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DNA damage response and repair in colorectal cancer: Defects, regulation and therapeutic implications

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ABSTRACT

DNA damage response, a key factor involved in maintaining genome integrity and stability, consists of several kinase-dependent signaling pathways, which sense and transduce DNA damage signal. The severity of damage appears to determine DNA damage responses, which can include cell cycle arrest, damage repair and apoptosis. A number of recent studies have demonstrated that defection in signaling through this network is thought to be an underlying mechanism behind the development and progression of various types of human malignancies, including colorectal cancer. In this review, colorectal cancer and its molecular pathology as well as DNA damage response is briefly introduced. Finally, the involvement of key components of this network in the initiation/progression, prognosis, response to treatment and development of drug resistance is comprehensively discussed.

1. Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide comprising 9% of all cancers [1], and mostly diagnosed in individuals older than 50 years [2]. There is also substantial number of younger patients with genetic predispositions, specifically familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC) [3]. Colorectal cancers usually begin from benign lesions and accumulate DNA damage on their path to become full blown cancers. Detection of the lesions in early stages will enable the clinician to extract them and pause the path towards cancer [4]. Therefore, various screening programs have been implemented in order to prevent the transformation of benign lesions [5]. Treatment is also heavily dependent on the stage of the disease. Low grade cancers are treated by local excision, while high grade ones are treated with systemic chemotherapy and possible metastasis excision [6]. Much attention has been given to new treatment methods, especially in chemo-resistant CRCs [7]. These options mainly focus on DNA damage/DNA repair mechanisms, growth factors and integrated relations [8,9]. This review aimed to discuss the role of DNA damage in CRC with regards to how it affects clinical presentation, DNA damage responses responsible for compensating for these defects, cell cycle checkpoints and their influence on preventing cells from becoming anaplastic as well as annihilating malignant cells via apoptosis.

2. Histopathology and molecular pathology of colorectal cancer

The intestinal wall consists of three well defined layers: the muscularis properia, submucosa and mucosa. Almost all CRCs originate from the mucosa as outgrowing defined as polyps [10]. Adenocarcinomas arising from the epithelial lining of the gastrointestinal tract comprise more than 90% of all CRCs and are the major clinical picture of the disease [11]. Adenocarcinomas are further divided into cribriform-comedo, mucinous, signet cell, medullary, micropapillary and

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serrated subtypes [12]. Adenocarcinomas have a specific pattern of immunohistochemical markers, which are used together with histologic appearance to differentiate them from other lesions [13]. Other histotypes of epithelial carcinomas include undifferentiated, adenosquamous, squamous and spindle carcinomas. The epithelial layer is also the cause of other non-carcinomatous lesions, such as premalignant lesions, serrated lesions, hamartomas and neuroendocrine neoplasms [14]. Some lesions arise from the mesenchymal layer, including leiomyoma, lipoma, angiosarcoma, gastrointestinal stromal tumor, Kaposi sarcoma and leiomyosarcoma [15–17].

CRCs are a set of heterogeneous diseases, which range from histopathological to clinical characters. It was previously speculated that the reason for this diversity lies in the molecular basis of the disease [18,19]. The results of previous studies have introduced three different molecular signaling pathways involved in pathogenesis of CRC. The main pathway thoroughly discussed is the chromosomal instability, which is the culprit in 80% of CRCs [20]. In this set of tumors, copies of tumor suppressor genes, namely APC, P53 and SMAD4 are lost due to external damaging factors [21]. Some individuals are born with defects in the APC pathway, in which the function of APC gene is lost [22]. APC generates potency by affecting the intracellular levels of β-catenin in the Wnt pathway [23,24]. Most sporadic CRCs also contain mutations in the APC gene. Studies focused on both familial and sporadic cases of CRC have presented a model for the cascade of mutations in CRCs with APC pathway defect [25]. In this model, mutations occur in the K-RAS and P53 genes after APC has been compromised, which in turn transform normal epithelial cells to carcinomatous cells [26].

The second pathway for development of CRC is the inactivation of genes, where products are responsible for repairing mismatch defects within the DNA, commonly referred to as mismatch repair genes (MMR) [27]. This mutation is observed in patients with HNPCC or Lynch syndrome while a defective copy of an MMR gene (MSH2, MLH1, MSH6 and PMS1) is present [28]. This pathway is also defective in cases with sporadic CRC. These individuals can elicit loss of MMRs function either by somatic shutdown or by promotor methylation and subsequently, inactivation of the products [29]. Recent clinical studies have indicated that patients with early onset polyposis and subsequent CRC, such as HNPCC show evidence of microsatellite instability and chromosomal instability but there is lack of mutations in genes associated with HNPCC or other conventional MMR genes [30]. These patients have mutations in proofreading domains of two DNA polymerase genes named POLE and POLD1 [31], and are in greater risk of brain, colon, ovary, endometrial, pancreas and small intestine cancers [32,33]. CRC can also be observed in the background of mutations in a base excision repair gene called MUTYH. This gene is responsible for the protection of DNA against reactive oxygen species [34], especially during cell division [35]. Another mutated base excision repair gene in patients with polyposis is NTHL1 [36]. This mutation show tendency for the development of heterogeneous cancers [37] in multiple anatomical locations [38]. Patients with defects in DNA repair, regardless of the gene or DNA sequence affected, are at risk of accumulating mutations in downstream tumor suppressor and proto-oncogene genes [39].

One particular set of mutations with hope for clinical implications is the BRAF mutations [40]. Patients with this mutation are at higher risk of poor differentiated tumors, with a mucinous glandular formation in the right colon [41]. Mutations are also seen in Bax receptors and transforming growth factor (TGF) β receptor genes [42,43]. Mutations in Bax genes have been associated with wide invasion and metastasis [44] and loss of function in TGF-β receptors which is thought to be responsible for limiting cellular proliferation linked to relapse after treatment and more efficient tissue invasion [45].

The third major pathway in carcinogenesis of CRCs is unique because of the alterations in epigenetic basis. Global hypermethylation of the genome results in switching off of tumor suppressor genes in the CpG island hypermethylation phenotype (CIMP) pathway [46], which leads to accumulation of defects in genes such as KRAS, BRAF and P53 [47]. Patients suffering from CRCs with evidence of hypermethylation tend to be older than the general CRC population and are most likely women. From histological point of view, their tumors consist of poorly differentiated cells which are of mucinous lineage located in the proximal colon [48]. The net survival of these patients is controversial, but most studies have shown low survival for this subgroup as compared to the other two [49].

3. DNA damage response

As previously mentioned, DNA damage is a key etiologic factor in the emergence of malignant cells and replication, invasion and metastasis [50,51]. The three pathways discussed earlier are common and damage to DNA is left un-sensed or unrepaired. Cells have an inventory and intricate network of enzymes and molecules to modulate and repair DNA damage, which is known as DNA damage response (DDR). Fault in the DDR system is associated with almost all types of cancer and some degenerative diseases [52,53]. DDR is a phosphorylation-driven signaling event initiated by damage sensing, which is mediated by DDR sensors, then transduction of damage signal to DDR mediators and downstream effectors by DDR transducers, and finally exerting an appropriate response according to severity of DNA damage [54,55]. ATM and ATR, as two important DDR transducers, interact with various molecules such as p53, checkpoint kinase (CHK) 1&2 and decrease the activity of cyclin-dependent kinase (CDK) [56]. This queues the cell division in checkpoints which aim to monitor DNA replication, control cell size and amend the possible mutations in DNA structure or terminate the cell if necessary [57]. The process of terminating the cell by control measures is called apoptosis [58]. After the cell cycle has stopped, the DNA repair mechanisms is initiated when there is required substances and sufficient time [59,60]. There are a couple of main pathways for DNA damage repair, direct repair, base excision and nucleotide excision repair, mismatch repair, homologous recombination and non-homologous end joining [61], which are all involved in removing the damaged sites to ensure stability and integrity of whole genome (Fig. 1).

4. DNA damage response in colorectal cancer

4.1. DDR sensors

The first step needed to protect the integrity of the genome against a wide range of damaging agents in the environment, is the sense of the damage. Following any damage to cellular genome, the first step of DDR and its key players- DDR sensors- enters to detect and sense DNA lesions and trigger an intricate cascade to eliminate deleterious damages. DDR sensors recruit the downstream transducer molecules to initiate a kinase-base phosphorylation cascade as well as create an appropriate response for maintaining genome integrity [62,63]. Two distinct protein complexes are involved in the detection of the two major types of DNA damage including single strand breaks (SSBs) and double strand breaks (DSBs) [62]. The DSB sensors involved in the ATM pathway are MRE11/RAD50/NBS1 (MRN) complex that recruits ATM at the DSB sites, and activates ATM to phosphorylate the target proteins [64]. In addition, ATM activation trigger one of the earliest events of DDR at the DSB site, which is the phosphorylation of the histone-variant H2 AX producing γH2 AX [64]. γH2 AX, in turn functions as a signal for DNA damage. Replication protein A (RPA), a single-strand DNA (ssDNA)-binding protein, functions as a sensor in the ATR pathway [65]. In ssDNA damages, RPA and RAD9/RAD1/HUS1 (9–1–1) act as sensors and activate ATR pathway [65]. Here, the role of each sensor in colorectal cancer is further discussed:

4.1.1. MRN complex

MRE11, RAD50 and NBS1 are responsible for sensing DNA double strand break. It has been shown that increased or decreased expression

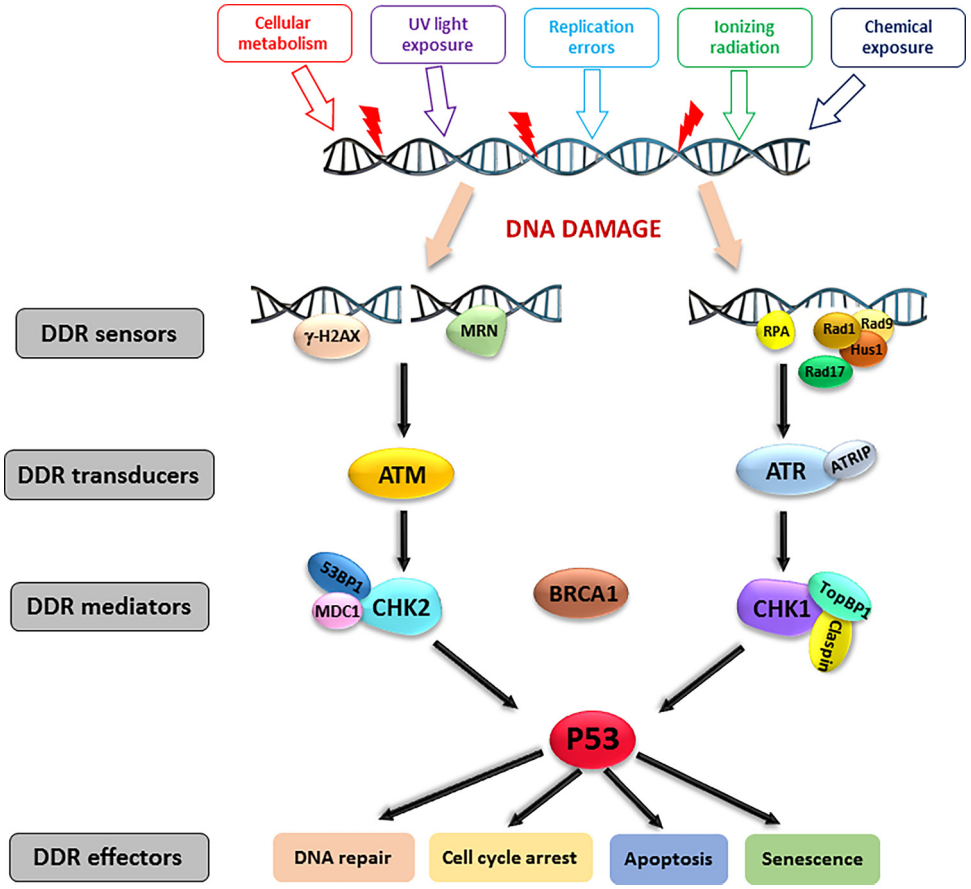

Fig. 1. DNA damage response network.

of NBS1 protein plays a critical role in tumorigenesis. NBS1 has a prominent role in interaction with H2 AX molecules, pointing out damaged foci, and starting the DDR, although, some studies have shown that polymorphism of the gene had no effect on capacity of cells to repair DNA [66–69]. Nijmegen breakage syndrome is an autosomal recessive disease with altered NBS function. Interestingly, heterozygosity in NBS1, especially the 657del5, I171 V and R215 W mutations, is also related to higher incident of cancer, in rather eventless individuals [70,71]. A study showed that VS11 + 2 in. T mutation was common in gastric and colorectal cancer, but was not related to other types of malignancies [72]. Also, a case control study among Chinese patients with colorectal cancer showed that the single nucleotide polymorphism of rs2735383C/G in the 3'-untranslated region (UTR) of NBS1 gene were strongly associated with increased probability of colorectal cancer [73]. Similar results were also shown in a study on microsatellite mutations in CRCs [74]. Levels of NBS1 are also of prognostic value in microsatellite stable tumors, as prompt expression of NBS1 is associated with higher survival in early stages of CRC [75].

4.1.2. MRE11

MRE11 is another component of the MRN complex, active in double strand break repair. The interaction between MRE11 and the other two substrates are necessary for optimal function of the complex [76]. It has been shown that MRE11 plays a role in stabilizing NBS1 and RAD50, and downregulation of MRE11 by small interference RNA caused downregulation of NBS1 and RAD50 together with inhibition of Chk2 action [77]. MRE11 is frequently a target for MSI and 83.7% of CRCs with MSI have the MRE gene affected, which adds to impaired NBS1 expression, and is related to advanced age and A/B stages of cancer. Biallelic mutations are related to lower grades of cancer [78]. A common peculiar mutation of MRE11 gene is the mutation of the poly (T) 11 repeat within the 4th intron of the gene, which results in a shorter and aberrant protein structure leading to a reduction in the MRN complex expression [79]. Studies have also shown that in non-CRC solid tumors, high expression of MRE11 is associated with more malignant behavior [80]. Additionally, microsatellite instabilities affecting the MRE11 region, make malignant cells susceptible to poly (ADP-ribose) polymerase inhibition by agents such as ABT-888 (Veliparib) or LT-626 [81,82]. Another significance of the MRE11 is involvement in the expression of per2, a clock gene proven to be of importance in carcinogenesis [83]. In a research study, levels of per2 in CRC specimens, as well as genes involved in per2 expression were examined, and it was found that proteins such as hus1, gadd45a, rb1, cdkn2a and mre11a were positively related to per2 expression, leading to a better prognosis [84]. However, other studies have shown that there is no direct relationship between levels of MRE11 and survival; thus, whether MRE11 expression could be of prognostic value still remains controversial [85].

4.1.3. RAD50

RAD50 is the final component of the MRN complex, which its mutations or altered expressions are seen in both MSS and MSI cell lineages. This is one of the most common targets for frame shift mutations, especially the (A) 9 repeat region [86,87]. hRAD50 is overexpressed in MSS cells, as a protective factor against further mutations, while its mutation and loss or altered function is effective in the emergence of MSI cancer cells [88]. Kim et al. [89] found that out of 75 MSI tumors, 23 cases had frame shift mutations in hRAD50, while there were no frame shift mutations of any kind in any gene, including RAD50 in MSI negative tumors. Therefore, RAD50 can be a potential target for therapy, especially in lineages of cells resistant to radiotherapy [90]. Chen et al. [91] conducted a study in which, RAD50 protein was knocked down in CRCs cells followed by measurement of

the sensitivity to radiation exposure. They found that cells with downregulated RAD50 were more susceptible to irradiation. They also found that higher levels of RAD50 were accompanied by lower survival rates. Furthermore Vilar et al. [92] showed that CRCs with mutations in RAD50 and MRE11 were more prone to irinotecan (CPT-11). The idea that RAD50 could be used as a possible prognostic factor was also brought up by Wang et al. [93]. who studied the expression of various genes in mucinous adenocarcinoma, a type of CRC, and found that weak expression of RAD50 with elevated expression of PINCH correlated with poor prognosis. RAD50 has also gained clinical significance because of the relationship with some new uncovered methods of carcinogenesis. Astrocyte elevated gene-1 (AEG-1) is one of the activators of NF-κB, which activates anti-apoptotic genes in the nucleus [94]. A study conducted by Gnosa et al. [95] showed that cytoplasmic and nuclear expression of AEG-1 in CRCs is positively correlated with RAD50, suggesting a link with the P53 pathway. The other new concept in tumorigenesis via RAD50 is its relation to CLOCK genes. CLOCK transfected cells of colorectal origin, were resistant to UV induced apoptosis, a phenotype also seen in RAD50 depleted cells. This is significant as there are various CLOCK binding elements in proximity to DDR proteins, the most prominent being RAD50 [96,97].

4.1.4. Human replication protein A (RPA)

RPA is one of the main sensors of DNA damage in the ATR pathway. RPA is composed of three subunits (RPA1-3), in which every subunit play a key role in tumorigenesis, and has a unique 3D structure of 6 oligonucleotide/ oligosaccharide, binding folds commonly observed in proteins binding to ssDNA [98,99]. RPA is necessary for almost all metabolic pathways pertaining to eukaryotic DNA [100]. RPA 2 contains a homologues molecule called the RPA4 which is not effective in cell growth, but rather supports genome integrity [101]. Previous studies have indicated the role of RPA in various cancers such as breast cancer, and a relation is also found in colorectal cancer [102]. Givalos et al. [103] studied the expression of RPA subunits in 130 colorectal cancer specimens and found that there was significant relationship between expression and labelling indices of RPA1-2 with advanced stage of CRC, labelling indices and presence of metastasis in the lymph nodes, the total number of involved nodes, and histological grading of the malignant cells. RPA was also seen to be directly related to overall and stage specific survival rates.

One of the interactions of RPA is the physical association with the tumor suppressor phosphatase and tension homolog (PTEN) gained more attention in CRC. PTEN facilitates RPA1 accumulation on replication forks existing on the DNA, and mutating PTEN or RPA results in the same phenotype [104]. Another important connection of RPA subunits is with the APC tumor suppressor. Immunohistochemistry studies have shown that APC-RPA32 increases in cells in contact with hydroxyurea. Further knocking, APC results in inhibited accumulation of RPA at DNA site. This is of clinical significance as lines of colon cancers such as SW480 have a truncated APC, which is defective in binding to RPA subunits; thus, these cells lack the ability to regulate cell cycle after induced stress [105]. RPA is also affected by DPYD, as cells with knocked DPYD have little ability to concentrate RPA at DNA damage cites [106]. Interestingly, RPA could also be utilized in favor of tumorigenesis. The heterogeneous ribonucleoprotein A18 (hnRNP A18) increases cell proliferation and survival by stabilizing the transcript of genes such as ATR and RPA. Some studies have shown that up to 60% of CRCs have higher levels of hnRNP A18 as compared to adjacent normal tissue. Taken together, hnRNP A18 and its correlation with RPA and ATR appears to be a possible future target for therapy [107]. The same relation is also seen between G9a and PP2 A-RPA, and tumorigenesis and susceptibility to chemo-radiotherapy [108].

Another significance of the RPA in colorectal cancer is the interactions to induce arrest at G1 phase of cell cycle. Kumamoto-Yonezawa et al. [109] studied the effect of conjugated eicosapentaenoic acid (c-EPA) on HCT116, a colon carcinoma cell line and found that exposure to the drug caused increased association of the DNA with RPA subunits, resulting in paused function of the replication forks. This occurred simultaneously with the activation of ATR protein in the aforementioned cells. One interesting observation in colorectal cancer cell lines was that hyperosmolar environments decreased the ability of cells to activate DNA damage response mechanisms. Dixon et al. [110] exposed gastric and colon cancer cells to etoposide in hyperosmolar environments with an osmolality of 600 mOsm/kg, and found that molecules such as ATM, RPA, NBS1 and P53 were inhibited. Currently, there are no specific therapies focused on RPA complex in colon cancers, and agents such as 5-Fluorouracil, which have been seen to sensitize CRC cells to double strand DNA (dsDNA) damage, have no effect on RPA [111].

4.1.5. 9-1-1 complex

The third damage signaling complex active in the ATR pathway is a complex of 4 molecules, in which three of them build a heterotrimeric complex also known as the 9-1-1 complex (Rad9-Hus1-Rad1) which resembles a PCNA- like sliding clamp and RAD17, part of the PCNA clamp loader. These four molecules interact with ATR and subsequently lead to phosphorylation of Chk1, which regulates checkpoint activation [112]. Studies have shown that RAD1 plays an essential role in the integrity of the heterotrimeric complex and loss of RAD1 results in the destabilization of RAD9 and Hus1, and annihilation of the clamp [113]. One well-understood pathway for tumorigenesis of colon cells has been suggested to be the mutations in human MYH gene leading to defective repairing of miscoding 7,8-dihydro-8-oxo-2′-deoxyguanine (8-oxo-dG), which results in a syndrome called MYH-associated polyposis (MAP) [114]. One key characteristic of MYH activity is the coordination with Rad9-Rad1-Hus1 complex in controlling the cell cycle, and loss of coordination leads to phenotypes similar to MAP. Turco et al. [115] studied the Q338H variant of MYH, which reduced ability to interact with RAD9:RAD1:HUS1. Brinkmeyer et al. [116] also found a similar trend with the Q324H variant. Moreover, mutations and abnormalities in the 9-1-1 complex could cause defective base excision repair (BER). For example, the $Hus1^{K136A}$ variant can physically interact with BER enzymes, but cannot stimulate them [114]. RAD9 interacts with the DNA and RAD1, which is responsible for recruiting further repair enzymes, and loss of function in them, likewise contributes to tumorigenesis [117,118].

4.1.6. RAD17

RAD17 is the fourth molecule which is phosphorylated in incidences of cellular stress such as radiation. Studies have shown that in tumors such as non-small cell lung cancers, the level of RAD17 is increased but such correlation was not seen in all colorectal cancers [119]. However, mutation in Rad 17 has been associated with the risk of colorectal cancer. In a case control study conducted in Japan, a stronger association of hRAD17 Leu546Arg with risk of CRC was observed in individuals with habit of smoking and alcohol consumption. It was reported that the aforementioned genotype had a protective effect (odds ratio: 0.68 (0.49-0.95)) [120]. Attention has also been given to Rad17 as a potential target for cancer prevention. A study performed by Luciani et al. showed that daily intake of 10–40 mg of aspirin, was effective in increasing phosphorylation of molecules active in the ATR pathway, including Chk1 and Rad17, which resulted in slowed down DNA replication and increased preservation of genetic stability [121]. In brief, it seems that similar to other molecules effective in the ATM and ATR pathways, down- or upregulation of RAD17 is related to cancer, as overexpression has been observed in some specimens to provide cells the power to endure chemotherapy and radiation, less aggressive and downregulation is related to highly mutating cells, prone to therapy [122].

4.1.7. Gamma-H2 AX

H2 AX, a component of the histones in the nucleosome is one of the first molecules phosphorylated in the DSB DDR pathway [123], which

is proposed to be a biomarker for DSB, apoptosis, a prognostic factor as well as a factor to assess responses to treatment [124–126]. It has been shown that caspase activity in particular, caspase 4, phosphorylates H2 AX and is related to apoptosis in human colon cancer cells [127,128], while contradicting studies have shown opposite responses [129]. There are others agents utilized in therapy against CRCs, which also increase the γ-H2 AX, including oncolytic adenovirus, valproic acid, Bufalin and HMP, a chalcone derivative (a steroid produced from toad venom), fibronectin and many others [130–133]. This increase is linked to susceptibility of malignant cells to treatment options, and the method used for assessment is quantification of the levels of antibody against γ-H2 AX [134]. Further, reduced levels of γ-H2 AX decrease the capability of malignant cells to repair DNA damage and subsequently provides the potential benefits for therapy. This is shown best with overexpression of BRG1 chromatin enzyme, a molecule essential for activating H2 AX. Overexpression leads to aberrant function of downstream molecules of H2 AX, including 53BP1, subsequently to defective DDR and increased sensitivity to radiation [135]. Another clinical aspect of γ-H2 AX has been the duration of focalization in stressed cell. Protein kinase 2 (Ck2) inhibitors such as 4,5,6,7-tetrabromobenzotriazole (TBB), has been shown to delay the dephosphorylating of H2 AX and reduce survival among WIDR colon carcinomas [136]. Another study investigated the effect of HMGA2 overexpression on colorectal cancer cells and found that this delayed clearance of γ-H2 AX in HCT-116 cells and dysfunctional DSB repair, is due to reduced affinity between Ku and DNA ends. The final effect of this overexpression was reduced survival rates with increased rates of metastasis [137].

H2 AX is related to the epithelial mesenchymal transition, a key step in metastasis of CRCs. It has been shown that cells deficient in H2 AX, show enhanced migration, activation of genes related to mesenchymal origins and suppression of those related to epithelial cells [138]. Similar results are shown when overexpression of Lin28 A, a RNA binding protein occurs. This molecule reduces the expression of H2 AX, and is linked to poor prognosis, and interestingly, chemo sensitivity to agents such as 5-FU [139].

4.2. DDR transducers

ATM and ATR, the heart of the DDR network, are members of phosphatidylinositol 3-kinase-related kinase (PIKKs) family with similar structure to PIKKs. Residues responsible for kinase activity located adjacent to carboxyl terminals are surrounded by highly conserved FRAP-ATM-TRRAP domains. ATM exists as dimers or oligomers when inactive. When DSBs are existent in cells, ATM undergoes autophosphorylation at the FRAP-ATM-TRRAP domains which results in break of oligomers and emergence of single ATM molecules [140]. As previously mentioned, interaction of MRN complex is necessary for ATM activation, and each component has a specific function [141]. ATR, another PIKK is responsible for ssDNA repair which is bound to a protein called ATR-interacting protein (ATRIP) phosphorylated by ATR. ATRIP has indisputable roles in ATR expression, as its loss causes loss of ATR expression and function [142]. The ATR-ATRIP is bound to intranuclear RPA, and is localized to damaged DNA [143,144]. RAD9–RAD1–HUS1 clamp is loaded to the damage site, which is facilitated by RAD17-RFC, which in turn is facilitated by RPA [145–147]. Finally, the S387 subunit of RAD9 is phosphorylated, enabling the interaction between topoisomerase 2-binding protein 1 and ATRs FATC domain and causing activation of ATR [145,148].

4.2.1. ATM

ATM is one of the genes commonly mutated in CRCs and refractory metastatic cancer [149–157]. Studies have shown that the expression levels of ATM in colorectal cells are significantly higher than adjacent normal and control tissues, and higher expression of ATM is correlated with well differentiated tumors [158–160]. More importantly, aberrant methylation of ATM or its promotor is likely etiologic in CRCs [161–165]. ATM signaling can be dependent on various factors in cells such as hypoxia, G protein-coupled estrogen receptor 1 (GPER) signaling [166], decreased phosphorylation, increased X-ray radiation resistance associated 1 (XRRA1) expression (which favors cell proliferation) [167] or oligo-fucoidan administration (a polysaccharide shown effective in cancer patients) [168]. BI-69A11 administration besides celecoxib [169] or Zerumbone, a sesquiterpene from ginger [170], and BEZ235, a dual PI3 K/mTOR inhibitor, also have the same effect [171]. AKT2 signaling is thought to reduce levels of ATM pathway molecules and inhibit the induced autophagy [172]. miR-18a overexpression inhibits ATM expression, thus inhibiting proliferation and migration [173,174]. The same is true with miR-203 [175]. Wang et al. [176] showed that low dose irradiation (LDIR) increased levels of ATM/p53 in HT-29 cell lines, prompting the possible role of LDIR as a complementary therapeutic procedure in CRCs. CBP-93872 was found to inhibit the phosphorylation of ATR and jamming the collaboration between ATR and ATM caused more sensitivity to a wide array of chemotherapy medications [177]. Quercetin also use this mechanism to render CRCs susceptibility to radiotherapy [178,179]. MUC13, a mucin glycoprotein, increases the phosphorylation of ATM, resulting in higher NF-κB activity, and sensitivity to chemotherapy [180]. Bortezomib has been also shown to increase ATM phosphorylation by increasing cellular reactive oxygen species (ROS) [181]. There is also a negative correlation between levels of special AT-rich sequence binding protein 1 (SATB1) and ATM. SABTB1 is associated with poor response to radiotherapy and short time to metastasis [182]. Smad1 is another molecule that increases ATM activation [183]. Lack of DNA-PKcs, is also associated with increased ATM activation and signaling [184]. Zeng et al. [185] showed that Bmal1, a circadian clock gene, also induced ATM pathway activation and G2-M arrest. A remarkable study showed that spironolactone, a diuretic, could have possible anti-cancer activity by upregulating ATM signaling [186]. The same results were seen with *Emilia sonchifolia* extract, a medicinal plant [187], daurinol, a topoisomerase inhibitor [188] and Nutlin-3, a MDM2 antagonist [189]. A study showed that knockdown of FOXF1 also triggered ATM activity [190]. A recent study showed that selenium activated the DDR via ATM dependent signaling, and concluded that Hmlh1 and ATM are necessary for its anti-cancer function [191]. Extra virgin olive oil also had anticancer activities, the most important mechanism was the increase in ATM-P53 cascade activation [192]. The other effective agent via ATM signaling is aspirin, which is commonly used to prevent CRC in elderly. It was shown in a study that aspirin effect is dependent on p21Waf1/Cip1 and the ATM pathway [193]. A study also showed that after N-methyl-N'-nitro-*N*-nitrosoguanidine-induced DNA alkylation, ATM had a surge in its activation. The results suggested that ATMs function in DDR is not limited by ionizing radiation and previously preserved damaging factors [194].

ATM and its various polymorphisms can have prognostic value in CRC patients [195], both as direct acting agents, or as a secondary involved factor [196]. Studies have shown that downregulations of ATM and Ku70, are associated with node metastasis and decreased 5-year survival [197]. ATM deficient neuroendocrine colorectal cancers had a grim outcome and over 85.7% of metastatic neuroendocrine cancers were ATM negative [198]. Suenaga et al. [199] examined the efficacy of TAS-102, and found that patients harboring a G allele in ATM rs609429, presented a higher overall survival rate and progression free survival. Kweekel et al. [200] found a possible relation between ATM variations and oxaliplatin efficacy in advanced CRC. Agents such as Kaempferol exert their anti-cancer effect via ATM phosphorylation, which was shown in HCT116 cell lines [201]. SK-CO-1 and HCT116 cell lines, deficient in ATM, are susceptible to poly (ADP-ribose) polymerase (PARP) inhibitors, namely Olaparib [202]; the same dynamic were also seen in HCT116 cell lines and susceptibility to neocarcinostatin [203], and CRCs deficient in ATM undergoing sodium iodide symporter gene therapy [204]. ATM is a predictive marker in response to treatment

with epidermal growth factor receptor (EGFR)-targeted therapies, as aggregated mutations in ATM are correlated with no-response to treatment [205]. Inhibition of ATM-CHK2-P53 pathway is the culprit for chemo-resistance to 5-FU, as 5-FU induces cell arrest in S phase using ATM and Chk1 [206,207]. This was shown in CRC samples with 53BP1 loss, which reduces ATM effectors, such as caspase 3 and 9, and results in suppressed signaling by the pathway [208]. Similar results were shown for radio sensitivity [209]. One important correlation of ATM with clinical significance is with PTEN [210]. Cells deficient in both PTEN and ATM endure catastrophic DNA damage, mitotic arrest and cell disintegration. Introduction of KU-60019, a ATM inhibitor to PTEN mutant cancer specimens has proved effective and indicates further benefits in the future [211]. Telomere-binding protein (TPP1) is one of the proteins that appears to be involved in chemo resistance, which increases cell cycle arrest in G2-M, by activating the ATM/ATR-Chk1 pathway [212]. Interaction between ATM and telomere function was previously reported [213]. Tamakawa et al. [214] studied the efficacy of telomerase 2 inhibitors in CRCs and found that the simultaneous inhibition of ATM and telomerase, resulted in better clinical outcome. Methylation in ATM, is both an etiologic and prognostic factor in CRC. A study showed that methylation of the proximal promotor of ATM caused sensitivity to radiotherapy [215].

4.2.2. ATR

ATR is a kinase which exerts its effect by phosphorylating CHK1, a downstream target. ATR and CHK1 guarantee cell survival throughout cellular stress and have proved effects in the stepwise progression of cells towards cancer [216]. As mentioned earlier, ssDNA activates ATR via the complementary interactions of RPA and ATRIP [143]. ATRs function has been shown to be insufficient and indispensable by other PIKKs versus ATM [217,218]. ATR-CHK1-Cdc25c pathway also plays an important role in G2/M arrest in human colon cancer cell lines (HCT116), which is not mediated throughout traditional ATR signaling [219,220]. ATR is also an influential player in apoptosis and some mechanisms of apoptosis, similar to how desferrioxamine induced-apoptosis is reliant on phosphorylation of SMC1 via ATR [221]. It has been shown that mutations in ATR is related to changes in clinical prognosis and response to treatment, especially in microsattelite instable colon cells [222,223]. It is noteworthy that ATR is more mutated in colorectal cancers among adolescents and younger patients [224]. Studies in the past decade have found selective inhibitors for ATR, namely VE-822 and AZD6738 [225]. Efficacy of VE-822 was shown in a study performed by Josse et al. [226] where treatment was done by a combination of topoisomerase and ATR inhibitors. In cells undergoing this treatment, ATR was not activated and an abrogated S phase caused better response to drugs such as irinotecan without additional toxicity, Abu-Sanad et al. [227] also reached similar conclusions utilizing ABT-888 and VE-821 on HCT-116 cell lines. Similar results were also shown by the combination of M6620, an ATR inhibitor and cisplatin or melaphlan [228], and KU55933 and CGK733 [229]. Use of 17-(allylamino)-17-demethoxygeldanamycin (17-AAG) with celecoxib, induced eventual downregulation of ATR and ATM and sensitized colorectal cells to radiation [230]. Inhibition of ATR was also shown to reduce number of CD133 positive cells, which are chemoresistant and tumorigenic [231]. One novel study focused on agents activating the ATR and ATM cascades and their implication in therapy and found that Americanin A, an extract from *Phytolacca americana*, activated downstream molecules of the two cascades which was reported to be successful in limiting the growth of HCT116 tumor cells [232]. A study by Song et al. [233] showed that hepatocyte growth factor leads to the activation of ATR via its binding with TopBp1 and subsequent activation of Chk1. This specific interaction has also been reported to have therapeutic and prognostic implications. Cheliensisin A, an isolate of *Goniothalamus cheliensis* increased levels of hydrogen peroxide via the ATR/Chk2 axis, which stabilized p53 in HCT116 cell lines, suggesting possible treatment options [234]. Levels of such increased activity were shown with dietary isothiocyanates as well [235]. Derivatives of Osthole, an extract of *Cnidium monnieri* and *Angelica pubescens*, induced activation of ATR kinases and had a tumorigenic effect [236].

4.3. DDR mediators

As mentioned earlier, DDR is a plethora of molecules. Simultaneous to activation of transducers, another subset of molecules called mediators or adaptors, which include 53BP1, MDC1, TopBP1, Claspin and BRCA1, are functioning [237]. These molecules have subtle roles in signaling and generally act as amplifiers of DDR transducers, which can be sidelined in robust signaling. Several studies have shown that cells lacking the function of these mediators end up harboring significant instability in the genome, hence signaling their crucial function and importance [238]. These molecules are further discussed below:

4.3.1. CHK1

CHK1, the downstream molecule of the ATR pathway is phosphorylated by ATR and phosphorylates other agents which act in the recovery from cell cycle arrest, DNA repair and cell death [239–241]. Mutations in CHK1, are a way for cells to escape cell death, and these cells accumulate multiple MSIs [242–244]. It has been shown that CHK1 can play an important role in cell proliferation via overexpression of specific molecules such a CCNB1. Interestingly, suppression of CCNB1 also resulted in lower levels of cdc25c and Cyclin-dependent kinase (CDK)-1 [245]. Further suppressed CHK1 reduces the intensity of tumorigenesis via the Wntmolecule [246]. Previous studies have shown that lower expression of CHK1 in CRC cells was related to higher rates of apoptosis [247]. As a central broker, various agents assert their effect directly by affecting the function of CHK1. MiRNAs have an established role in drug resistance among colon cancer cells, which mainly target CHK1 [248]. NF-κB also had similar effect by upregulating E2F1 levels which contributed to enhanced CHK1 signaling and consequently resistance to oxaliplatin [249]. However, some studies have shown the positive effect of CHK1 on colon cancer cells. For instance, Wu et al. showed that MUS81 knockdown resulted in activation of CHK1 pathways (CHK1/CDC25 A/CDK2 and CHK1/p53/Bax) which promoted apoptosis [250]. Therapeutic agents also act on CHK1, and expression of CHK1 is a predictive marker for response to treatment [251]. NSC30049 (NSC49 L) is an orphan molecule, which acts alone or in combination with 5-FU, by targeting CHK1 function [252]. The use of CHK1 inhibitors can also be indicated in patients with no specific mutation in CHK1 itself or rather in APC mutated cells. Martino-Echarri et al. showed that the use of CHK1 inhibitors with 5-FU increased chemo sensitivity in CRC cells [253]. The same effect was shown with LY2603618, a CHK1/2 inhibitor with irinotecan and gemcitabine [254,255] and SCH900776 with platinum based chemotherapy agents such ascisplatin [256]. V158411 is another agent that is under investigation for its synergistic effects with conventional chemotherapy agents [257]. It was suggested that examining the levels of phosphorylation of γH2 AX and CHK1before treatment could guide clinicians in prescribing CHK1 inhibitors with gemcitabine or camptothecin [258,259]. UCN-01 is another agent with anti CHK1/2 activity, which promotes cellular death secondary to radiation exposure [260]. This activity is done independent of P53 [261]. UCN-01 also showed increased toxicity of arabinosyl cytosine [262]. Lidamycin, an enediyne antibiotic, also acts on colon tumor cells via the CHK1 molecule. It increases the phosphorylation of CHK1, CHK2 and Cdc25C, and the expression of cyclin B. These changes caused the arrest of the HT-29 cells at the G2 arrest position of the cell cycle [263]. Trifluridine, an important component of TAS-102, induces cell arrest by p53 accumulation, which results in transient phosphorylation of CHK1 [264]. Inhibition of CHK1 is also obtained by introducing Pb-TCMC-trastuzumab to colon cells, which results in higher rates of apoptosis [265]. A novel observation added to these experiences was made by Origanti et al. who showed that inhibition or loss of p21 further sensitized cells to DNA

damage induced by therapeutic measures [266]. CHK1is also associated with the anti-tumor effect of Loratadine. Loratadine directly damaged the colorectal cell DNAs and caused activation of CHK1, promoting G2/M arrest. These effects were seen in conjugation to radiotherapy [267]. Similar to CHK2, CHK1 is associated with microtubules and their role in the cell cycle. A research study showed that Tubulozole, a microtubule damage agent, had more efficacy in inducing cell arrest in cells with higher levels of CHK1 [268]. It should be noted that the use of CHK1 inhibitors is reliant on factors such as mTORC1 and DNA-PKcs and situations where agents act as prognostic factors for response to treatment (as antagonistic factors) [269]. The same was also shown for Cyclin B1. Xiao Z et al. suggested that colon cancer cells with increased levels of Cyclin B1, were more susceptible to CHK1 inhibitors [270]. CHK1 phosphorylates Cdc25C and causes accumulation of Tyr-15-phosphorylated Cdc2. This was further proved by inhibiting the results via introducing CHK1 inhibitors to the colon cancer cells [271].

4.3.2. 53BP1

P53-binding protein 1 (53BP1), a protein that binds to P53, is an important molecule that determines whether cells will enter the homologous recombination (HR) or classical non-homologous end joining (NHEJ) DNA repair pathways [272]. Similar to H2 AX, 53BP1 is also used as a surrogate marker for DSB DNA damage [273,274]. Interestingly, it has been shown that 53BP1 has two distinct functions. Studies on SW480 colon cells have shown that the two functions are separated, and one can be carried out independent of the other [275]. This molecule has also been deemed to be a predictive marker for susceptibility to treatment, especially PARP-1 inhibitors. Although no study has been done to evaluate this in CRC cells [276]. The same was also seen between 53BP1 and 5-FU, as 53BP1 deficient cells were resistant to the aforementioned agent [208]. 53BP1 loss also caused HCT116 cells to acquire radio-tolerance, as it reduced the expression of ATM and CHK2, which are central acting agents in DDR [209]. 53BP1 has also been recognized to be a marker of malignant potency, both in CRCs and other tumors [277]. A study revealed that levels of 53BP1 were related to the size of the tumor and the clinical and histological stage of the disease, with deficient cells having more malignant characteristics and bigger size [278]. During cancer progression (low grade neoplasia to invasive carcinomas), DSB appears to be inefficient in colorectal cancer cells. This was shown with reduced number of H2 AX and 53BP1 foci. This makes quantifying the levels of 53BP1 beneficial in suggesting a prognosis for patients [279]. 53BP1 has also been suggested as a possible target for treatment. A study found that Lanatoside C was effective in sensitizing HCT116 CRC cells to radiation by decreasing the recruitment of 53BP1 to DNA damage sites. This was achieved via defects in degradation of KDM4A/JMJD2 A molecules [280].

4.3.3. MDC1

Mediator of DNA damage checkpoint protein 1 (MDC1) is an important molecule in DDR, specifically in the ATM pathway. This molecule is rich in FHA and BRCT domains, and plays an essential role in mitotic progression with its involvement being proved in various cancers, such as gastric, lung and gliomas [281]. MDC1 actively plays with H2 AX and is co-localized together in DDR [282]. MDC1 enhances the phosphorylation of H2 AX, and via this step, it has an important role in the formation of 53BP1, BRCA1 and MRN [283]. Another role of MDC1 is in HR repair pathway. A study has shown that knocking out MDC1 resulted in sensitivity to mitomycin C and ionizing radiation. This study also suggested that MDC1 had a special role in retaining RAD51 to chromatin [284]. Taken together, there is still lack of evidence supporting the role of MDC1 in colorectal cancers; therefore further studies would be of merit.

4.3.4. TOPBP1

Topoisomerase IIβ binding protein 1, an essential molecule in DDR via the ATR pathway, is one of the molecules connecting the ATR to the ATM pathway, by facilitating ATR activation by the ATM molecule [285]. TOPBP1 is activated in part by E2F1-4 [286], and represses apoptosis by E2F1, which is a path to cancer [287]. Inhibiting TOPBP1-AKT pathway by targeting phospholipase D1 promoted E2F1-dependent apoptosis in colon cancer cells [288]. TOPBP1 has been associated with various cancers and specific single nucleotide polymorphisms (SNPs) have been associated with the risk of CRC [289]. Similar to the other molecules in DDR pathway, clinical significance has been suggested for TOPBP1. It has been shown that agents such as hepatocyte growth factor affected CHK1 in colon cancer cells via upregulating TOPBP1 and increasing TOPBP1-ATR conjoint formation [233]. Another study showed that TOPBP1 correlated with response to curcumin and ascorbic acid in HCT116 colon cells [290]. The concept of TOPBP1 and Claspin in relation to sensitivity to treatment has also been proposed. A study performed by Choi et al. revealed that resistance to ionizing radiation was higher in lung cancer cells with higher levels of TOPBP1 and Claspin expression [291]. To the best of our knowledge, there is no similar study with regards to CRC cells.

4.3.5. Claspin

Claspin is a central factor to the phosphorylation process of CHK1 by ATR. Claspins have an essential function in cellular genome maintenance (the ATR-Claspin-CHK1 pathway), and it is thought that this molecule acts as a tumor suppressor gene while its inactivation is a vital step in carcinogenesis [292,293]. Claspin has also been introduced as a marker of aberrant proliferation. A study conducted by Tsimaratou et al. revealed that malignant cells expressed higher levels of Claspin (14-fold) in comparison to normal cells. This association was even stronger than KI67 [294]. In a study that examined the effect of 5-ASA and its analogues on colon HCT116 and HT29 cells, it was found that this group of agents were effective in inducing S-phase arrest in cells, accompanied by increased recruitment of RPO and Claspin to the nucleus [295].

4.3.6. BRCA1

BRCA1, located in the 17q21 genomic region, a region with well-known effects on carcinogenesis [296,297], is a central molecule in DDR, with two main functional domains, the RING domain with an ability to catalyze ubiquitiylation and a BRCT domain, which acts as a facilitator in phosphor-protein binding. The latter domain actively interacts with BRCA1 and the proteins previously phosphorylated by ATM. The role of BRCA1 has been shown in HR, NHEJ, and SSA repair mechanisms. It has also been shown to take part in checkpoint activation [298]. Several studies have shown that sensing of DNA damage and its repairs via BRCA1 are independent [299]. Another role of BRCA1 is its ability to alter the expression and regulation of several molecules effective in DDR and cell cycle, in an independent manner from p53, in contrast to its role in regulation of type 1 insulin-like growth factor receptor (IGF-IR), including GADD45, GADD153 and cyclin B1 [300,301]. BRCA1 is also the downstream molecule of MSH2, which to some extent explains the mutations in various types of cancers [302]. These alterations were also shown to exist in CRC [303]. BRCA1 is a tumor suppressor which is inherited in an autosomal dominant matter, with a high penetrance [304]. This molecule is mutated in various clinical syndromes, such as Lynch, which was previously discussed [305].The role of BRCA1 has been strongly established in CRC, in contrast to BRCA2, and its association with CRC has been undermined in more recent studies compared to older studies [306–308]. Mutations, SNPs and epigenetic alteration related to BRCA1 have been reported to be associated with earlier onset of CRC [309], anatomical location of the tumor (right colon) [310,311], resistance to treatment (such as vincristine) and effectiveness of radiotherapy [312–314], progression and lymph node metastasis [315], and overall poor prognosis(nuclear expression, in contrast to cytoplasmic expression which is related to better overall survival) [316–319]. A study performed on a

predominantly Ashkenazi population showed that having mutations in BRCA1/2 was related to having left sided cancer, mucinous tumors and anal carcinoma [320]. Agents decreasing the amount of BRCA1 renders cell susceptible to malignant transformation and division disarray. This was exhibited with Keratin23 [321]. BRCA1 has also been recognized as a possible therapeutic target in CRC. A study revealed that depleting cells of BRCA1 would make them dependent on the S phase functions of CHK1, subsequently leading to a better clinical outcome of CHK1 inhibitors in these cells. This strategy may work effectively for subsets of tumors already lacking BRCA1 [322]. A study performed recently found that cells with high levels of BRCA1 and matrix metalloproteinase (MMP)-1 had better response to bevacizumab [323]. In line with the previously discussed molecules, certain miRNAs such as miRNA-26b, can lead to cancer by deregulating BRCA1 expression in ulcerative colitis patients [324]. Other partner binding molecules of BRCA have also been the subject of various studies. BARD1 is one of such molecules which functions as a stabilizer for BRCA1 and facilitates HR repair. It has been proposed that assessing the amount of full-length BARD1 in colon cancers cell can act as a prognostic factor, of which higher levels show a better total survival [325]. Another study found that expression of N and C-terminal epitopes bestowed increased survival while expression of middle epitopes signaled a shorter survival [326]. Studies have also reported that existence of splice variants of BARD1could determine response to PARP-1 Inhibitors [327]. Another subsidiary of BRCA1 is BRCA1-associated protein 1 (BAP1), a deubiquitinating enzyme located in the nucleus. A study performed by Tabg et al. revealed that BAP1 was significantly related to clinical stage and local invasion of the tumor, in which patients with higher expression survived longer [328].

4.4. DDR effectors

The ultimate purpose of DDR is to take appropriate measures in determining the fate of a cell which has endured DNA damage. Cells can enter DNA repair pathways, queue temporally in the cell cycle, enter senescence, or go through apoptosis. This determination of a cells fate is a complex process, where P53 plays a key role [329]. P53, directly or indirectly guides cells through the appropriate pathway to incapacitate cells that have taken a serious blow and avoid the possibility of mutation of cells multiply and invade normal tissue [330]. In this review, first the function of P53, and then the most important molecules active in each fate, are discussed.

4.4.1. P53 the centerpiece of DDR

This protein is a tumor suppressor that acts in conjugation with various downstream molecules to prevent cancer. P53 is capable to determine whether a cell initiates DNA repair, enters cell cycle arrest, enters senescence or initiates apoptosis. P53 exerts several effects via downstream molecules which will be discussed later. Molecules such as the pro-apoptotic Bcl-2 family proteins, p21, GADD45 and others are related to cell cycle arrest, p16 and related molecules that are effective in the induction of senescence, and finally the DNA repair cascades [331,332]. P53 is activated via different stimuli, by upstream molecules mentioned previously, which phosphorylase the N-terminal of p53, leading to activation and increased half-life, and subsequently accumulate inside the cell [333]. In stress free cells, activation of p53 leads to the activation of MDM2 which is a E3-ubiquitin ligase, affects p53 and leads to degradation [334]. Various mutations can alter the function of p53, including mutational inactivation of p53, activation of proto-oncogene such as MDR1 and c-myc by a mutated p53, increased degradation of p53, dysfunctional distribution of p53 and mutations in target genes or post-translational alterations [335,336]. The most prominent molecules active in the regulation of p53 activate transcription factor 3, which is either a target gene or a co-transcription factor for p53 and miRNAs, with functions by targeting UTRs in p53 and post-translational regulation of expression of genes associated with stress response [332].

P53 has been shown to be a major factor in CRC, as some studies have reported mutation rates of up to 76.8% in [337]. Also expression of p53 in relation to the prognosis of CRC as functional p53 was accompanied with a better prognosis [338]. Overall, the function of p53 has been associated with such characteristics of the tumor like site of origin, stage of disease and response to treatment [339]. As earlier mentioned, one of the main functions of p53 is to facilitate DNA repair. Here, in summary, we review the main interactions of p53, and then each method is discussed further in details. The first discussed method of DNA repair is nucleotide excision repair (NER). Studies have shown that cells with loss of function of p53 are sensitized to UV radiation [340]. Further, evidence exists that p53 adheres to various molecules active in NER such as XPC, XBP and CSB [341]. More recent studies have classified the function of p53 in NER into two groups: transcriptional and non-transcriptional effects. The non-transcriptional function are the modulation of helicase activities of XPD and XPB, coupled with modulation of the accessibility of the chromatin for repair [342,343]. The second major DNA repair pathway is the BER. P53 has proven interactions with apurinic and apyrimidinic endonucleases (AP) such as APE1/Ref-1. Multiple studies have revealed that Ref1 increased DNA binding of p53 and promotes tetramerization of p53, and in part modulate the effects of p53 on the targets [344]. P53 appears to modulate the function of BER, as in non-critical damage and damage in the early phases of the cell cycle, p53 increases BER, but in late stages such as the transition from G2 to M, apoptosis is increased [345]. It also has regulatory effect on expression of OGG1 and MUTYH [346,347], and has potentiating effects on downstream molecules such as DNA polymerase β [348]. P53 has clear roles in HR, which are both transactivation dependent and non-dependent. P53 directly affects the expression of RAD51as an inhibitory force restricting unnecessary recombination. This is in part also done with the effect of p53 on RAD54 [349,350]. P53 negatively regulates HR by becoming phosphorylated via ATR, in instances of SSB. This phosphorylation leads to the interaction with RPA [351]. The last major pathway is NHEJ. Studies have shown that in contrast to HR, NHEJ is prone to many errors as it is a dynamic process and can lead to joining of wrong ends. The exact role of p53 in NHEJ is not fully known, but studies have shown that a genetic link does exist [350].

4.5. DNA repair

4.5.1. NER

Nucleotide excision repair (NER) is a well-described DNA repair mechanism in human cells, and abnormalities and aberrancies in this pathway which is composed of two modes of the global genome NER (GG-NER) and transcription coupled NER (TC-NER), are associated with genetic syndromes such as xerodermapigmentosum, trichothiodystrophy and Cockayne syndrome, together with predisposition to various malignancies [352–354]. NER is responsible for eliminating some of the damages to DNA, caused by environmental factors to DNA, which are responsible for CRC, including smoking and meat cooked in high temperatures. Genetic variants of NER with reduced function, such as ERCC6 1213 G, XPC 492H, Gadd45a and XPC-Glu939Glu have been shown to be significantly associated with CRC [355–357]. Another study found a positive association between the XPC 499 AV + VV genotype and a negative association between XPC 939 QQ with CRC in African Americans [358]. NER could be dependent on environmental factors, as a study had shown that oxidative stress on piglet colon cells reduced the capability to conduct NER, thus suggesting a prophylactic anti-oxidative regimen, to avoid CRC [359]. NER has been a target for therapy in multiple studies. In a study by Barakat et al. it was revealed that by inhibiting the interaction between XPA and ERCC1, two essential components of NER sensitized CRC cells to UV radiation [360]. Another study concluded that inhibition of NER by UCN-01 increased the sensitivity of cells to acylfulvene, an alkylating compound [361].

Cetuximab had the same potentiating effect for oxaliplatin, by inhibiting NER and DNA replication [362]. Nucleolin, a marker of cell division and growth rate, also disrupted NER by binding to PCNA, and sensitized cells to UV radiation [363]. Arnould et al. conducted a study which aimed to determine factors effective in sensitivity to oxaliplatin in CRC cells and found that expression of ERCC1 was correlated with sensitivity to oxaliplatin; also, post treatment XPA levels were related with IC [50] of the agent [364].

4.5.2. BER

Base excision repair (BER) is a multistep pathway, in which DNA damage resulting from oxidation is corrected via enzymes which remove the targeted base and after various steps, fill the gap with the appropriate base. BER has been reported to be associated with aging and cancer in various studies [365]. This association has also been revealed in CRCs [366]. For example, mutations in the MUTYH gene, which encodes a glycosylase that is responsible for BER [367]. It has been shown that deficiency in MUTYH is associated with a form of polyposis. These genes were shown to be downregulated in hypoxic states, which consequently lead to genomic instability and cancer progression [368]. Overall, alterations in the genes effective in BER have prognostic and therapeutic importance. But it should be mentioned that not all genes involved in BER are equally or simultaneously altered in expression in all cases, rather, most CRCs only have a single or few alterations [369]. Alterations in O(6)-methylguanine-DNA methyltransferase (MGMT) are evident in CRC and are to some extent associated with drug resistance [370]. Further, higher levels of MGMT and MPG are associated with more aggressive cancers. XRCC1 was increased in poorly differentiated cells and so was PARP1 in CRCs with lymphatic involvement [369]. Increased expression of XRCC1, MPG and Polβ are all associated with poor pathologic outcome [371].

4.5.3. HR

Homologous recombination (HR) comprises various molecules active in amending DNA damage in the form of DSBs. HR uses sister chromatin, which results in error free repair. HR is controlled both by DNA damage and the cell cycle, mainly via cyclin dependent kinases, which limit HR to S, G2 and M phases of the cell cycle. HR has been a target in cancer therapy, and various agents act via their interactions with HR proteins [372]. Various methods are introduced for HR including gene conversion dependent on BRCA2 and XRCC2, transcription associated HR, dependent on BRCA2, and spontaneous HR, which is not dependent on any of the above molecules [373–375]. As there are up to 200 molecules in HR, various mutations in these proteins cause cancer. It has been shown that mutations in RAD54 and CtIP (which is related to BRCA2) is associated with CRC [376]. Another study found a relation between polymorphisms of the XRCC3 and XRCC2 genes with CRC [377]. Interestingly, the mutation in XRCC2 with clinical importance as cells with a non-functional XRCC2 are deficient in MMR, with HR being more susceptible to thymidine [378]. The same mechanism of targeting proteins involved in HR is also seen in treating cell lines with splice variants of BARD1 with PARP-1 inhibitors [327]. Furthermore, it involves treating KRAS mutated HCT116 which upregulate RAD51with pharmacological inhibition [379]. Aside from the above mentioned, new molecules effective in HR have received attention, such as BLM, in which carrying BLM genes with deletions are at an increased risk of colorectal cancer [380].

4.5.4. NHEJ

As mentioned before, NHEJ is responsible for DSBs, and has an established role in CRC. Similar to the other pathways, mutations and aberrations affecting proteins involved in NHEJ could cause cancer. One of these is Ku70, which is essential for colorectal cell homeostasis, and lack of Ku70 causes inflammation, dysplasia and adenocarcinoma [381]. Also the error prone nature of this type of repair of any kind of increase in DNA binding of KU70, which promotes NHEJ, increases the possibility of gaining mutations [382]. Agents involved with Ku70 such as Cdx2, a gene belonging to the paraHox cluster, which via Ku70, inhibits DNA-PKcs, subsequently inhibiting NHEJ [383]. DNA-PKcs are important mediators in NHEJ [384], which can regulate NHEJ and HR together, as its downregulation results in increased HR. Inhibiting DNA-PKcs with agents such as IC486241 (ICC) increases the effect of conventional anti-cancer therapy drugs like irinotecan on CRC cells [385]. Also, the function of DNA-PKcs results in extra chromosomal double minutes, which leads to methotrexate (MTX) resistance. Inhibiting DNA-PKcs appears to increase the response to MTX treatment via disappearances of the double minutes [386]. A study revealed that inhibiting DNA-PKcs by KU-0060648 increased the cytotoxicity of etoposide and doxorubicin in DNA-PKcs proficient cells [387]. Molecules regulating DNA-PKcs such as AKT1 and 2, like DNA-PKcs, are also important in response to treatment in CRC. There are studies suggesting that inhibiting these molecules could be used as a method to sensitize CRC to radiation [388]. One other molecule effective in chemoresistance of CRCs is Dicer, which is effective in both HR and NHEJ. It has been revealed that decreased expression of Dicer increased chemosensitivtiy. This was due to reduced function of Dicer which repressed the recruitment of molecules in the NHEJ pathway. Another aspect of NHEJ involvement in CRC is the DNA ligase IV, which has shown strong differential promoter methylation in CRC specimens [389].

4.5.5. TLS

Translesion synthesis (TLS) is one of the DDR pathways in which special DNA polymerases utilize segments of the damaged DNA as a template and insert nucleotides into the double strand DNA. Only the Y family and some members of X and A family have shown this capacity [390]. Since the Y family performs TLS as a main function, this study focused on it. Various DNA polymerases are in this group, including Polβ, Pol η, Pol κ and Pol ι. These polymerases enables cells to tolerate the genotoxic stress imposed by various agents, yet their function is error prone, and these polymerases do not possess a proofreading mechanism such as PCNA or RPA [391].

The role of TLS in CRC has been thoroughly investigated. It has been shown that mutations in pol B can be seen in CRC [392]. Of interest, downregulation of Polβ causes sensitization to platinum agents in CRC, and is also a possible prognostic factor, as higher levels are seen with lymph node metastasis and distant metastasis and overall lower survival [393]. Other polymerases are also associated with CRC. A study revealed that the levels of polymerases kappa, iota and zeta, all active in TLS, were decreased in human with CRC [394]. A study that focused on Pol κ found an existed repressive region for Pol κ contrary to previous knowledge. Any alteration in activating regions of Pol κ, such as alterations in 237-bp region which contains cyclic AMP-responsive element (CRE)-binding and stimulating protein-1 (SP1) sites, would decrease the total amount of Pol κ. These were all shown in CRC cells where introduction of ectopic SP1 or CRE-binding protein (CREB) increased Pol κ expression [395]. Another study found that overexpression of poly Q was significantly associated with poor survival. The deregulation of pol Q was shown to occur at early stages of cancer [396].

4.6. Cell cycle checkpoint

4.6.1. p21

The cyclin-dependent kinase inhibitor, p21, is one of the molecules responsible for cell cycle arrest in cells. Various stimuli such as DNA damage, oxidative stress and cytokines activate p21 and cause cell cycle arrest by the inhibitory effect of p21 on CDK1/2. P21 also interacts with PCNA and inhibits DNA replication. This is extra to other direct inhibitory effects of P21 on genes, such as E2FI and signal transducer and activator of transcription 3 (STAT3) [397]. P21 also has important functions in DNA repair, as its interactions with PNCA inhibits MMR and BER [398,399]. It has been proven that p21 plays an important role

in tumorigenesis of various cancers, including CRCs. This effect is exerted by interactions of p21 with molecules such as TP53 and KLF4, and also direct effects of p21 [400]. It has been shown that downregulation of p21 via various agents such as BRAF activated non-coding RNA (BANCR), and promoted CRC proliferation [401,402]. It has been shown that P21-activated kinases (PAKs) 1 and 4 are significantly increased in infiltrative and metastatic CRCs [403]. Antibodies against p21 are higher in patients with CRC compared with the normal population. In addition, levels of antibody are correlated with disease stage and lymph node involvement [404]. P21 has also been shown to be a mediator in drug resistance, as a study found that miR-520 g exerted drug resistance to 5-FU via the down regulation of p21 [405]. P21 in conjugation with tumor suppressor genes is the medium of efficacy of some anti-cancer medication. For example, Sludinac and Celecoxib upregulate p21/p53 and induce apoptosis in early stages of cancer [406].

4.6.2. WEE1

WEE1 is a kinase, in the family of Ser/Thr kinases, which is active in the control of cell cycle in theG2 arrest, via its effect on the Cdc2/cyclin B complex [407]. Expression of WEE1 has been revealed to be altered in various cancers. Recent evidence has emerged to support its role in CRC, as higher levels of WEE1 mRNA correlates with hepatic metastasis, distant metastasis and nodal involvement, and overall low survival [408]. Various molecules are important in the interplay of WEE1 and CDKs. One of these is Cables, a CDK-interacting protein which enhances phosphorylation of CDK2 by WEE1, and decreases the rate of cellular proliferation [409]. Studies have shown that Inhibition of WEE1, by agents such as MK-1775, increases the efficacy of medication such as 5-FU [410].

4.6.3. Cdc25

Cdc25 is a family of molecules with three members of Cdc25 A, B and C, which play an important role in the transition of the cell cycle from G1 to S phase and entry into mitosis [411]. Cdc25C is of the most importance, as it acts from the medium into entry to mitosis. DNA damage prior to initiation of mitosis activates CHK1 and Cds1, which phosphorylate Cdc25 and subsequently prevent Cdc2 dephosphorylating [412]. Evidence has emerged that Cdc25 molecules could be involved in CRC carcinogenesis. It has been shown that downregulation of Cdc25 A mediates G1/S delay. This downregulation is shown to be mediated by miRNA-21. CRC cell lines with reduced amount of miRNA-21 have shown to have elevated levels of Cdc25 A [413]. Downregulation of Cdc25 has also been known to be associated with inhibition of cell proliferation in CRC cell lines. A study revealed that introduction of 6-Shogaol, a product of Ginger, induced cell cycle arrest, which was alongside the upregulation of p53, p21 and GADD45α, and reduced the amount of Cdc25 A [414]. Smad7 is shown to be increased in CRC cells. This inhibitor of TGF-β has been shown to affect various processes in neoplastic cells, and interplay with a wide range of molecules. One interaction of interest has been with Cdc25, as knockdown of Smad7 caused a decrease in levels of Cdc25 A and resulted in the accumulation of cells in the S phase and reduced fraction of neoplastic cells in proliferation [415]. Another significance of Cdc25 molecules have been their possible role in determining response to therapy and prognosis. CRCs deficient in p53, when encountered with accumulated levels of CDC25B, show increased rate of mitosis, and sensitization to radiation and genotoxic medications [416].

4.7. Apoptosis

4.7.1. BAX

Bcl-2-like protein 4, or commonly referred to as BAX, is a key mediator in the intracellular pathway of apoptosis, in which the release of cytochrome c from the mitochondria causes apoptosis. BAX is a member of BCL-2 family, in which 2 groups of pro (Bax, Bak, Bid, Bad, and Bok) and anti (Bcl-2, Bcl-xL, and Bcl-w) apoptotic agents exist. Apoptosis is an important action in which cells with corrupt or damaged DNA are removed, and any blow to the process of apoptosis potentiates cancer [44]. The direction of a cell in the apoptosis pathway is determined by the ratio of pro- and anti-apoptotic molecules. This ratio has been shown to have prognostic value in CRCs. Lower levels of BAX compared to Bcl-2 correlated with higher age and tumor location (more colonic sites than in sigmoid and rectum) [417]. Intratumoral heterogeneity of BAX has also been shown in CRC. A study found that frameshift mutations of BAX were observed in 31% of cells with microsatellite instability [418]. Apoptosis has also been a major focus of treatment in CRC. It has been shown that flavonol agents, previously used in chemoprevention of different types of cancer, had a pro-apoptotic characteristic by increasing the ratio of BAX/Bcl2. It also increased the release of apoptosis inducing factor from the mitochondria, but had no effect on the cleavage of caspase 3 and 9 [419]. Similar pro-apoptotic results were seen by Virosecurinine, an alkaloid derived from *Securinega suffruticosa,* on SW480 cells [420].

4.7.2. PUMA

P53 upregulated modulator of apoptosis (PUMA), a Bcl-2-binding component 3, is a pro-apoptotic molecule which functions by affecting Bcl-2 and similar molecules, and inhibiting their suppressive role on pro-apoptotic molecules such as BAX and Bak [421,422]. Various regimens of treatment target the apoptotic pathway, and some are dependent on interactions of PUMA with other molecules [423]. A study revealed that treatment with proteasome inhibitors in CRC caused apoptosis via the cross link of Bax, PUMA and p53. Knockdown of PUMA resulted in significantly reduced activation of Bax by these agents, and reduced rates of apoptosis [424]. Gemcitabine was also similarly dependent on the actions of PUMA to initiate and maintain apoptosis [425]. Some multiple tyrosine kinase inhibitors such as sunitinib have also shown this dependence on PUMA [426]. Crizotinib, a dual MET and ALK inhibitor also exerts its effect via p53-PUMA [427]. Prognosis after treatment of 5-FU in stages 2 and 3 is similarly related to cellular contents of PUMA and Bim, and these two molecules but not NOXA, were significantly linked to overall survival [428].

Additionally, PUMA has been known to be the target of miRNAs, such as mi-RNA-203. In HCT116 cells, when exposed to adriamycine, there is an increase in both miRNA-203 and PUMA, which is dependent on the function of p53. Of importance, knockdown of p53 accompanied with elevated levels of miRNA-203 resulted in increased PUMA, indicating an independent role for miRNA-203 [429].

4.7.3. NOXA

NOXA is a BH3-only family molecule with fairly subtle pro-apoptotic effects. This molecule is classified in the sensitizers subgroup of BH3-Only family, as it increases apoptosis mainly in conjunction with other activator molecules such as PUMA [430]. The importance of NOXA in CRC remains controversial as studies have failed to report any significant relation between NOXA levels and CRC [431]. However, there is evidence that NOXA could be a factor consider during treatment. It has been shown that induction of NOXA by agents such as bortezumab can sensitize CRCs with intact Mcl-1 to ABT-737, a BH3 like molecule [432]. Also, some cell lines of CRC resist chemotherapy regimens by increased removal of NOXA, by silencing the expressing of UCH-L1, which removes Lys (48)-linked polyubiquitin segments. This interaction is thought to have a potential to be a target for treatment [433]. Physalin B is one of these agents with evident efficacy in triggering apoptosis via effecting the ubiquitin-proteasome pathway [434].

An interesting interaction of NOXA is with KRAS, which is mutated in large number of CRC. Activation of KRAS trans-activates pro-apoptosis molecules, such as ERK2 and NOXA, and thus determines chemosensitivity. Studies have shown mixed results on targeting this interaction in different stages of CRC malignancies and also the exact role of KRAS in yielding chemo-sensitivity. For example, a study by Conti et al.

revealed that KRAS was the determinant of chemo-sensitivity in only premalignant lesions, while de Bruijn MT et al. concluded that this effect of KRAS was also exerted in advanced CRC [435,436]. Okamoto et al. revealed that KRAS mutations were responsible for chemo-resistance, targeting the balance of pro-apoptotic and anti-apoptotic proteins could enhance sensitivity to treatment [437].

4.8. Senescence

4.8.1. p16

This is a cyclin-dependent kinase inhibitor, 2 A or p16, which plays a vital role in the cell cycle by regulating the passage of G1 to S phase. P16, in conjugation with p53 and other molecules, causes cellular senescence, which is the permanent arrest of cellular growth, and lysosomal and proteasomal enzyme pathways [438]. It has been shown that p16 is expressed aberrantly in colorectal adenomas and carcinomas. Expression of p16 is significantly related to the overexpression of p53, which can signal a grim outcome [439,440]. Furthermore, hyper-methylation of the promotor region of p16 has been strongly associated with overall low survival among CRC patients and invasive behavior [441–444]. Further studies suggested that hypermethylation of the promotor of p16 discriminated a specific entity among low differentiated tumors, which are those with low frequency in the distal tumor, and a better prognosis to other low differentiated tumors without increased methylation [445]. Noteworthy, some studies do not accept the prognostic effect of p16, and limits its role to adenomas [446,447]. It has been suggested that utilizing quantitative methylation-specific polymerase chain reaction could be used to determine the levels of p16 promotor methylation which can be used as a medium to screen cancer, especially those at higher stages [448]. There are agents which promote CRC. Some of these like ubiquitin-like with plant homeodomain and ring finger domains 1 (UHRF1) potentiate cancer via their effect on p16 (ink4a). Theoretically, separating lesions which can alter the function and expression of p16, could lead to new therapeutic options [449].

5. Conclusion

We have mainly discussed the contribution of key component of DNA damage response, including sensors, transducers, mediators, and downstream effectors in the various aspects of colorectal cancer. This review highlighted the significance of DNA damage and repair pathways in colorectal cancerpathogenesis, from development to progression and prognosis. As such, further studies focused on cellular DNA damage and repair machinery will increase our understanding of colorectal cancer etiology and help to designtherapeutics specifically targeting the defective pathway in individual patients.

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