Chapter 7
DNA Repair Mechanisms in Other Cancer Stem Cell Models

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Abstract Stem cells are often referred to as the mother of all cells, meaning that they sit at the apex of a cellular hierarchy and, upon differentiation, give rise to all the mature cells of a tissue. DNA damage constantly arises from DNA replication, spontaneous chemical reactions and assaults by external or metabolism-derived agents. Therefore, all living cells must constantly contend with DNA damage. It is particularly crucial for survival of organisms how DNA damage is handled in stem cells, including tissue specific stem cells. While tissue-specific stem cells share the same purpose of maintaining organ functionality, recent studies have shown that the mechanisms of their response to DNA damage, the outcome of their DNA damage response, and the consequence of DNA repair for genomic stability vary greatly between tissues. Striking differences in the outcome of DNA damage response (DDR) have been seen in hematopoietic stem cells from different species and at different developmental stages. Furthermore cell cycle and metabolic states of stem cells seem to affect choices of DNA repair pathways and a choice between cell survival and death.

7.1 Introduction

The cancer stem cell (CSC) model of tumor development and progression states that tumors, like normal adult tissues, contain a subset of cells that both self renew and give rise to differentiated progeny [1]. A number of CSCs have been identified, including leukemia, breast, brain, melanoma, prostate, head and neck squamous cell carcinomas (HNSCC), colon and pancreatic tumors [2–13]. The cellular origin of CSCs remains elusive. However, these CSCs functionally resemble tissue specific stem cells, and share surface markers with adult stem cells. Therefore, it is believed that CSCs are derived from tissue specific stem cells or converted from progenitor cells. Recent studies indicate that CSCs may take advantage of the mechanisms of DNA repair used by tissue specific stem cells to mediate resistance to chemo- and radiotherapy [14]. Understanding of DNA damage response controls in CSCs has

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emerged particularly in glioblastoma and breast CSCs (see Chaps. 5 and 6). However, it is still largely unknown how CSCs respond to DNA damage despite its importance in therapies. Unlike tissue specific stem cells, cancer cells are heterogeneous in nature, and often carry mutations in DNA repair and damage response genes. The background mutations might affect the DNA damage response of CSCs. This chapter focuses on various CSCs giving overviews of their DNA damage responses (DDR).

7.2 Cancer Stem Cells in Leukemia

Leukemia was the first disease for which human cancer stem cells, or leukemic stem cells (LSCs) were isolated through the groundbreaking work of Bonnet and Dick [15]. The hematopoietic system is one of the best tissues for investigating cancer stem cells, since the developmental hierarchy of normal blood formation is well defined and distinct subsets of mature and immature hematopoietic cells can be isolated by fluorescence-activated cell sorting (FACS) based on expression of known surface markers [16].

Leukemias often arise due to deregulated hematopoietic stem cell (HSC) functions or acquisition of extended self-renewal capabilities by more mature progenitor cells [14, 17]. Existence of CSCs in several types of human leukemias have been shown [15, 18, 19]. Like hematopoietic stem cells (HSCs), the populations of human LSCs were found to be mainly quiescent [20, 21], and thereby refractory to most of the conventional treatments and as such relapse [16]. LSCs also use other prospective mechanisms of HSCs, including localization to hypoxic niche, and DDR mechanisms, to specifically escape chemo- and radiotherapies that kill the bulk of the tumor cells [14, 22].

Chronic myeloid leukemia (CML) is sustained by a rare population of primitive, quiescent BCR-ABL^{+} cells and represents an excellent example of a malignancy in which CSCs represent the key to disease eradication [23]. In CML, the expanded clone is believed to be initiated in a pluripotent hematopoietic stem cell, by chance occurrence of a rare mutational event, the translocation of t(9;22), giving rise to the Philadelphia (Ph) chromosome and expression of the oncogenic fusion protein tyrosine kinase breakpoint cluster region-abelson (BCR-ABL) [24]. Although the BCR-ABL tyrosine kinase inhibitor imatinib mesylate has revolutionized CML treatment owing to its remarkable clinical efficiency, it does not appear to be fully curative, owing to the likely survival of BCR-ABL expressing HSCs in patients [16, 23, 25].

CML is a two-stage blood disease that can be separated into chronic and acute phases. The patients with chronic phase disease usually respond to treatments with ABL tyrosine kinase inhibitors. However, some patients who respond initially later become resistant. The pleiotropic effect of constitutive BCR-ABL activity seems to cause epigenetic changes [26, 27]. Expression studies demonstrated that BCR-ABL dramatically perturbs the CML transcriptome, resulting in altered expression of genes [28]. The posttranscriptional, translational, and posttranslational effects of high BCR-ABL levels result in the constitutive activation of factors with mitogenic, anti-apoptotic and anti-differentiation activity (e.g. MAPK$^{ERK1/2}$, MYC, JAK2, YES-1,

LYN, hnRNP-E2, MDM2, STAT5, BMI1, and BCL-2) and inhibition of major key regulators of cellular processes, such as those regulated by the tumor suppressors p53, CCAAT/enhancer binding protein-α (C/EBPα), and PP2A [26, 27, 29–31]. Therefore, it is likely that increased BCR-ABL activity promotes clonal evolution and survival of the tumor. Furthermore, there is a direct correlation between the levels of BCR/ABL, the frequency of clinically relevant BCR/ABL mutations and the differentiation arrest of myeloid progenitors [31–34]. It is highly possible that disease progression and maintenance of the CML stem/progenitor cells are caused by the right combination of genetic and epigenetic abnormalities.

The transition from the chronic to the acute stage is poorly understood, but the deregulation of DDR pathways and acquisition of additional chromosomal aberrations and mutations resulting in overall genomic instability in both HSCs and their downstream progeny are believed to play a crucial role in the transition to the malignant state. BCR-ABL-expressing cells have been found to accumulate genetic abnormalities, but the mechanism leading to this genomic instability is controversial [35]. BCR-ABL-transformed cell lines and $CD34^+$ CML cells contain about 2–6 times more reactive oxygen species (ROS) than their normal counterparts, and accumulate 4–8 times more double-strand breaks (DSBs) [36–38]. Unfaithful and/or inefficient DNA repair of ROS-induced oxidized DNA bases and DSBs could lead to a variety of chromosome aberrations [39]. Effects of BCR-ABL on many DNA repair pathways have been described.

7.2.1 Double-Strand Break Repair in BCR-ABL Cells

It is well documented that partial deletions, duplications and translocations are commonly observed in patients with the acute stage disease [40]. These chromosomal aberrations could arise from unfaithful repair of DSBs. Effects of BCR-ABL in DSB repairs have been demonstrated.

Enhanced homologous recombination repair efficiency as well as sister-chromatid exchange frequency in BCR-ABL expressing cells have been shown [41–43]. Indeed the fusion tyrosin kinase-dependent upregulation of Rad51 expression is reported [42]. Furthermore, c-Abl kinase phosphorylates Rad51 in response to ionizing radiation (IR) [44]. Interestingly downregulation of BRCA1, which is a regulator of Rad51, was observed [43].

Non-homologous end joining (NHEJ) repair usually occurs in a cell cycle dependent manner. It is a preferred pathway when cells are in G0/G1 phase of cell cycle. Therefore, the CML cells, which are in a quiescent state, might utilize this pathway preferentially to repair double-strand breaks (DSBs). In fact, NHEJ activity was approximately two-fold higher in BCR-ABL expressing 32Dcl3 cells compared to the parental cells, and four-fold higher in the case of 5′ overhang repair activity. Additionally, more frequent small additions and larger deletions were found in the BCR-ABL expressing cells [41]. Another group confirmed these results in CML patient cells. BCR-ABL-expressing CML patient samples and K562 cells exhibited

a three- to five-fold increase in end-ligation efficiency compared to normal $CD34^+$ cells. Larger deletions, 30–400 bp, were observed in the CML cells. It remains controversial whether the activated NHEJ pathway is a cause for genomic instability in CML cells or not. In other studies, no difference in blunt-end repair was seen between K562 myeloid leukemia cells with a p53 mutation and normal human lymphocytes. However, the p53-negative K562 cells induced fewer repair products with 5′ overhangs than normal lymphocytes [45]. Downregulation of DNA-PKcs but not Ku70 and Ku80 were observed by one group [46]. It is not clear whether elevated levels of DNA damage are driving error-prone repair by NHEJ in CML cells or CML cells activate the NHEJ pathway inducing genomic instability.

7.2.2 Other Repairs in BCR-ABL Cells

BCR/ABL oncogenic tyrosine kinase exhibits two complementary roles in cancer development. The first and best-characterized role is stimulation of signaling pathways that eventually induce growth-factor independence and affect the adhesive and invasive capability of leukemia cells. The second is modulation of response to DNA damage rendering cells resistant to genotoxic therapies and causing genomic instability as described above. BCR/ABL-induced genomic instability may lead to mutations and chromosomal translocations frequently observed during the transition from a relatively benign CML chronic phase (CML-CP) to an aggressive blast crisis (CML-BC) [26, 37, 47, 48]. Mechanisms leading to resistance include amplification of the BCR/ABL gene and acquired additional genomic alterations, which are likely to be caused by deregulation of DSB repair pathways as discussed above. Beside these gross chromosomal changes, numerous small mutations are detected in the BCR/ABL gene itself encoding for resistance to imatinib mesylate [37, 49, 50]. ROS induced by BCR/ABL expression and clonal selection during evolution of the disease seems to be a cause of the mutations that are detected in patient cells.

It has also been reported that BCR/ABL inhibits mismatch repair (MMR) leading to accumulation of mutations. Impaired MMR activity is associated with better survival, accumulation of p53 and lack of activation of Caspase 3 after N-methyl-N′-nitro-N-nitrosoguanidine (MNNG) treatment [51]. Microsatellite instability was observed in CML-BC but not in relatively benign CML-CP. This microsatellite instability seems to reflect multiple replication errors due to defective MMR [52].

Connections between nucleotide excision repair (NER) and BCR/ABL have been indicated. Interaction between XPB and p210 BCR/ABL (but not p185 BCR/ABL) has been shown. It was later suggested that NER defect seen in BCR/ABL cells might be a result of BCR/ABL interfering with overall formation of TFIIH complex formation [53–56]. Ectopic expression of p210 BCR/ABL in murine lymphoid cell line inhibits NER activity *in vitro*, promoting hypersensitivity of these cells to ultraviolet (UV) treatment and facilitating a mutator phenotype. However, expression of p210 BCR/ABL in human and murine myeloid cell lines and primary bone marrow cells resulted in the increased NER activity and resistance to UV irradiation [57]. Furthermore, it was shown that stably expressing BCR/ABL human hematopoietic cell lines

as well as fibroblast cell lines repaired UV-induced damage much more quickly and showed markedly reduced apoptosis compared to their parental counterparts [58]. However, these results have not been confirmed in fresh patient cells.

7.2.3 Cell Cycle Checkpoint in BCR-ABL Cells

Studies have shown that $CD133^+$-glioma stem cells activate cell cycle checkpoint pathway more efficiently compared to $CD133^-$ cells ([59], see Chap. 5). BCR/ABL-positive CML cells can repair DSBs more efficiently than the normal counterparts and eventually survive genotoxic treatment. Elevated levels of drug-induced DSBs are associated with higher activity of checkpoint kinase ATR, and enhanced phosphorylation of histone H2AX. This gamma H2AX eventually starts to disappear in BCR/ABL cells, while continues to increase in parental cells. In addition, expression and ATR-dependent phosphorylation of Chk1 kinase on serine 345 are often more abundant in BCR/ABL cells [55]. Furthermore, BCR/ABL stimulates expression of Nbs1, a member of Mre11-Rad50-Nbs1 complex that plays crucial roles in DNA repair and checkpoint activation. Enhanced ATM-dependent phosphorylation of Nbs1 on serine 343 was observed after damage [60]. A number of other reports have also shown that BCR/ABL-positive cells display enhanced G2-M checkpoint activation in response to various DNA damaging agents including cisplatin, MMC, etoposide and daunorubicin. This enhanced activation of the checkpoint seems to cause resistance to chemotherapies [42, 55, 61–64]. This effect might be due to ATR- and ATM-mediated phosphorylation of p53, leading to its accumulation causing upregulation of $p21^{Waf1}$ and GADD45 [65]. In fact, increased p53 accumulation after DNA damage has been reported in CML primary cells [66]. This effect was associated with ABL kinase-dependent stimulation of ATR/ATM and p53 phosphorylation. Moreover, a checkpoint kinase ATM is shown to phosphorylate c-Abl in response to irradiation [44]. However, in contrast to these observations, one report shows an opposite result. BCR/ABL kinase protein translocates to the nucleus, associates with ATR and disrupts ATR-dependent intra-S-phase checkpoint, leading to a radio-resistant phenotype and prolonged G2-M checkpoint after etoposide treatment [67]. Although the reason for this discrepancy is unknown, the differences in the cells and cell lines used in these studies might be responsible. The latter used an inducible model, and the others used stably expressing BCR/ABL cell lines and/or primary patient cells. Constitutive but not inducible expression of BCR/ABL might better mimic the conditions in established Philadelphia chromosome-positive leukemia cells [60].

As described above, different results have been reported on similar experiments for investigation of DDR pathways in BCR/ABL-expressing cells. It is highly possible that this was caused by differences in cell/cell line system utilized in those studies. The majority of experiments are performed with $CD34^+$-fresh or short-term cultured patient cells from bone marrow, comparing to $CD34^+$ cells from healthy donors. This setting is probably the best for understanding DDR regulation in leukemia and also in leukemia stem/progenitor cells *in vitro*. In some cases, similar results were

obtained from fibroblasts or transformed cells with artificial expression of BCR/ABL, indicating that overexpression of the oncoprotein itself effects DDR. Alteration of this response could be caused by the direct effects of BCR/ABL on DNA damage response proteins and/or gene expression, or by induction of DNA damage such as ROS. There have not been comprehensive studies to investigate DDR in true LSCs comparing to progenitor and differentiated cells to date. Such studies will be valuable in unraveling reasons why chemotherapies fail and cause relapses in some cases.

7.3 Cancer Stem Cells in CNS Tumors

The most common and well-characterized CNS tumor is glioblastoma. It still remains controversial, however an enhanced DNA repair capacity and preferential activation of DNA damage checkpoint pathway have been reported in $CD133^+$ glioma stem cells ([59], see Chap. 5). Similar results were demonstrated in another CNS tumor, atypical teratoid/rhabdoid tumor (AT/RT) [68]. AT/RT is a rare, aggressive, and highly malignant tumor that commonly occurs in infancy and childhood [69–72]. In the past, the majority of AT/RTs were misclassified as primitive dermal tumors (PNET) and medulloblastoma (MB) at supratentorial sites because of the similarities in radiological and histological features of these tumors [73, 74]. As the word *teratoid* indicates, AT/RTs show multiple-lineage developmental characteristics of malignant teratomas of neuroectodermal, mesodermal, and endodermal lineages [73–75]. Clinical data have indicated that the amount of $CD133^+$ cells in AT/RTs correlated positively with degrees of resistance to radiation therapies. Increased phosphorylation of checkpoint proteins, ATM, RAD17 and CHK1 as well as increased expression of BCL-2 in $CD133^+$ cells as compared to $CD133^-$ cells were observed after radiation. Furthermore, $CD133^+$ cells were found to be more resistant to ionizing radiation (IR) in combination with cisplatin-and/or TRAIL-induced apoptosis [68].

Another pediatric CNS tumor medulloblastoma contains CSCs in a perivascular niche. It has been speculated that the CSC population gives rise to recurrence following radiation. A mouse medulloblastoma model showed that the nestin-expressing perivascular stem cells survive radiation, activate PI3K/Akt pathway, undergo p53-dependent cell cycle arrest, and reenter the cell cycle, whereas the proliferating cells in the tumor bulk undergo radiation-induced p53-dependent apoptotic cell death. Activation of Akt signaling via PTEN loss transforms these cells to a non-proliferating extensive nodular morphology [77]. Effects of Akt activation on DNA repair and checkpoint responses were not investigated in the study. However, involvements of Akt in DDR pathways have been demonstrated. Activation of Akt in response to IR and temozolomide depends on ATM and ATR [78, 79]. Activation of the Akt pathway has been linked to chemoresistance in colon and breast cancer cells as well as in $CD133^+$ hepatocellular carcinoma [79, 80]. However, another study reported that Akt activation suppresses Chk2-mediated temozolomide-induced G2 arrest in a glioma cell line [81].

7.4 Cancer Stem Cells in Pancreatic and Prostate Cancer

Increased expression of DNA repair genes were found in invasive human pancreatic cancer cells [82–86]. The same trend was observed in other cancers including cervix [87], head and neck [88], brain [89], kidney [90] and bladder [91]. Similar results were obtained from invasive human prostate cancer cells. These cells undergo an epithelial to mesenchymal transition during the process of invasion [92]. In the invasive pancreatic cells, the upregulated genes included BRCA1, FANCI and RAD51. It was demonstrated that the invasive prostate cancer cell population exhibited cancer stem cell-like properties such as high tumorigenicity in mice and elevated expression of stem cell markers [82]. Cells overexpressing RAD51 showed higher rate of survival compared to cells that expressing basal levels of RAD51 after a DSB-inducing drug [93]. Furthermore, overexpression of Rad51 causes dysregulated homologous recombination (HR) and elevated genetic instability [94, 95]. Therefore, Rad51 overexpressing cancer stem cells might acquire survival advantage and accumulate genomic instability leading to progression of tumors. An enhanced level of BRCA1 foci without damage and faster repair after a cytotoxic pyrimidine-analog drug, gemcitabine, treatment were observed [82]. The link between an invasive population of cancer cells and CSCs alls fits within "the cancer stem cell hypothesis" (see Chap. 1). The small population of CSCs has the ability to survive after chemo- and radiotherapies leading to aggressiveness and relapse of tumors. In fact, resistance to gemicitabine was shown to be associated with cancer stem cell-like phenotype, although causes of the resistance were not addressed [96]. One possible reason is enhanced DNA repair and damage response capacity in the population.

7.5 Cancer Stem Cells in Colon Cancer

Consistent with reports in glioma and breast CSCs (see above Chaps. 5 and 6), preferential activation of the checkpoint in $CD133^+$ colon cancer stem cells was recently observed [97]. In this study, enhanced activation of Chk1 was observed after treatment with the intra-crosslinking agent mitomycin C. Inhibition of the ATR but not ATM pathway depleted $CD133^+$ tumorigenic cells *in vitro* and *in vivo*. Caffeine, a non-specific inhibitor of checkpoint-modulating phosphoinositide 3-kinase related (PIK) kinases, increased proliferation and apoptosis of $CD133^+$ colon CSCs. Induction of stalled replication forks by mitomycin C increased the effect of ATR/Chk1 inhibition on the $CD133^+$ population. The Fanconi anemia pathway is required for intra-crosslink DNA repair, and is mediated by the ATR pathway [98, 99]. However, no significant differences in the $CD133^+$ population in FANCC and FANCG deficient cells were observed [97]. ATR has also been shown to be required for normal stem cell maintenance, and furthermore, ATR is an essential gene for embryonic development [100]. However, ATR conditional knockout mice exhibit dramatic reduction of tissue-specific stem and progenitor cells and exhaustion of tissue renewal and homeostatic capacity [101]. Similarly, ATM is required for self-renewal

of hematopoietic stem cells, but is not important for proliferation or differentiation of progenitors. ATM knockout mice older than 24 weeks showed progressive bone marrow failure from a defect in HSC function that was associated with elevated ROS [102]. Requirement of ATR but not ATM for tumorigenicity of colon CSCs might be due to its requirement for cell survival. Enhanced activation of the ATM pathway might be observed with different damaging agents such as radiation in the CSCs.

7.6 Cancer Stem Cells in Lung Cancer

Preferential activation of the checkpoint and faster repair were reported in non-small-cell lung cancer (NSCLC) stem cells as compared to differentiated progenies [103]. The authors compared Chk1 activation and gamma H2AX status of NSCLC stem cells and differentiated cells after treatments with various chemotherapeutic agents. Chk1 was activated more efficiently, and much fewer gamma H2AX foci were detected in the CSCs compared to the differentiated counterparts. Furthermore, chemotherapy resistance of NSCLC stem cells was associated with rapid and sustained Chk1 activation regardless of their p53 status. Combination of chemotherapeutic drugs with Chk1 inhibitors prevented DNA repair, suggesting that NSCLC stem cells lose the ability to repair damaged DNA in the presence of Chk1 inhibitors. In contrast, differentiated progenies died after long exposure to chemotherapeutic agents independently of the presence of the Chk1 inhibitors. These data were further confirmed in mouse xenograft models *in vivo*.

$CD133^+$ epithelial specific antigen positive ($CD133^+$ ESA^+) NSCLC stem cells were shown to be highly tumorigenic and were spared by cisplatin treatment [104]. In this study, the DNA damage response in the cancer stem cells was not investigated, but association of the drug resistance with expression of multidrug transporters of the ATP-binding cassette (ABC) superfamily protein ABCG2 was described. In another study, association of radiation resistant cells with presence of ALDH1 but not with other stem cell markers CD133, Sox2 and Oct4 was found [105]. ALDH1 has been discussed as a putative CSC marker for various cancer entities, such as breast, brain, and HNSCC [5, 106–109]. The authors enriched radioresistant cells from a lung cancer cell line, and then investigated whether the radioresitant cells present with CSC characteristics, including enhanced DNA damage response. The radioresitent cells exhibited enhanced DSB repair judged by lower amount of gamma H2AX foci formation after irradiation. Phosphorylation of DNA-PKcs at S2056 was enhanced in the resistant cells compared to the parental cells although the expression level of DNA-PKcs was comparable in both cells [105].

7.7 Future Directions

DDR controls in tissue specific stem cells came into view by recent studies [110–113]. These studies clearly demonstrated the existence of common mechanisms to limit the amount of DNA damage, to restrain them from undergoing massive

apoptosis and being exhausted following DNA damage, and to preserve overall tissue function [14]. Quiescent stem cells choose to survive by inhibiting apoptotic pathways and repair damaged DNA by error-prone repair pathways such as NHEJ, leading to accumulation of genomic instability. This mechanism is important to maintain tissue function in the short term, but might meet the long-term consequences such as cancer development, aging, and tissue atrophy. Proliferating stem cells in the cases of umbilical cord blood hematopoietic stem cells, which are still considered to be of fetal origin, and intestinal stem cells choose to undergo massive apoptosis after damage, avoiding accumulation of genomic instabilities.

The cellular origins of CSCs are still under debate. However, speculation exists that CSCs are derived from tissue specific stem or progenitor cells. If that is the case, CSCs might inherit the preferences of DDR pathways of their origin. However, proliferation statuses of CSCs are generally not determined *in vivo,* except in some cases such as leukemic stem cells which have been sown to be quiescent similar to hematopoietic stem cells. It is possible that quiescent stem cells acquire a proliferative status during the process of tumorigenesis. It is an important question to address in order to understand evolution of tumors and also to develop efficient therapies which are toxic to CSCs but not to the normal counterpart.

Unlike tissue specific stem cells, situations in cancer stem cells are much more complicated due to heterogeneous features of cancer cells. DDR and cell proliferation genes are often mutated in cancer cells. The background mutations of tumors might change DDR of cancer stem cells greatly. Furthermore, isolation methods and stem cell markers for solid cancers are not as well defined as LSCs. In most cases, unlike the hematopoietic system, the normal tissue developmental hierarchy has not been identified or characterized. This makes the selection of candidate markers more difficult. These factors might lead to controversial results. Future studies on defined CSCs are required in order to obtain clear results.

Most experiments on DDR of CSCs are performed *in vitro*. However, existence of tissue specific stem cells as well as CSCs require stem cell niches which are often found in perivascular regions. The regions are known to be hypoxic and might induce high levels of ROS, changing the physiology of the cells found in this area. Environments around the stem cell niche might affect DDR of CSCs. Therefore, it is essential to confirm *in vitro* results further *in vivo*.

Although further intensive studies are required, we now recognize enhanced DDR activities in many types of CSCs. It is well accepted that CSCs are a cause of failures and relapses of chemo- and radiotherapies. Chemotherapeutic agents are often DNA damaging agents, and radiation causes DSBs and ROS. The next stage in this field is to compare DDR of malignant (aggressive and invasive) versus benign, primary versus recurrent, and primary versus metastatic or secondary CSCs.

Addressing the questions above will lead us understanding the mechanism of tumor development and revolutionize cancer therapies.

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