2, MSH3, MSH6, PMS2, MSH4, MSH5, PMS2L3), nucleotide excision repair (XPC, RAD23B, CETN2, DDB1, RPA1, RPA3, ERCC2, GTF2H2, GTF2H3, CDK7, CCNH, MNAT1, ERCC1, LIG1, UVSSA, MMS19), homologous recombination repair (RAD51, RAD50, XRCC2, XRCC3, RAD54L, RAD54B, BRCA1, MRE11A, RBBP8, MUS81, GIYD1, GIYD2, GEN1), non-homologous end joining repair (XRCC5, PRKDC, LIG4, XRCC4, NHEJ1), Fanconi anemia (FANCA,B,D2,E,F,I,L,M,N,O, RFWD3), base excision repair (MBD4, UNG, TDG, NEIL3, APEX2, LIG3, PNKP, POLG, PCNA, REV1L).

5. Increased DDR in CSC and chemoresistant cancers and prognostic markers

Increased DDR in CSC and chemoresistant cancer cells may in general be used as a DNA repair prognostic marker. Subsequently, a recent study for a panel of DNA repair proteins, including Pol β, FEN1, APE1, XRCC1, SMUG1, PARP1, BRCA1, ATR, ATM, DNA-PKc, CHK1, CHK2, p53, and TOPO2, allowed separating patients in a prognostic group with high levels of DDR markers to a group with a higher risk of death ($p < 0.001$) [131]. We reasoned that if the abundance of DDR genes and encoded proteins correlates with the presence of CSC, then co-occurrence of stem cell markers and high expression levels of DDR genes could be a hallmark for poor prognosis. Multivariate analysis of breast cancer patients ($n = 5143$) revealed that median survival rate in the group of TNBC with higher expression of genes from major DDR pathways was significantly lower than that of all types of breast cancers (Fig. 2). In addition, only TNBC group was correlated with high levels of co-expressed stem cell genes.

Checkpoint kinases CHK1 and CHK2 may have a role in breast cancer pathogenesis and influence response to chemotherapy. Phosphorylation of CHK1 was associated with DNA damage response (ATM, RAD51, BRCA1, KU70/KU80, DNA-PKCα and BARD1) and predicted shorter survival in patients who received cyclophosphamide, methotrexate and 5-florouracil chemotherapy [132]. At the same time, phosphorylation of CHK1 at serine345 is a predictor of early local recurrence and radio-resistance in breast cancer [133]. Resistance to DNA-damaging treatment in non-small cell lung CSC was linked to increased basal γH2AX expression and diminished DNA damage-induced phosphorylation of DNA-PK, ATM, Krüppel-associated protein 1 and monoubiquitination of FANCD2 [134]. Finally, patients with activated ATR after neoadjuvant therapy had worse chemotherapy response and poorer overall survival (32 months vs. > 140 months) than those without ATR activation [135].

6. Clinical implications

It has long been recognized that defective DNA repair pathways leads to tumour susceptibility. Due to the enhanced DDR in most types of CSCs and resistant cancer cells, modulation of the DDR in these cells became a new therapy strategy in the combinatorial treatment with DNA damaging agents. It has therefore been speculated that DDR inhibition might enhance the effectiveness of chemo- or radiotherapy. Not surprisingly, several DDR-inhibitory drugs are now in pre-clinical and clinical development to test this premise [136–138]. So far, the following targets have been proposed to decrease DDR: PARP1, RAD51, CHK1, CHK2, ATM, ATR [139]. Here, we summarize existing DDR targets and corresponding drugs or stimuli aiming to chemo- or radiosensitize certain tumour types or reduce CSC population within tumors (Table 2).

6.1. PARP inhibitors

Although initially developed to exploit synthetic lethality in cancers associated with defective DNA repair, nowadays PARP inhibitors are applied both in cancer with select chemotherapeutic agents and in non-malignant diseases [140]. The growth, self-renewal, and DNA damage repair capacity of glioblastoma CSC can be inhibited by PARP inhibitor olaparib, leading to an enhanced sensitization of GSC to radiation [95]. Olaparib was able to decrease population of TNBC CSC by decreasing RAD51 level [99]. This inhibitor also has substantial antitumor and anti-CSC activity in breast cancer cell lines of nonfamilial origin [141]. Radiosensitization effect of PARP inhibitor, talazoparib, was demonstrated on glioblastoma stem cells [142].

6.2. CHK1/CHK2 inhibitors

Inhibitors of CHK1 and CHK2 modulate the response of the cell to DNA damage, which leads to checkpoint abrogation and inhibition of DNA repair [143]. $CD133^+$ glioma stem cells contribute to glioma radio-resistance and tumor regeneration through the activation of CHK1/2 and DDR. A specific inhibitor of the CHK1 and CHK2, debromohymenialdisine (DBH), has been demonstrated to target $CD133^+$ GSC and reverse the radio-resistance of GSC [129]. Phosphorylation of CHK1 was significantly enhanced in $CD133^+$ CSC-like cells in colon cancers as compared with $CD133^-$ cells treated with ICL agents. Consistently, the chemoresistance of $CD133^+$ cells toward DNA ICL agents was overcome through inhibition of ATR/CHK1-signaling [144]. Downregulation of CHK2 was demonstrated to reduce stemness in multiple myeloma cancer cells treated with DNA damaging agents [73]. In addition, NSCLC-stem cell survival can be dramatically reduced by CHK1 inhibitors (SB218078 and AZD7762) in combination with chemotherapy [107]. Radio-sensitization by inhibition of CHK1 activation by ATR inhibitor (VE-821) and inhibition of CHK1 (V158411) was observed in MDA-MB-231 (p53 mutant) and MCF-7 (p53 wild-type) breast cancer cells [145].

6.3. HR targeting

Overexpression of RAD51, a recombinase involved in HR, is associated with a more aggressive cancer phenotype and treatment resistance in a variety of tumors, including ovarian, prostate, colorectal cancer, and malignant gliomas [146,147]. The resistance of CSC from TNBC is mediated by RAD51 and suggest targeting RAD51 to increase the therapeutic efficacy of PARP inhibitors [99]. Decreased expression of DNA repair proteins RAD51, KU70 and RIF1 by the hypoxia-activated prodrug tirapazamine reduced the colon CSC [148]. Inhibition of RAD51 by siRNA or resveratrol sensitized CSC derived from HeLa cells to apoptosis [149]. RAD51 inhibitor RI-1 targeted radioresistant glioblastoma stem-like cells [150]. In patient-derived glioblastoma stem cells, the small-molecule RAD51 inhibitors RI-1 and B02 prevented RAD51 focus formation, reduced DNA DSB repair, and caused significant radio-sensitization [98]. The B02 was also shown to potentiate breast cancer cells *in vitro* and *in vivo*. Oncolytic herpes simplex viruses (oHSVs) targeting RAD51 eliminated patient-derived glioblastoma stem cells [151].

RAD50 represents another challenging target to modulate DDR. Recently, we identified RAD50 as an abundant protein in TNBC CSC and chemoresistant cancer cells. Ours and others works demonstrated that RAD50 targeting impaired DDR and chemo-sensitized human breast cancer cells [152]. Adenovirus containing a dominant negative mutant Rad50 gene directed against RAD50 zinc hook domain was able to radio-sensitize human nasopharyngeal carcinoma cells [153]. Natural compound streptonigrin targeting RAD54 was shown activity against melanoma CSC [154]. ATM inhibition by KU55933 in non-small cell lung CSC increased their cisplatin resistance, as demonstrated by reduced PARP cleavage [134]. Inhibition can also be achieved by miRNAs. miRNA (miR-18a-5p) targeting ATM was applied to radiosensitize lung CSC [155]. Finally, TH588 and TH1579, small molecule inhibitors of MTH1 responsible for modulation of nucleotide pools were able to target glioblastoma stem cells [83].

6.4. NER inhibitors

Inhibition of RPA2 phosphorylation at Ser33-a by telomestatin was shown to target glioma CSC [156]. Sorafenib, a potent inhibitor of Raf kinase and VEGF receptor, could reverse the resistant phenotype in head and neck squamous cell carcinoma and CSC and enhance the antitumor effects of chemo- and radiation treatment by downregulating ERCC-1 protein [157]. Ovarian CSC subpopulation can be maintained via cancer cell dedifferentiation, and DDB2 is able to suppress

Table 2
DDR targeting drugs.

Drugs or stimuli		Target	Outcome	Ref
PARP inhibitors	Olaparib	PARP1	Radiosensitization of glioblastoma stem cells	[95]
			Inhibition of TNBC CSC	[99]
			Anti-CSC in breast cancer	[184]
	Talazoparib	PARP	Radiosensitization of glioblastoma stem cells	[142]
CHK1/2 inhibitors	Debromohymenialdisine	CHK1/2	Inhibition of glioma CSC	[129]
	UCN-01	CHK1	Inhibition of colon CSC	[144]
	shRNA	CHK2	Reduction of multiple myeloma CSC	[73]
	SB218078	CHK1	Reduction of NSCLC stem cell	[107]
	AZD7762	CHK1	Reduction of NSCLC stem cell	[185]
	MK-8776	CHK1	Inhibition of TNBC cell proliferation	[145]
HR inhibitors	–	RAD51 pDNA-PKc	Inhibited and radiosensitized lung cancer cells	[99]
	Tirapazamine	RAD51	Inhibition of colon CSC	[148]
		KU70		
		RIF1		
	Resveratrol and siRNA	RAD51	Promoting CSC-like to apoptosis	[149]
	RI-1	RAD51	Inhibition and radiosensitization of glioblastoma CSC	[150]
	B02	RAD51	Patient-derived glioblastoma CSC	[98]
			Breast CSC	[186]
	oHSVs	RAD51	Eliminated patient-derived glioblastoma CSC	[151]
	Ad-RAD50	RAD50	Radiosensitization of nasopharyngeal CSC	[153]
	Streptonigrin	RAD54	melanoma CSC	[154]
	KU55933	ATM	NSCLC CSC	[134]
	miR-18a-5p	ATM	radio-sensitization of lung CSC	[155]
	TH588, TH1579	MTH1	Inhibition of glioblastoma CSC	[83]
NER inhibitors	Telomestatin	RPA2	Inhibition of glioma CSC	[156]
	Sorafenib	ERCC1	Inhibition of HNSC CSC	[157]
		Raf		
	NCT-501	DDB2	Suppression of ovarian CSC	[158]
	AOH1160	PCNA	Resensitization cancer cells to cisplatin	[159]
NHEJ inhibitors	PU-H71	HSP90	sensitizes cancer cells to heavy ion irradiation	[160]
	LY294002	DNAPKc	Inhibition of breast CSC	[161]

conversion to CSC by repression of ALDH1A1 transcription. Treatment with a selective ALDH1A1 inhibitor NCT-501 blocked DDB2-mediated expansion of CSC, and halted orthotopic xenograft tumor growth [158]. PCNA plays an essential role in regulating DNA synthesis and repair. PCNA inhibitor (AOH1160) interferes with DNA replication, blocks homologous recombination-mediated DNA repair, and causes cell cycle arrest. It induces apoptosis in cancer cells and CSC and sensitizes them to cisplatin treatment [159].

6.5. NHEJ targeting

The purine scaffold HSP90 inhibitor PU-H71 sensitizes cancer cells to heavy ion radiation by inhibiting HR and NHEJ [160]. DNA-PKc inhibitor LY294002 was shown to suppress breast CSC [161].

7. DDR independent mechanisms of CSC resistance

It is also noteworthy that other factors independent from up-regulation of the DDR can be responsible for the development of resistant phenotype in CSC. In particular, sustained hypoxic microenvironment might promote therapy resistance by activation of hypoxia-inducible factor (HIF) [162,163]. HIF pathway confers chemo- and radio-resistance of certain tumors [164–166]. Mitochondria represent another defense line against DNA insults caused by reactive oxygen species (ROS) during radio- or chemotherapy [167]. The RedOx system of these organelles provides a universal protection against ROS excess and helps eliminating oxidative damage without activation of DDR pathways [168]. High activity of aldehyde dehydrogenases (ALDHs), the enzymes responsible for the scavenging of radiation-induced free radicals and the production of the antioxidant NAD(P)H, is also characteristic of chemoresistant cancer cells [169] and CSC [170] but not the regular cancer cells. In many cancers however, mitochondria are dysfunctional under hypoxia resulting in increased glucose uptake to cover high energetic demands of growing tumors. This should diminish mitochondria scavenging roles to enhance effects of anticancer therapies. In contrary, mitochondria of CSC and chemoresistant cancer cells behave similarly to normal cells [171]. This may explain why both CSC and resistant cancer cells demonstrate great efficiency in scavenging of ROS and therefore eliminating the primary cause of DNA insults [172,173]. Several other mechanisms might decrease efficiency of radio- and chemotherapy in CSC comparatively to non-CSC. Among those are autophagy [174,175], microRNAs [176] and exosome-containing microRNAs [177] and EMT-related pathways contributing to tumor cell reprogramming into CSC [178,179].

8. Discussion

Increased DDR may reflect poor clinical outcome in certain categories of patients, especially in the groups with chemo- or radio-resistant phenotypes or those groups with aggressive or recurrent cancers which are linked with the overexpression of stem cell markers. Conversely, in other groups of patients somatic DDR alteration is associated with improved clinical outcomes, as for example in cisplatin-treated patients with advanced urothelial carcinoma [180]. One has to underline that DDR activation is not a universal mechanism of CSC resistance. For example, reduced DSB repair capacity was found in glioma CSC compared with the glioma cell lines [181]. An alternative scenario may include releasing drug-mediated ROS which in turn activate survival pathways, including enhanced DDR. All these facts suggest existing alternative mechanisms of CSC resistance. Recent work revealed that not only DDR but also cell cycle status contributes to CSC survival in genotoxic insults. In this study, esophageal CSC

preferentially stayed quiescent as compared to the non-CSC and were more resistant to DNA damage agents. The reduced DDR was also reported in esophageal CSC [182]. In another study, DDR was examined in five stem and nonstem glioma cell lines. The population doubling time was significantly increased in stem compared with nonstem cells, and enhanced activation of CHK1 and CHK2 was observed in $CD133^+$ compared with $CD133^-$ cells. However BER was not increased in $CD133^+$ compared with $CD133^-$ cells. Authors concluded that glioma CSC displayed elongated cell cycle and enhanced basal activation of checkpoint proteins which contributed to their radioresistance, whereas enhanced DDR was not a common feature of these cells [183]. Possible explanations for such phenomena could be some mutations in DDR machinery, existence of genetic heterogeneity in cancer, or variability of CSC isolated from different cell lines and patients which resulted in different DDR. Although research in the field is progressing very fast, proof of concept for the resistance of CSC and chemoresistance of cancer cells is still lacking and key questions remain unanswered, e.g. the cell of origin for these cells.

9. Conclusion remarks

Distinct DNA repair pathways can neutralize the cytotoxicity of chemo- and radio-therapeutic agents, driving resistance and tumor relapse. It seems that a subpopulation of CSC sharing similar qualities with chemo- and radio-resistant cancer cells is responsible for tumor initiation, maintenance and recurrence and they appear to be more resistant owing to their enhanced DDR. Beside their increased DNA repair capacity in comparison with non-stem tumor cells, some CSC show a constitutive and enhanced expression of DDR that enables them to survive to treatments in a quiescent, non-proliferative state. Consequently, cancer cells are often more reliant on a subset of repair pathways and are therefore more susceptible to DDR inhibition than are normal cells that maintain full DNA-repair/DDR capacity. The targeted inhibition of DDR-related proteins can contribute to eradicate the CSC population and can have a potential therapeutic impact at sensitizing resistant cancer cells to treatments, improving patient selection for clinical practice and future study enrollment as well as the overall survival of patients.

Declaration of competing interest

The authors declare that they have no competing interests.

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