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Fanconi Anemia/Brca Pathway and Head and Neck Squamous Cell Carcinomas

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1. Introduction

DNA repair defect is one of the hallmarks of tumorigenesis, and is intimately linked to various human cancers, both inherited and sporadic (1). The two best examples are perhaps the DNA mismatch repair pathway in colorectal cancer, and the Fanconi Anemia/Brca (Fanc/Brca) pathway in head and neck squamous cell carcinomas (HNSCCs) (1). In this book chapter, I will review the updated knowledge of Fanc/Brca pathway in human cancers particularly in HNSCCs.

Fanconi anemia is a rare autosomal recessive or X-linked chromosomal instability disorder, with incidence of 1 to 5 cases per millions. The affected children have multiple congenital defects, and typically develop bone marrow failure during the first decade of life. They are at the risk for developing hematological cancers with the acute myelogenous leukemia (AML) the most frequent (2). Recently studies also showed a predisposition of Fanconi anemia patients to multiple solid tumors (3, 4), particularly to HNSCCs (5). Other tumors include gynecologic SCCs, and tumors of esophagus, liver, and skin (3, 4). Since Fanconi anemia is characterized by spontaneous chromosome breakage and cellular hypersensitivity to DNA cross-linking agents, such as mitomycin C, or diepoxybutane (DEB), the DEB-induced chromosome-breakage assay is widely used as a diagnostic test for Fanconi anemia patients, and the complementation test is used to define the Fanconi anemia subtypes. Androgens, hematopoietic growth factors, or stem-cell transplantation is currently used for treating bone marrow failure in Fanconi anemia patients(2).

The Fanconi anemia pathway is complex and interacts with other DNA repair pathways (6, 7). The pathway itself is regulated by so far thirteen Fanconi anemia proteins (FANCA, B, C, D1, D2, E, F, G, I, J, L, M and N). Among those proteins, eight are assembled in a nuclear ubiquitin E3 ligase complex (FANCA/B/C/E/F/G/L/M), known as the Fanconi anemia core complex, which mono-ubiquitinates FANCD2 and FANCI. The mono-ubiquitinated FANCD2/FANCI complex is targeted to chromatin, where it interacts, either directly or indirectly, with additional downstream Fanconi anemia proteins (FANCD1, FANCN, and FANCJ) (6, 7). The first evidence of the convergence of Fanconi anemia pathway with

the Breast cancer (Brca) pathway came from the finding that the breast cancer susceptibility gene, Brca2 is actually identical to a Fanconi anemia gene, FANCD1 (8). Later studies showed that Fanconi anemia proteins form foci with Brca1, another major breast cancer susceptibility gene, and Rad51 for DNA repair (9). In addition, Brca1 and Brca2 also interact with another Fanconi anemia protein, FANCN (10, 11). Thus the Fanconi anemia and Brca pathways are intimately connected, and are summarized as Fanc/Brca pathway [Figure 1].
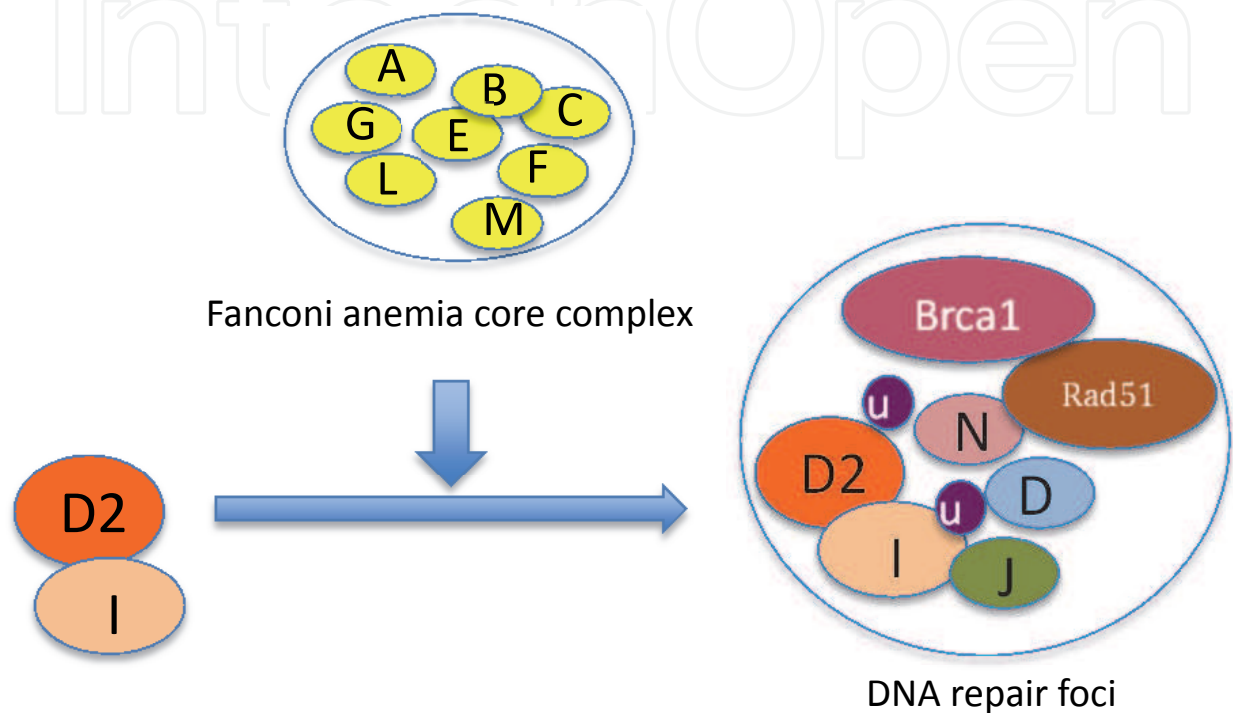

Fig. 1. Schematic of Fanc/Brca pathway in DNA repair. A-D1, D2, E-G, I-J, N stands for Fanconi anemia proteins FancA-D1, FancD2, FancE-G, FancI-J, and FancN.

2. Fanc/Brca pathway and human cancers

As briefly mentioned in the introduction section, the correlations of Fanc/Brca pathway and human cancers are well demonstrated by at least three lines of evidence: I). Susceptibility to various human cancers, including both hematologic and solid tumors in homozygous Fanconi anemia patients (3, 4). About one-third of Fanconi anemia patients will develop either hematologic or solid tumors by the age of 40 years. While AML is the predominant among hematologic cancers, squamous cell carcinomas (SCC) are the majority group of solid tumors developed in Fanconi anemia patients (3, 4). SCC of head and neck region is the most common (5), followed by SCC of gynecological system (vulva and cervix), esophagus, and skin (3, 4). II). Increased risk of cancers in heterozygous carriers of gene mutations in the Fanc/Brca pathway. The most common cancers in the heterozygous carriers of the Fanc/Brca gene mutations are breast and ovarian cancers (2, 12). In addition, development of pancreatic cancer was also reported in the heterozygous carriers of Fanc/Brca gene mutations, including FANCC, FANCG, and FANCN/PALB2 (13-15). Other cancers associated with heterozygous Fanc/Brca gene mutations are mainly prostate, lung, gastric cancer, and melanoma (16, 17). III). Molecular alterations of Fanc/Brca pathway genes in

sporadic human cancers. The most common molecular alteration of the Fanc/Brca pathway genes in sporadic human cancers is epigenic silencing of FANCF gene, which is most frequently seen in ovarian (18), cervical cancers (19), non-small-cell lung cancers (20), and HNSCC (20). In addition, methylation of Brca1 has also been reported in breast, ovarian, and non-small-cell lung cancers (20, 21).

3. Fanc/Brca pathway and HNSCCs: Clinical and molecular studies

HNSCC refers to SCCs arising from oral cavity, tongue, pharyngeal and laryngeal regions, and is the 6th most common human cancer worldwide. There are about 600,000 new cases and 350,000 cancer deaths worldwide each year (22, 23). HNSCCs usually occur in relatively late age of life, and higher in male with well known etiological factors of tobacco and/or alcohol (22, 23). However, the incidence of HNSCC is increasing recently in women with relatively young age, and correlates with human papilloma virus (HPV) infection (22, 23). The inherited form of HNSCC is very rare, in comparison with those in colorectal or breast cancers. Thus, the higher incidence of HNSCC developed in Fanconi anemia patients is both interesting and surprising. Thus, the Fanconi anemia patients may represent the first and perhaps the only one example of hereditary cancer syndromes predisposing to HNSCC.

The first evidence of high incidence of HNSCC in the Fanconi anemia patients came from studies of a 20-year perspective on 754 Fanconi anemia patients from the International Fanconi Anemia Registry (3, 5). These studies combined with another study showed that incidence of HNSCC is about 500 to 700 times increased in Fanconi anemia patients than those in general population (3-5). The Fanconi anemia patients ranged from 15 to 49 years of age, and comprised subtypes of FANCA, C, D2, F, G and nontype ones, and patients with HNSCC were found in these subtypes except FANCD2 and FANCF (3, 5). The incidence of HNSCC is even higher in the Fanconi anemia patients after hematopoietic stem cell transplantation (24). Compared to about 3% of HNSCC incidence in the Fanconi anemia patients before bone marrow transplantation, the incidence of HNSCCs increases more than 3 fold to about 10% in the Fanconi anemia patients after bone marrow transplantation (24).

While most of the Fanconi anemia patients develop bone marrow failure before their cancer development, there are about 20% of patients, often with milder physical and hematologic phenotypes, having developed solid tumors before the diagnosis of Fanconi anemia. These so-called adult head and neck cancer and hematopoietic mosaicism have been described in patients as mosaicism of 2 populations of cells in blood, one carrying FA defect, and the other seemingly normal (25). These findings have great impact on understanding the causal pathway of head and neck cancers in general population. Although there are no reports of genetic mutations in Fanc/Brca pathway in HNSCCs, FANCB and FANCF methylation have been described in about 31% and 15% of sporadic HNSCCs, respectively (20, 26). In addition, loss or reduced expression of FANC/Brca pathway genes, such as FANCB, FANCF, FANCJ, FANCM, Brca1, Brca2, FANCD2 and FANCG have been reported in sporadic HNSCCs (27, 28). Interestingly, reduced expression of FANCA and FANCG is more common in young HNSCC patients than older ones, suggesting different molecular mechanisms of HNSCC tumorigenesis between younger and older patients (29).

Given the clinical characteristics of HNSCC in Fanconi anemia patients, it is speculated that the molecular characteristics of HNSCC from Fanconi anemia patients might be different from sporadic HNSCC patients. It was suggested that Fanconi anemia patients have higher susceptibility to HPV-induced HNSCC (30). However, separate studies failed to show the

link between Fanconi Anemia and HPV-associated HNSCC (31), and molecular characteristics of HNSCC from Fanconi Anemia patients are not significantly different from sporadic HNSCC, except for the sensitivity to the chemotherapy drug, cisplatin (32). Interestingly, a study showed that cigarette smoke, one of the major etiological factors in sporadic HNSCC, induces genetic instability by suppressing FANCD2 expression (33), suggesting the molecular similarities shared between HNSCC from Fanconi Anemia patients and sporadic HNSCC.

4. Fanc/Brca pathway and HNSCCs: Lessons from animal models

Utilizing genetically engineered mouse models of Fanc/Brca pathway provides a powerful platform to study the causal role of Fanc/Brca pathway in human cancer development, including HNSCC (34). The first mouse model demonstrating the role of Fanc/Brca pathway in epithelial cancer development is the FANCD2 knockout mouse (35). FANCD2 is the common downstream effector of the Fanconi anemia nuclear complex, and acts as readout for the Fanc/Brca pathway. In addition, it forms nuclear foci with Rad51 and Brca1 for functional DNA repair (6, 7) [Figure 1]. Similar to human Fanconi anemia patients, FANCD2 knockout mice exhibited sensitivity to DNA interstrand cross-linking agents. Further more, these mice developed epithelial cancers in various organs, including mammary, bronchoalveolar, lung, and ovarian cancers (35). Knockout FANCD1/Brca2 developed breast and ovarian cancers; in addition, high incidence of squamous cell carcinoma of forestomach was seen in these mice (36). Cancer development, progression, and latency of both models were further enhanced by combination with p53 knockout (37, 38). Mice with germline knockout of FANCA and FANCC also developed sarcoma, lymphoma, and adenocarcinomas (34).

Using tissue specific promoters, such as Keratin 5, or 14, which target gene specifically in stratified epithelial cells (39), several studies showed that disruption of Fanc/Brca pathway lead to development of squamous cell carcinoma in multiple organs. For example, tissue specific deletion of Brca1 driven by Keratin 5 in mice developed squamous cell carcinomas in skin, ear canal, oral cavity, esophagus, and forestomach (40). Furthermore, another study, using tissue specific promoter Keratin 14-driven HPV mice crossed with FANCD2 knockout mice, showed an increased susceptibility to HNSCC when treated with a chemical carcinogen, supporting the hypothesis that Fanconi anemia patients have increased susceptibility to HPV-associated HNSCC observed in human samples (41).

Although the germline or tissue specific knockout mouse models of Fanc/Brca pathway suggested a causal role of this pathway in HNSCC tumorgenesis, the various types of cancers developed in multiple organs still hampered the study of this pathway specifically in HNSCC pathogenesis. To overcome this problem, we recently developed an inducible head-and-neck region specific knockout system (42, 43). This system uses the Keratin 5 or Keratin 14 promoter to direct head-and-neck specific expression of CrePR1, a fusion protein comprised of Cre recombinase fused to a truncated progesterone receptor ligand binding domain (ΔPR). In this system, RU486 treatment causes the CrePR1 fusion protein to translocate into the nucleus where it excises DNA sequences that have been flanked by loxP sites ("floxed"). Since the Keratin 5 or 14 promoter targets transgene expression to epithelial stem cells of the basal layer of stratified epithelium, such as head and neck epithelia, once RU486-induced excision occurs in stem cells, the stratified epithelium will eventually be replaced by cells in which the targeted gene is deleted for the lifetime of the mice (42, 43) [Figure 2].
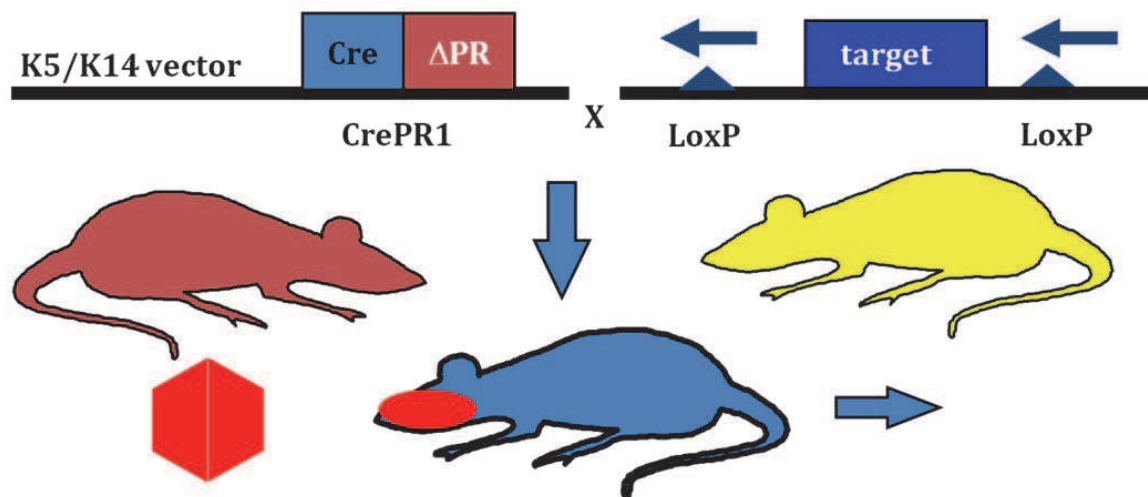
Fig. 2. Inducible head and neck specific gene knockout system.

We have used this system to establish a metastatic HNSCC mouse model in which Smad4, the central signal mediator of transforming growth factor β (TGFβ) is specifically deleted in the head and neck epithelia (43). TGFβ is a multifunctional cytokine that regulates cell proliferation, apoptosis, tissue remodeling, and angiogenesis. In addition, TGFβ is also known to regulate genomic stability (44). The TGFβ signaling initiates from ligand binding to heteromers of TGFβ type I and type II receptors, and activate intracellular signal mediators Smad2 and Smad3 through phosphorylation. Smad3 binds to the smad-binding element (SBE) of a target gene, and subsequently recruits Smad4 to the same SBE. The Smad complexes then translocate to the nuclus to regulate gene expression of Smad targets involved in a wide variety of cancer-related processes (44) [Figure 3]. When the Smad4 gene is specifically deleted in mouse head and neck epithelia, the mice developed spontaneous HNSCC (43). Interestingly, the Smad4-/- head and neck epithelia and tumors exhibited genomic instability as revealed by abnormal centrosomes, increased genomic aberrations, and increased sensitivity to mitomycin C. Further molecular analysis found that Fanc/Brca pathway gene expression and function correlate with Smad4 expression level. Specific knockdown of Smad4 in normal keratinocytes decreases expression of Fanc/Brca pathway genes, such as FancA, FancD2, Brca1, and Rad51. Restoration of Smad4 in a Smad4-null HNSCC cell line Cal27, increases the expression of Brca1 and Rad51 and the number of DNA repair nuclear foci. Interestingly, SBE sites were found in the promoters of FancA, FancD2, and Brca1 genes, suggesting that these genes may be transcriptional targets of TGFβ/Smad4 signaling pathway (43). Thus, the TGFβ/Smad4 signaling pathway is directly connected with the Fanc/Brca pathway in HNSCC tumorigenesis [Figure 3].

5. Components of FA/Brca pathway as targets for cancer therapy

DNA repair genes, including Fanc/Brca pathway, critically regulate the cellular response to chemotherapy and radiation therapy (45). The Fanc/Brca pathway regulates genomic stability required for cellular resistance to DNA cross-linking agents, thus the defects of this pathway contribute to chemo-, or radiation sensitivities (46).

The milestone discovery for Fanc/Brca pathway conferring chemosensitivity came from the discovery of epigenic silencing of FANCF in ovarian cancer (18). Ovarian cancer cells
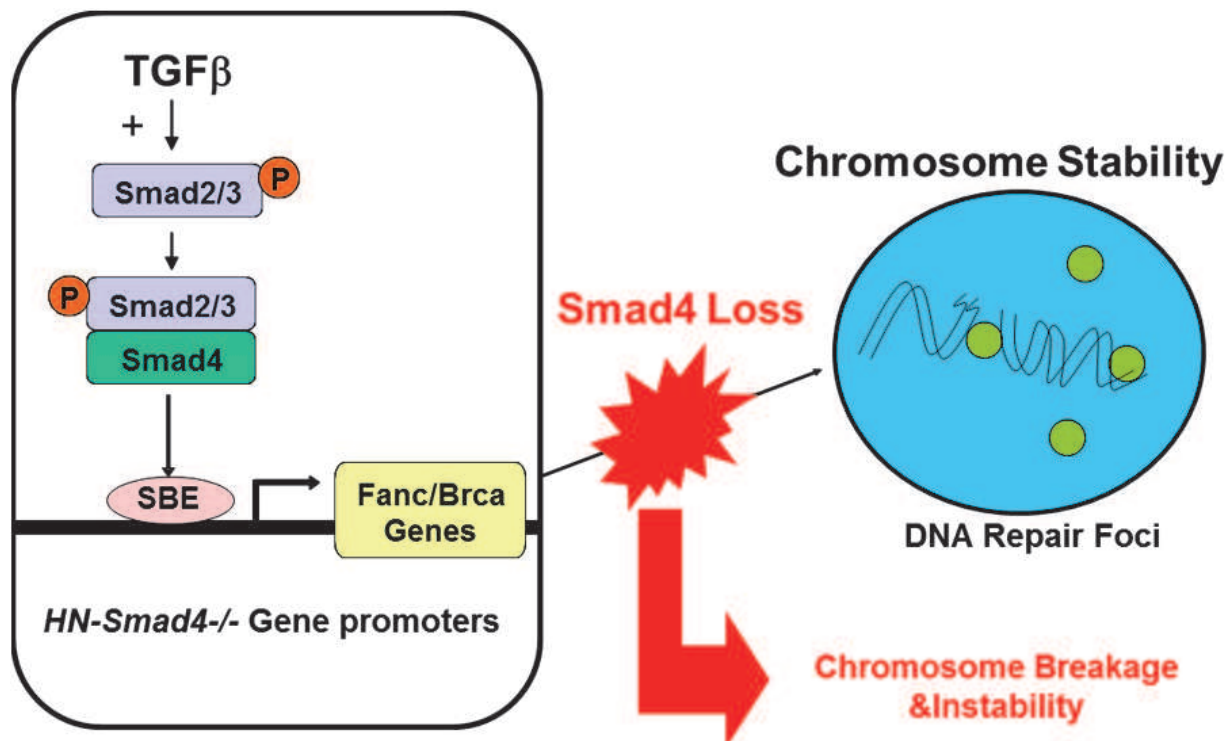
Fig. 3. Potential mechanism for chromosome instability in *HN-Smad4-/-* Lesions. HN: head and neck

are usually hypersensitive to chemotherapeutic drug, such as cisplatin initially, but become resistant to the drug over time. The underlying molecular mechanism was revealed to be due to DNA methylation of the CpG island of FANCF, and the resistance is correlated with demethylation of FANCF (18). This study questioned the application of demethylation agents in treatment of ovarian cancer, and suggested that targeted disruption of Fanc/Brca pathway may be a better therapeutic option for ovarian cancer (18). While similar results of targeting Fanc/Brca pathway in sensitizing chemotherapy were reported in other types of cancers, such as colorectal cancer, peritoneal carcinomas, and multiple myeloma (47-50), the results from HNSCC are still controversial. It was reported that targeting Fanc/Brca pathway by the histone deacetylase inhibitor phenybutyrate sensitizes human HNSCC cells to cisplatin (51). However, a separate study failed to correlate Fanc/Brca pathway inactivation with cisplatin sensitivity based on lack of evidence of FANCF methylation, and down-regulation of other Fanconi anemia genes (52). Another interesting finding for the mechanisms of cisplatin resistance in ovarian cancer is to identify secondary mutations of Brca2/FANCD1 (53) and Brca1 gene (54). Similar mutations of Brca2/FANCD1 have also been detected in pancreatic cancers (55). All these results highlight the functional importance of Fanc/Brca pathway in modulating sensitivity of cancer chemotherapy (50).

Recent studies showed that cancer cells deficient in DNA repair pathways become highly dependent on alternative pathways for survival (45). For example, cancers deficient in Brca1 or Brca2 usually exhibit impaired ability to repair double-stranded DNA breaks via homologous recombination (56, 57). Moreover, in the setting of defective homologous recombination, inhibition of a second DNA repair pathway, such as base excision repair, is often a lethal event (56, 57). This so called "synthetic lethality" has been utilized in designing the ultimate cancer therapy (45). One of the best examples is to apply

poly(ADP-ribose) polymerase 1 (PARP1) inhibitors in breast or ovarian cancer patients with Brca1 or Brca 2 mutation (56-59). PARP1 is a nuclear protein that rapidly binds to DNA single-strand breaks and facilitates DNA repair (60). Use of the PARP1 inhibitor also induced significant sensitization to radiation therapy in HNSCC cells (61). Although alterations of Brca1 and Brca2 are rare in human HNSCC, HNSCC with loss of Smad4 are common and exhibit Fanc/Brca pathway defects in DNA repair as we showed previously (43), thus, providing a promising rationale and biomarker in utilizing PARP1 inhibitor for cancer therapy in HNSCC with Smad4 loss. In addition to the sensitivity to PARP1 inhibition, Fanc/Brca pathway-deficient tumor cells are also hypersensitive to inhibition of ataxia telangiectasia mutated kinase ATM (62), and checkpoint kinase CHK1 (63). With discoveries of more pathways, defects in which confer synthetic lethality with defects in Fanc/Brca pathway, more sophisticated and efficient therapeutic approaches will be designed and tested.

6. Future perspectives

Defect of Fanc/Brca pathway represents by far the only genetic predisposition to HNSCC through clinical genetic studies. Given the complexity of this pathway and its interaction with other DNA repair pathways, there are still lots of unanswered questions about the molecular mechanisms of this pathway in HNSCC tumorigenesis. However, with more biomarkers being identified and utilized to stratify HNSCC patients with particular defects of Fanc/Brca pathway, a personalized therapy with more efficacy and less side effect will ultimately be available, which will have significant impact on HNSCC management.

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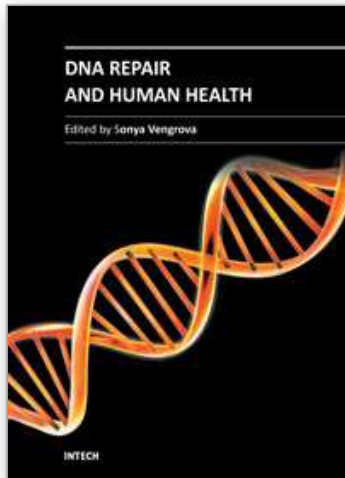
DNA Repair and Human Health

Edited by Dr. Sonya Vengrova

Over the past decades, great advances have been made in understanding the cellular DNA repair pathways. At the same time, a wealth of descriptive knowledge of human diseases has been accumulated. Now, the basic research of the mechanisms of DNA repair is merging with clinical research, placing the action of the DNA repair pathways in the context of the whole organism. Such integrative approach enables understanding of the disease mechanisms and is invaluable in improving diagnostics and prevention, as well as designing better therapies. This book highlights the central role of DNA repair in human health and well-being. The reviews presented here, contain detailed descriptions of DNA repair pathways, as well as analysis of a large body of evidence addressing links between DNA damage repair and human health. They will be of interest to a broad audience, from molecular biologists working on DNA repair in any model system, to medical researchers.

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