

# Epigenetics in DNA Repair Mechanism and their Relation to Cancer

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## Abstract

The epigenetic model for the development of cancer is based on the concept that cancer develops due to overall hypomethylation of the genome with concomitant hypermethylation of promoters of oncogenes. Recent research unravels the epigenetic mechanisms of the malignant transformation of the cell and it contributes to the development of more efficient therapies.

**Methods.** Detailed investigation of recent literature on PubMed using the keywords DNA repair, epigenetics

**Conclusions.** It is known that a prominent mechanism of the surveillance of the integrity of the genome is the DNA repair system that protects the cell from deleterious insults by the recruitment of the DNA Damage Response (DDR). Mutations of the genes of this complex system are associated with immunodeficiencies and a predisposition to cancer. Recently, defects of the epigenetic DNA repair sequential regulation are described in cancer tissues. The epigenetic dysfunction involves changes in the methylation patterns of promoters and genes, aberrant histone modifications and the expression of variants, deregulation of histone readers and miRNA processing which will be analyzed in the review.

## Introduction

Theories on the process of the malignant transformation of the cell include the epigenetic involvement and as a general conception it is supported that cancer initiation and progress are accompanied by generalized hypomethylation of cytosines and gene specific hypermethylation which is usually associated with gene silencing<sup>1</sup>. Recent literature reports that a number of 'hits' lead to the malignant transformation of the cell including gene translation, the conformational changes of histones known as histone modifications and the expression of small RNAs named ncRNAs that influence gene expression. This review will concentrate on the recent literature related to the epigenetic involvement on the DNA repair and its association with cancer.

## Methods

Recent literature on epigenetic modulation of the DNA repair damage expands the knowledge on the function of this mechanism. The manuscript included the analysis of reports published on PubMed using the keywords DNA repair, epigenetics

## Results

DNA Damage Response (DDR) is a conserved response of the cell to insults including UV radiation, oxidative stress and toxic pollutants. The response is a safeguarding mechanism of the integrity of genome and the viability of the organisms. It is unique

because it has flexibility and it is versatile. Although it is dependent on a series of strict spatial-temporal regular regulations, it is not programmed since damage could occur any time and in any part of the genome<sup>2</sup>. The process includes the cellular response to damage, the activation of checkpoints, and the activation of the apoptosis and death pathways, when the damage is significant and it cannot be tolerated by the cell or recovered<sup>3</sup>. It implicates sensors of the damage, the up and down regulation of genes and chromatin conformational changes to start the repairing process as well as mechanisms to restore the damage on the previous configuration. The model is known as Access-Repair-Restore (ARR) model<sup>2</sup>.

DNA repair consists of different pathways which include Homologous Recombination (HR) that is based on the sensors MRE11/Rad50/NBS1 complex, the PAR protein which protects the ends of chromosomes from exonuclease activity and BRCA2 ligase, while Non-Homologous End Joining (NHEJ) is based on the function of the Ku70/Ku80 complex and DNA-PKcs activity with coenzymes the Artemis, the X-ray cross-complementation group 4 (XRCC4), Cernunnos with trimmer activity, Polμ and Polλ creating compatible ends and the closing of the damage by DNA ligase IV and finally the Alternative End joining of repair. The above pathways could repair deleterious Double Strand Breaks (DSB) or Single strand Breaks (SSB)<sup>4</sup>. A recently identified enzyme, Artemis, a hydroxylase with endonuclease activity, is implicated in 20-50% of breaks due to ionizing radiation<sup>4</sup>. Moreover, the MMR repair mechanism, the MisMatch Repair system, the NER, the

Nucleotide Excision Repair, and BER, the Single Damage Base repair, could correct single base errors<sup>5</sup>. Additionally, the DNA Damage response implicates checkpoint homologous that regulate the cell cycle to avoid replication errors until the damage is fixed such as the activation of p53, ATM and ATR<sup>6</sup>. When damage of the cell is significant the activation of cell death pathways and apoptosis are activated (Table 1).

The expression of the repair genes is regulated on many levels. Many activating and repressor genes have been identified. BRCA2, DNA-PKs as well as p53B, ATM and ATR function as tumor suppressor genes and they contribute to repair pathway choice. Emerging regulators include thyroid hormone receptor interactor 13 (TRIP13), ubiquitin-like with plant homeodomain (PHD) and RING finger domains 1 (UHRF1), Shieldin, and polymerase theta<sup>7</sup>. P53B is an important transcriptional factor which regulates DNA repair, the cell cycle and apoptosis and it is activated by the checkpoint proteins CK1 and 2. Moreover, it links genome instability together with chromatin fragments enriched by the variant γH2A.X to mitochondrial regulated molecular circuit of inflammation and senescence<sup>8</sup>. The transcription of p53 and APE1 protein are reported to be the most significant proteins in the activation of DNA repair genes<sup>9</sup>. In addition, APE1 is an important enzyme of BER and it stimulates the binding activity to protooncogenes (c-fos, c-jun) by redox signals and it acts a suppressor signal in RNA processing<sup>10</sup>. APE-1 activation is generated by deacetylation of SIRT1, a protein involved in CLOCK regulation, connecting genetic and epigenetic pathways<sup>11</sup>.

Table 1. Genetic and Epigenetic involvement in DNA repair process

DNA repair process	Mechanism	Example
Genes	HR, NHEJ, AEJ, MMR, NER, BER	Ataxia-telangiectasia (ATM) associated with immunodeficiency, accelerated age and predisposition to cancer
	Transcriptional regulation of the genes	P53B regulates repair and apoptosis
	Hypermethylation of gene or promoter	MGMT (O6-methylguanine-DNA methyltransferase), silenced in many cancers
Nucleosome changes	DNA sequence cis changes	loss of helical torsion and increased accessibility to DNA
Sensors of DNA damage	PARP1 (poly-[adenosine diphosphate (ADP)-ribose] polymerase 1), ATM, ATR, γH2A.X, Sirtuitins	Recruitment of modified histones and variants
Histones Remodeling	posttranslational modification	serine phosphorylation, lysine ubiquitylation, acetylation and deacetylation, and lysine and arginine methylation are the main histone modifications around the damage
	ribosylation	Poly (ADP-ribose) ation, sensor of DNA damage
	Phosphorylation	γH2A.X, conformation of histones around the damage
	Acetylation	acetylation of histone H3 and H4, relaxation of chromatin machinery around the break
	Ubiquitination	Lys 63-linked ubiquitin polymers, tumor suppressor histones
	Methylation	methylation of H3K79me and H4K20me, chromatin retention
	readers and erasers	active marks H3K4me3 and H3K36me3 as well as repressive marks H3K9me3, H3K27me3 and H4K20me3
	histone variants	H2A.Z, open chromatin structure
NcrNAs	mi-RNA-488-3p	inhibits DNA-PKcs, resistance to chemootherapy

ICL interlink repair is accomplished by 13 Fanconi anemia genes<sup>1</sup>. Mutations of the DNA repair genes are usually present with immunodeficiency syndromes, accelerated ageing and cancer predisposition.

Overall, more than 200 genes have been identified as part of the repair mechanism<sup>12</sup>. The repair system coordinates with metabolic activity of the cell by the family of enzymes called Sirtuins, which play important role in sensing the environmental stress. SIRT1 regulates the activity of many enzymes implicated in sensing of DSB (WRN) as well as in the HR pathway (NBS1, RAD), NHEJ (ATM, HDACs) and NER pathway (XPC), while SIRT6 stabilizes DNA-PK promoting NHEJ and telomere maintenance by deacetylating H3K9 and H3K56. An important sensor of DNA damage, PARP1 (poly- [adenosine diphosphate (ADP)-ribose] polymerase 1) is the first target of SIRT6<sup>12</sup>.

Transcriptional regulation of the DNA repair genes (Table 1) modulates the function of these genes only transiently, while epigenetic modifications have a more permanent and sustained role and they are frequently associated with gene silencing commonly detected in tumors<sup>13</sup>. A common epigenetic mechanism involved in the regulation of genes is the methylation patterns of the gene or the promoter region (Table 1). The more frequent change in tumors is hypermethylation of promoters<sup>14</sup>. A good example of this process is the hypermethylation of the MGMT (O6-methylguanine-DNA methyltransferase) gene which is epigenetically silenced in many cancers such as glioblastomas, colon cancer, non-small cell lung cancer, gastric carcinoma, head and neck squamous cell carcinoma<sup>1</sup> and up to 40% of cancers generally<sup>4</sup>. It is reported that it can be used as a prognostic marker for cancer treatment, since the methylation pattern of the gene correlates with response to treatment (4). Moreover, inhibition of the protein would offer advantage in the treatment of tumors by alkylating agents<sup>9</sup>. Mutations of the MSH2 gene lead to hereditary non polyposis cancer (Lynch syndrome), while methylation silencing of the promoter is detected in colorectal cancer, oral squamous cell cancer and ovarian cancer. Werner syndrome protein is hypermethylated in colorectal cancer (37.9%), NSCLS (37.5%), and chondrosarcoma (33.3%) followed by gastric cancer (25%), non-Hodgkin lymphoma (23.7%), prostate cancer (20%), breast cancer (17.2%), thyroid tumors (12.5%), osteosarcoma (11.1%), acute lymphoblastic leukemia (9.5%) and acute myeloblastic leukemia (4.8%), The CK2 checkpoint protein promoter is methylated in lung cancer, while XPC hypermethylation was detected in 33.5% of lung non-smokers cancers<sup>4</sup>. Fanconi anemia FANCF is silenced by hypermethylation in ovarian cancer, while hypermethylation of FANCC promoter in different forms of leukemia. Hypermethylation of the BRCA1 promoter is reported in breast cancer<sup>3</sup>. Epigenetic silencing of the

NER genes is associated with hypersensitivity to cancer treatment. Epigenetic silencing has been reported also in MMR genes and it is associated with colorectal tumors. Similarly, BER genes hypermethylation is reported in ovarian and colorectal cancers, while the FEN1 gene is hypomethylated in many cancers. Repression of genes as in the case of MLH1 of the MMR pathway could lead also to cancer<sup>4</sup>. On the contrary, activation and high levels of DNA-PKcs are detected in many cancers such as esophageal and colorectal cancers<sup>3</sup>. Generally speaking, within each repair pathway specific genes are usually hypermethylated due to either selection of genes or preference of methylation of specific genes<sup>1</sup>.

As far as chromatin conformational changes are concerned, it is reported in the literature that DDR is associated with core histone changes which include demethylation of H3K9me3 and phosphorylation of EZH2 leading to chromatin relaxation<sup>15</sup>. DSB form microscopically foci which include chromatin and enzymes<sup>6</sup>. Research unravels a histone code which supports the repair process. The epigenetic mechanism of DDR includes nucleosome liability, posttranslational modification of histones, the filling of gaps by histone variants, readers and erasers of the architectural structure which alter chromatin dynamics and ncRNAs which modulate the expression of genes Table 1<sup>16</sup>. Any dysregulation of the histone regulating code would lead to malignant transformation of the cell. Epigenetic DNA repair is accomplished either by hydrolysis requiring ATP consumption or by enzymes implicated on histone remodeling<sup>17</sup>.

Starting with nucleosome liability (Table 1), nucleosome sequence is a primary determinant of the epigenetic state of the cell together with proximity to repetitive elements and nuclear architecture. It is reported that genetic polymorphisms in the cis form influence the epigenetic state<sup>18</sup>. Constitutive heterochromatin rich in repetitive sequences is compartmentalized and marked with di- and tri-methylated histone H3 lysine 9 (H3K9me2 and H3K9me) and its reader heterochromatin 1 (HP1) which stabilize chromatin and it has a safeguarding role<sup>19</sup>. Many studies report the dysregulation of heterochromatin in the development and progression of cancer and loss of blocks of H3K9 are related to the phenotypic plasticity of cancers<sup>15</sup>. DNA damage manifests with increased histone mobility of the region<sup>20</sup>. For example, methylation of heterochromatin protein 1 $\beta$  (HP1 $\beta$ ) is related to nucleosome liability, while ubiquitination of H2AX and H2A stabilizes the complex<sup>21</sup>.

Secondly, DNA repair is associated with the remodeling of histones (Table 1). The process of remodeling refers to the changes of histones and subsequent reposition of the them to nucleosomes. They include the cis changes along the same template or trans from one template to another, the loss of helical torsion and the increase of accessibility

to the DNA sequence which increases its vulnerability<sup>16</sup>. Genome wide studies confirm posttranslational modifications after UV irradiation including H3K27 and H3 and H4 histones. Damage-induced histone modifications, such as  $\gamma$ H2AX, H2AK15 ubiquitination, and H4K20 methylation are important for chromatin configuration around the break<sup>2</sup>. Chromatin remodelers' function in association with chaperone proteins and they contribute to chromatin dynamics as well as to the recruitment of non-histone chromatin components<sup>2</sup>. The remodeling processes include histone posttranslational modifications which are acetylation, methylation, phosphorylation and ubiquitination at the N-terminal tails. Generally speaking, these modifications are reversible and they are related to the activity of chromosomal loci. For example, acetylation of lysine residues at the N-termini of the histones H3 and H4 is associated with active chromatin, while methylation of lysine residues at 9 and 27 position is associated with condensed silent chromatin. Additionally, histone acetylation and phosphorylation reduce the charge of histones leading to reduced binding to backbone DNA, while methylation regulates binding of effector molecules to the DNA sequence<sup>22</sup>.

The main posttranslational modifications in DNA repair process are serine phosphorylation, lysine ubiquitylation, acetylation and deacetylation, and lysine and arginine methylation. Methylation of lysine predominates as mono-, di or tri-methylation. The modification of histones depends on opposite enzyme pairs for example acetylation of lysine is regulated by histone acetyltransferases (HATs), while deacetylation by deacetylases (HDACs), which are transcriptional repressors. Methylation of cytosine by DNMTs is accompanied by gene silencing, while demethylation by mononuclear Fe (II)-containing enzymes is implicated in the regulation of gene expression<sup>23</sup>. The AlkB family of dioxygenases could restore damage by methylating agents. In addition, TET family enzymes which are enriched in DNA damage loci support the unmethylated state of heterochromatin<sup>24</sup>.

The earliest modification of DNA damage response is Poly (ADP-ribose)ylation, which ribosylates core histones in an amino terminal position and histone modifiers and it leads to positional silencing of chromatin in order to avoid collisions<sup>18</sup>. ATM and ATR are important sensors of DNA damage, and they are connecting gene repair machinery with epigenetic rearrangements. The phosphorylation of DNA-PKcs and ATM is associated with phosphorylation of the histone H2AX variant at the serine 139 position with concomitant acetylation of H3 and H4 termini and acetylation of H2A and ubiquitination of H2AX, respectively, which contribute to the relaxation of chromatin. These initial modifications consist the recruitment platform of other proteins around the break<sup>25</sup> due to conformational

changes of the nucleosome<sup>26</sup>. The negative feedback of excessive phosphorylation  $\gamma$ H2AX is accomplished by Akt protein<sup>3</sup>. The phosphorylated  $\gamma$ H2AX is an important histone variant of DNA repair process functioning as a sensor of the damage<sup>25</sup>. It constitutes the 2-25% of the H2.X pool and it is detected in few minutes after DNA irradiation to reach its peak within 30minutes. It is not limited in the near vicinity of the break, but it expands up to a 2Mbp region<sup>25</sup>. Novel g-Components accumulate also to the area of the H2AX species including g-H2AX<sup>26</sup>. Further on, dephosphorylation of ATM/ATR by the enzyme WIP1 induced by p53B is followed by dephosphorylation of  $\gamma$ H2AX and the reconstitution of the damage<sup>18</sup>.

Many other posttranslational modifications have been described. The phosphorylation of lysine residues on core histones and HP1 and histone H4 phosphorylation at Ser 1 which coincides with H4 deacetylation are important for DNA restoration after damage. Moreover, phosphorylation of H2B S14 and H2B on lysine 23 are related to apoptosis and they initiate later than H2AX phosphorylation<sup>27</sup>. A number of reports suggest that acetylation of histones contributes to repair after ionizing irradiation such as acetylation of histone H3 and H4 by TATA box-binding protein-free TAFII (TFTC) and NuA4 HAT complex, respectively<sup>5</sup>. Acetylation by Arp part of the ATP-dependent chromatin remodeling complex INO80/SWR1 is responsible for resection of the damage<sup>5</sup>. Histone deacetylases, HDAC1 and HDAC2 deacetylate Lys 56 of histone H3 (H3K56) and Lys 16 of histone H4 (H4K16) stimulating NHEJ. Similarly, acetylation by acetyltransferase TIP60 contributes to chromatin relaxation<sup>18</sup>. Other modifications include H4 acetylation and H2A S129 phosphorylation and H3 K79 and H4 K20 methylation in damage checkpoints<sup>15</sup>.

Waves of acetylation and deacetylation are detected during the repair process as acetylation of H3 K56 along with H2A S129 phosphorylation<sup>20</sup>. Recent literature reports that lysine deacetylases are dysregulated in many cancers such as in colorectal, stomach, esophagus, breast, ovary, lung, pancreas, thyroid, prostate, melanoma, neuroblastoma and oral cancers, while HDAC4 is down regulated in glioblastoma. Treatment with HDAC inhibitors, which suppress the DNA repair of cancer cells, improves prognosis<sup>28</sup>.

Ubiquitination is less frequently reported and Lys 63-linked ubiquitin polymers concentrate in the region which promote the recruitment of caretakers of the genome and they considered as tumor suppressors histones<sup>23</sup>. Ubiquitylation of H2B on lysine 123 is the most important<sup>28</sup>. Polycomb and NuRD recruit ubiquitin ligases that also suppress translation by the contribution of macroH2A by the APLF (aprataxin-PNK-like factor) modifier<sup>18</sup>. Finally, histone H4 methylation of H4 by Set9 histone lysine methyltransferase (HLMT) localizes Crb2 and it increases cell survival after damage

(5). Moreover, methylation of H3K79me and H4K20me accumulates 53BP1 and it is associated with chromatin retention<sup>18</sup>. Chromatin coordination is overall important for effective DDR<sup>20</sup>.

Thirdly, the histone code is decoded by histone readers. The process of repair is based on the strict progress of events and it has a tight spatial-temporal regulation. Research has unraveled several readers of transcription-related modifications such as active marks H3K4me3 and H3K36me3 as well as repressive marks H3K9me3, H3K27me3 and H4K20me3. Almost all m0 readers are sensitive to lysine methylation<sup>29</sup>. At DNA break loci histones are modified by writers and erasers. For example, accumulation of H2A.Z histone is associated with the choice of the DNA repair pathway for efficient repair<sup>17</sup>. Moreover, around 4120 proteins named ZF factors, which possess an array of two-cysteine two-histidine motifs, migrate to the site of the damage to regulate effective repair<sup>24</sup>.

Fourthly, at the restoration step chromatin is organized as before damage. However, newly synthesized histone marks are located in the region as memory marks such as H3.1 variant and core histone H2A and H3.3<sup>15</sup>. The deposition of the H3K9me3 mark predisposes to the position of nucleotide variants and other alterations which they could predict up to 40% of mutation load of cancer cells. Increased methylation of H3.3 is associated with stable heterochromatin and better response to chemotherapy<sup>17</sup>. Point transcription silencing and mutations of H3.3 were detected in many cancers, particularly brain tumors<sup>14</sup>.

Fifthly, histone variants replace canonical histones in DNA breaks and change histone dynamics<sup>30</sup>. The H1.R is reported to be implicated in HR since mutants reduce gene targeting, impair sister chromatid exchange and contribute to chromosomal aberrations at the G2 phase. The accumulation of the phosphorylated H2A.X variant coincides with the active repair process, while acetylation at lysine 5, and subsequent ubiquitination, restores the repair. The accumulation of macroH2A1.1 and local chromatin compaction is accomplished in a PAR dependent manner. H2B ubiquitination contributes to the formation of foci. Later on, the damage is enriched by acetylated H2A.Z. Late repair steps include the deposition of H3.1, H3.2 and H3.3 variants<sup>31</sup>. Dysregulation of variants has been detected in many cancers. For example, in melanoma and lung cancers macroH2A is reduced with subsequent overexpression of oncogenes including the CDK8 oncogene and it is associated with the outcome of the disease. The increase of H2A.Z is associated with poor outcome of breast cancers<sup>2</sup>.

Finally, the production of ncRNAs is a quick response mechanism to oxidative stress (Table 1). Many DNA and RNA processing mechanisms with positive and negative feedbacks supervise RNA maturation and they produce high

quality RNAs which respond to environmental changes<sup>7</sup>. ncRNAs is established as an active and dynamic substrate on the regulation of genes by promoting translation or by degradation of mRNAs. Their function could be reversed by epigenetic regulation of the AlkB dioxygenases and demethylation of methyl-adenosine and cytosine. Different miRNAs have been implicated in cancer sensitivity to treatment such as mi-RNA-488-3p which inhibits DNA-PKcs changes sensitivity of melanoma to cisplatin<sup>15</sup>. RNA modifications are usually by methylation. For example, ALKBH2 dioxygenase is frequently down-regulated by miRNAs in gastric cancer, brain tumors, colorectal and bladder cancer<sup>32</sup>.

Recent literature emphasizes that depending on the diverse genetic damage such as irradiation or oxidative stress, the process of repair is different. Moreover, scars of the repair process could be heritable and they could influence the ageing process and disease<sup>33</sup>. Ageing is characterized by accumulation of repressive heterochromatic marks including H3K9me3, H3K27me3, and H4K20me3, redistribution of chromatin and an increased risk for the development of cancer<sup>34</sup>. Advances on the study of tumor microenvironment show that lactate impact on non-histones, such as p53 and PD-L1, and they contribute to the tumorigenesis and tumor progression<sup>35</sup>.

## Conclusion

Concluding DNA repair mechanism depends on the type of the damage, the phase of the cell cycle, the accessibility of the DNA repair mechanism and tumor microenvironment. It could be completed with the transcription of DNA repair genes, but also configuration of chromatin and chromatin modification dynamics. Histone modifications consist the platform for repair by relaxation, compaction, signaling and recruitment of a number of enzymes for the repair processing. Euchromatin is early repaired in contrast to heterochromatin. Recent literature suggests the use of biomarkers related to the epigenetic repair mechanism to accurate diagnosis and prognosis of cancers. Moreover, targeting the DNA repair capacity of the cell is an additional treatment in the chemotherapy of cancer<sup>36</sup>.

Although the review presents the steps of DNA repair mechanisms including the epigenetic model, the limitations of the study is the lack of detailed analysis and presentation of many important mechanisms.

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