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Hypoxia Inhibits DNA Repair to Promote Malignant Progression

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1. Introduction

DNA repair is essential to genomic integrity of the cell. Numerous studies have provided compelling evidence that hereditary defects in DNA repair are linked with predispositions to cancer, shedding light on the mechanism of DNA repair and its importance in cancer biology. The majority of human cancers however rarely undergo somatic mutations in DNA repair genes, yet they acquire genetic alterations as they progress. Little is known about the mechanism of genetic alteration during malignant progression. We and others have shown recently that hypoxia—oxygen deficiency—plays an important role in inhibiting DNA repair. Tumor hypoxia gives rise to the over-expression and activation of hypoxia-inducible factor 1 α (HIF-1 α), an oxygen-sensitive transcription factor commonly over-expressed in human cancers. Although HIF-1 α is best known for its transcriptional up-regulation of a host of target genes responsible for tumor growth and survival, in this chapter we describe a novel mechanism by which HIF-1 α inhibits DNA repair, thereby promoting genetic alterations and malignant progression.

2. Tumor hypoxia and hypoxic response

2.1 Role of hypoxia in tumor progression

In mammals, molecular oxygen is required for aerobic metabolism to maintain intracellular bioenergetics and to serve as an electron acceptor. Although the oxygen concentration in ambient air is approximately 21%, oxygen levels in mammalian tissues are generally maintained at 2–9%. Tissues become hypoxic when oxygen levels drop below 2% and severely hypoxic or anoxic when they are less than 0.02% (Bertout et al, 2008). Whereas mild hypoxia is part of normal development and physiology, as well as pathophysiology, severe hypoxia occurs mostly in pathophysiological conditions.

Human cancers frequently experience mild to severe hypoxia arising from rapid cell proliferation that outstrips oxygen supply and aberrant angiogenic processes that yield vascular anomaly, such as vessel tortuosity, arteriovenous shunts, and blind ends. Consequently, despite rampant angiogenic response, necrotic lesions become conspicuous

as a result of severe hypoxia or anoxia, especially in advanced human cancers accompanying cell proliferation. By contrast, benign tumors are less hypoxic, with cells proliferating at a pace compatible with vasculature development. Therefore, the degree of malignancy appears to be associated with the severity of hypoxia.

Many studies have indicated that hypoxia promotes tumor metabolism, angiogenesis, and metastasis (Bertout et al, 2008; Giaccia et al, 2003; Harris, 2002; Semenza, 2003). Solid tumors manifest enhanced glucose consumption resulting from hypoxic switching to anaerobic glycolysis from the tricarboxylic acid cycle for bioenergetics. In advanced human gliomas, tumor angiogenesis is rampant and frequently accompanied by rapid cell proliferation. Hypoxia confers metastatic potential by altering extracellular matrix function and increasing the motility of tumor cells.

Moreover, it has long been recognized that tumor hypoxia is tightly linked with DNA damage, mutation, and over-replication (Bindra & Glazer, 2005; Bristow & Hill, 2008; Huang et al, 2007). It is proposed that hypoxia provides a physiological selective pressure in tumors for the expansion of apoptosis-resistant variants by acquiring p53 mutations (Graeber et al, 1996). Hypoxia also induces genomic rearrangement through activation of fragile sites, thereby triggering breakage–fusion–bridge cycles and, in turn, gene amplification (Coquelle et al, 1998). Furthermore, hypoxia is known to contribute to the development of resistance to radiation therapy and chemotherapy by, for example, up-regulating the expression of the multidrug resistance gene *ABCB1*, also known as *MDR1*.

2.2 Hypoxic response

Through evolution, mammals have developed a coordinated physiological system to cope with hypoxic stress (Bunn & Poyton, 1996; Semenza, 1999). Respiratory, circulatory, and hematopoietic systems are developed at the systemic level for oxygen uptake, transport, and delivery. Oxygen-sensing and responsive mechanisms are widely present in mammalian cells to maintain oxygen homeostasis by altering DNA replication, gene expression, and metabolism. In particular, the identification of HIF-1 α (Wang & Semenza, 1993; Wang & Semenza, 1995) has immensely advanced the understanding of hypoxic response at the molecular level.

HIF-1 α is an oxygen-sensitive transcription factor that belongs to the PAS (Per-ARNT-Sim) superfamily (Wang et al, 1995) (Fig. 1). Upon dimerization with ARNT (arylhydrocarbon receptor nuclear translocator; also known as HIF-1 β), HIF-1 α recognizes the hypoxia-responsive element (5'-RCGTG-3') in the promoter and/or enhancer of its target genes via a basic helix–loop–helix domain at the amino terminus (Semenza, 1999). HIF-1 α heterodimerization depends on both the helix–loop–helix domain and the downstream PAS domain, which can be divided into two subdomains: PAS-A and PAS-B. Whereas PAS-A has been implicated in the heterodimerization and interaction with other proteins such as the heat shock protein 90 (Gradin et al, 1996; Semenza, 1999), the role of PAS-B remains less understood. HIF-1 α harbors an oxygen-dependent degradation (ODD) domain that mediates proteolysis by the ubiquitin–proteasome pathway (Huang et al, 1998; Pugh et al, 1997). Hypoxia-stabilized HIF-1 α recruits the transcription coactivator p300/CBP for transcriptional activation of its target genes via a potent transactivation domain at the carboxyl terminus (Arany et al, 1996; Gu et al, 2001; Kallio et al, 1998). Likewise, HIF-2 α (also known as EPAS1) (Tian et al, 1997) shares similar structural domains with HIF-1 α and binds to ARNT.

HIF-1 α is regulated primarily at the post-translational level (Huang & Bunn, 2003). Whereas both HIF-1 α and ARNT are constitutively expressed at mRNA and protein levels, HIF-1 α is

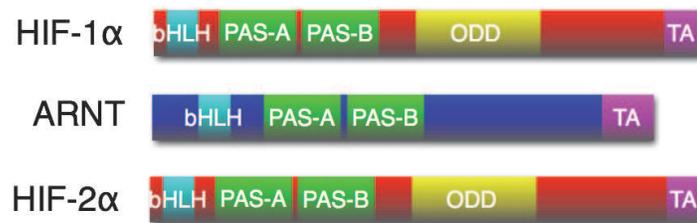


Fig. 1. Schematic representation of HIF-1 α , ARNT, and HIF-2 α . HIF-1 α possesses a basic helix–loop–helix (*bHLH*) domain, a Per–ARNT–Sim (*PAS*) domain that can be divided into PAS-A and PAS-B, and a transactivation (*TA*) domain. Although similar domains can be found in ARNT based on sequence homology, an oxygen-dependent degradation (*ODD*) domain is uniquely present in HIF-1 α . HIF-2 α shares strong sequence homology with HIF-1 α .

extremely sensitive to proteolysis under oxygenated conditions (Gradin et al, 1996; Huang et al, 1996; Pugh et al, 1997). The ODD domain is crucial for HIF-1 α proteolysis and is targeted for polyubiquitination by the E3 ubiquitin ligase containing the von Hippel-Lindau protein (pVHL) (Cockman et al, 2000; Ohh et al, 2000; Tanimoto et al, 2000). pVHL binding requires hydroxylation of two proline residues (Pro-402 and Pro-564 within the ODD domain) (Ivan et al, 2001; Jaakkola et al, 2001). Prolyl hydroxylation is catalyzed by a family of prolyl-4-hydroxylases (Egln1, Egln2, and Egln3, which are widely known as PHD2, PHD1, and PHD3, respectively) that belong to the 2-oxoglutarate-dependent oxygenase superfamily (Bruick & McKnight, 2001; Epstein et al, 2001; Kaelin & Ratcliffe, 2008). Accordingly, these prolyl-4-hydroxylases sense and transduce oxygen signals through hydroxylation, resulting in polyubiquitination and degradation of HIF-1 α . By contrast, hypoxia inhibits the oxygen-dependent enzymatic activity, thereby preventing HIF-1 α degradation. Consequently, a stabilized HIF-1 α exerts its transcriptional function through heterodimerization, DNA binding, and recruitment of p300/CBP for transactivation (Fig. 2).

Given the widespread over-expression of HIF-1 α and/or HIF-2 α in solid cancers, this canonical mechanism of HIF-1 α has been the guiding light for elucidating many of the pathological processes crucial for tumor growth and progression through the identification of numerous target genes of HIF-1 α and HIF-2 α (Bertout et al, 2008; Giaccia et al, 2003; Harris, 2002; Semenza, 2003). In particular, HIF-1 α and HIF-2 α have been shown to contribute to tumorigenesis, angiogenesis, metastasis, metabolism, and stem cell maintenance (Bertout et al, 2008; Majmundar et al, 2010). Despite these remarkable advancements in understanding the molecular basis of tumor hypoxia, the key question—whether HIF-1 α and HIF-2 α are responsible for genetic alterations that drive malignant progression—remains unanswered.

3. Regulation of DNA repair by hypoxia

3.1 DNA repair and human cancer

Hereditary defects in DNA repair have been linked with genetic instability and predispositions to cancer (Vogelstein & Kinzler, 2004). Genetic mutations in a host of DNA repair genes have been attributed to the development of a variety of human cancers including breast, colon, brain, and skin cancers, as well as leukemias and lymphomas. These genes participate in different pathways of DNA repair, such as mismatch

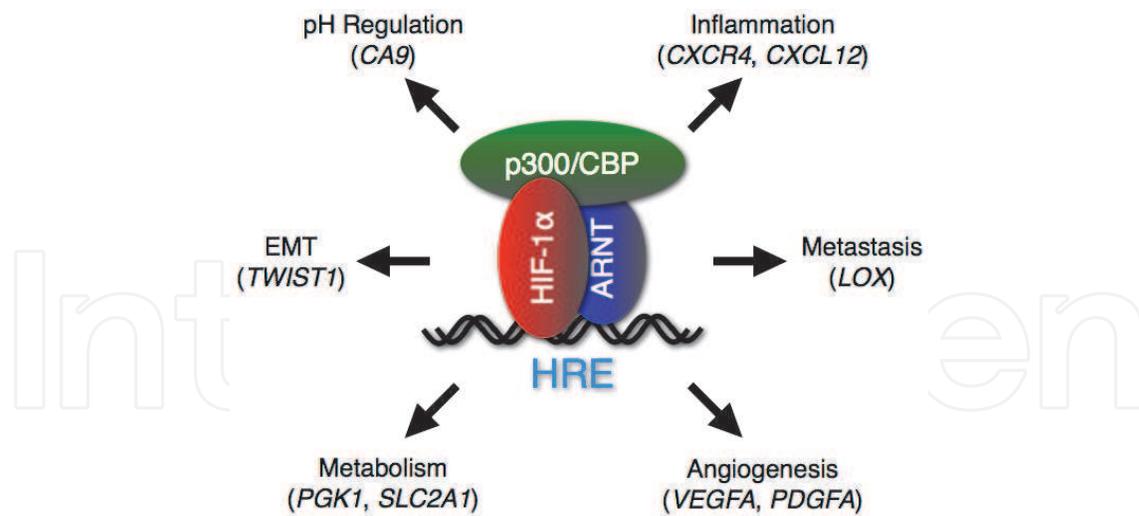


Fig. 2. The canonical mechanism of HIF-1 α is responsible for the expression of various relevant genes and pathological processes in tumor development and progression. *HRE*, hypoxia-responsive element; *EMT*, epithelial–mesenchymal transition.

repair (*MSH2*, *MSH6*), base excision repair (*MUTYH*), nucleotide excision repair (*XPA*), and double-strand break repair (*NBS1*, *BRCA1*). A wealth of knowledge has been gained that significantly advances our understanding of the biology of DNA repair and the mechanism of cancer development, and yet the role of DNA repair in the majority of cancers remains obscure because somatic mutations are rarely detected in DNA repair genes of sporadic cancers.

3.2 Functional impairment of DNA repair by hypoxia

To account for genetic alterations in sporadic cancers, functional impairment rather than genetic defect in DNA repair has been proposed on the basis of the evidence that hypoxia inhibits the expression of genes involved in DNA mismatch repair and double-strand break repair (Bindra & Glazer, 2005; Bristow & Hill, 2008; Huang et al, 2007). Indeed, multiple studies have shown hypoxic suppression of DNA repair genes including *MLH1* (Mihaylova et al, 2003), *MSH2* and *MSH6* (Koshiji et al, 2005), *RAD51* (Bindra et al, 2004), *BRCA1* (Bindra et al, 2005), and *NBS1* (To et al, 2006). Furthermore, it appears that hypoxia specifically inhibits homologous recombination but not non-homologous end joining, thereby inappropriately shunting double-strand break repair from high-fidelity homologous repair to error-prone non-homologous end joining. Moreover, hypoxic down-regulation of DNA repair genes results in DNA damage and genetic alteration, further supporting the notion that functional impairment of DNA repair induced by hypoxia contributes to genetic alterations in cancer. A challenging puzzle, however, is identifying the underlying mechanism by which hypoxia inhibits DNA repair. Some studies suggest that hypoxic down-regulation of *RAD51* and *BRCA1* involves formation of the E2F4/p130 repressive complex that occupies E2F sites in the target promoter (Bindra et al, 2005; Bindra & Glazer, 2007). It remains unclear, however, how hypoxia signals the E2F4/p130 complex and whether this mechanism of genetic alteration is relevant *in vivo* to cancer biology.

3.3 Mechanism of hypoxic inhibition of DNA repair

In the process of understanding how hypoxia inhibits DNA repair, we made the following observations (Koshiji et al, 2005): *i*) HIF-1 α but not HIF-2 α was required for hypoxic

induction of microsatellite instability and down-regulation of *MSH2* and *MSH6* in *MSH2*-proficient colon cancer cells; *ii*) ectopic expression of HIF-1 α but not HIF-2 α was sufficient to recapitulate the hypoxic effects; *iii*) whereas the transcriptional activator c-Myc was required for maintaining *MSH2* and *MSH6* expression, HIF-1 α competed with c-Myc for occupying the target gene promoter via the DNA-binding factor Sp1; and *iv*) HIF-1 α DNA-binding and transactivation domains were dispensable for *MSH2* and *MSH6* down-regulation. Hence, these findings have led us to propose a distinct mechanism by which HIF-1 α inhibits DNA repair (Fig. 3), which is referred to hereafter as the HIF-1 α -c-Myc pathway, in contrast to the aforementioned canonical mechanism as the HIF-1 α -ARNT pathway.

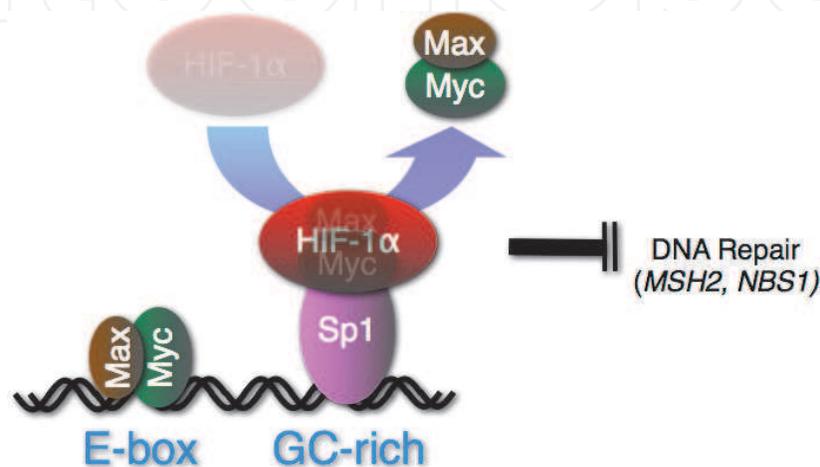


Fig. 3. A schematic representation of the HIF-1 α -c-Myc pathway, in which HIF-1 α competes with c-Myc for Sp1 binding to the promoter of DNA repair genes, resulting in c-Myc displacement and therefore inhibition of DNA repair.

In keeping with the finding that hypoxia inhibits DNA mismatch repair, we showed that the HIF-1 α -c-Myc pathway also accounted for hypoxic inhibition of *NBS1* and induction of DNA double-strand break (To et al, 2006). We not only identified HIF-1 α PAS-B as necessary and sufficient to mediate the HIF-1 α -c-Myc pathway, but also elucidated the molecular distinction between HIF-1 α and HIF-2 α that engenders functional difference in DNA repair. We demonstrated that despite strong sequence homology in the PAS-B subdomain, subtle differences between HIF-1 α Val-317, Ala-321, and Thr-327 and the corresponding amino acid residues of HIF-2 α essentially enabled HIF-1 α to inhibit DNA repair (To et al, 2006). This important finding has prompted us to test the hypothesis that the HIF-1 α -c-Myc pathway is crucial to malignant progression.

4. A mechanism of genetic alteration that drives malignant progression

Although we provided a molecular mechanism by which HIF-1 α but not HIF-2 α mediates hypoxic induction of genetic alteration by inhibiting DNA repair, whether such mechanism is relevant to cancer biology had yet to be demonstrated. Given the close association of malignant progression with genetic alteration, we sought to test our hypothesis that the HIF-1 α -c-Myc pathway is crucial to malignant progression by inducing genetic alterations. To isolate the HIF-1 α -c-Myc pathway from the HIF-1 α -ARNT pathway, we elected to uncouple the two pathways by inactivating each individually with site-directed

mutagenesis. Mutations were carried out in the context of a stabilized form of HIF-1 α , designated as HIF1 α (PP) (Kageyama et al, 2004), in which the prolyl hydroxylation sites Pro-402 and Pro-564 had been destroyed to prevent oxygen-dependent proteolysis (Fig. 4). Subsequently, the HIF-1 α -c-Myc pathway was inactivated by substituting the aforementioned Val, Ala, Thr residues in the PAS-B domain with those of HIF-2 α , yielding the mutant HIF1 α (PP)+VAT (Yoo et al, 2011). Likewise, the HIF-1 α -ARNT pathway was disabled by mutating residues critical for DNA binding and transactivation (Gu et al, 2001; Koshiji et al, 2004; Land & Tee, 2007) to create the mutant HIF1 α (PP)+RFC. Our results showed that the two pathways are functionally independent because HIF1 α (PP)+VAT was functional only in the HIF-1 α -ARNT pathway, while HIF1 α (PP)+RFC was active only in the HIF-1 α -c-Myc pathway (Yoo et al, 2011). In contrast, HIF1 α (PP) was active in both pathways.

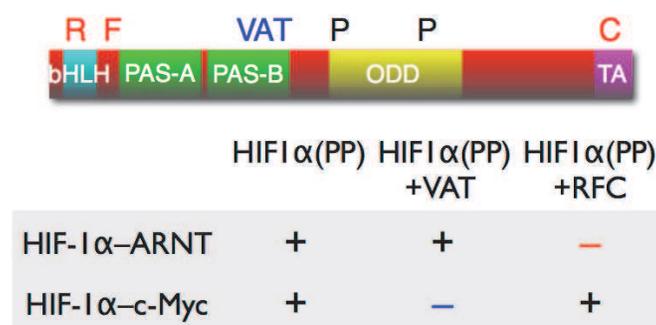


Fig. 4. The HIF-1 α -ARNT pathway and the HIF-1 α -c-Myc pathway are functionally independent. Both pathways are inactivated individually by site-directed mutagenesis with substitutions of specific amino acid residues, as indicated, in the functional domains.

After retroviral transduction with HIF1 α (PP) and HIF1 α (PP)+RFC, tumor cells exhibited conspicuous DNA double-strand breaks as indicated by a sharp increase of γ -H2AX foci in the nucleus and microsatellite instability when analyzed with specific mononucleotide and dinucleotide markers (Yoo et al, 2011) (Fig. 5). Furthermore, there was a loss of the tumor suppressor genes *FHIT* and *WWOX* at the genomic level, indicative of chromosomal fragile site instability (Yoo et al, 2011). However, none of these DNA damage and genetic alterations were detected in cells expressing HIF1 α (PP)+VAT, which was functional only in the HIF-1 α -ARNT pathway.

Importantly, all of these cells that had undergone genetic alterations not only acquired malignant traits including anchorage-independent growth and tumorigenicity but also became malignantly aggressive in mouse xenograft models, as indicated by rapid tumor growth, massive hemorrhagic necrosis, and rampant invasion of neighboring tissues (Yoo et al, 2011; Yoo et al, 2009). Moreover, advanced malignant progression was recapitulated in cells expressing HIF-1 α PAS-B alone but not its VAT mutant. Altogether, these studies strongly indicate that the HIF-1 α -c-Myc pathway is the underlying mechanism of malignant progression by inhibiting DNA repair and inducing genetic alterations.

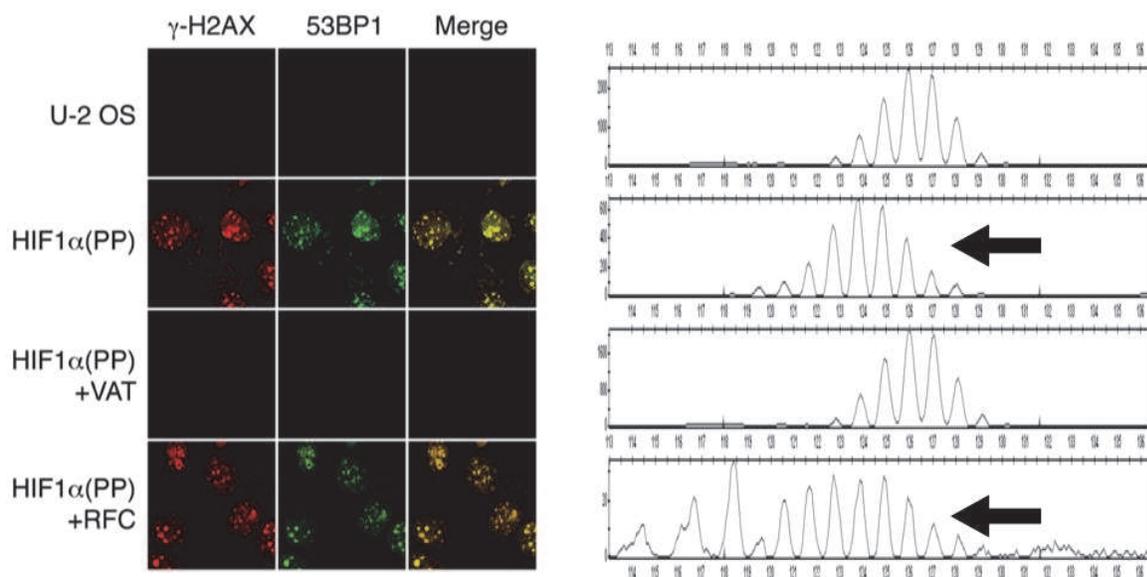


Fig. 5. The HIF-1 α -c-Myc pathway is responsible for DNA damage and genetic alteration. *Left*, Human osteosarcoma U-2 OS cells transduced with HIF-1 α variants as specified were determined with immunofluorescence for colocalization (*Merge*) of the phosphorylated histone variant γ -H2AX foci with those of 53BP1. Both serve as indicators of DNA damage, which were absent in the parental and HIF1 α (PP)+VAT cells. *Right*, The transduced cells were also analyzed for microsatellite instability, as indicated by the shortening (shift to the left) of genomic DNA fragments amplified with the mononucleotide marker BAT25. (Figure modified with permission from Yoo et al, 2011.)

5. Conclusion

Cancer remains one of the most deadly diseases overall and the leading cause of death in persons under the age of 85 years in the United States (Jemal et al, 2007). Technological advancements in cancer prevention and early detection have greatly reduced cancer incidence and mortality, yet the progressive nature of the disease seems to inevitably drive cancer to the advanced stage, posing an insurmountable challenge to the available treatments. The identification of the mechanism of hypoxia-driven malignant progression at the genetic level may provide a molecular basis for controlling the evolutionary process in tumors, a strategy proposed 35 years ago to combat tumor progression (Nowell, 1976).

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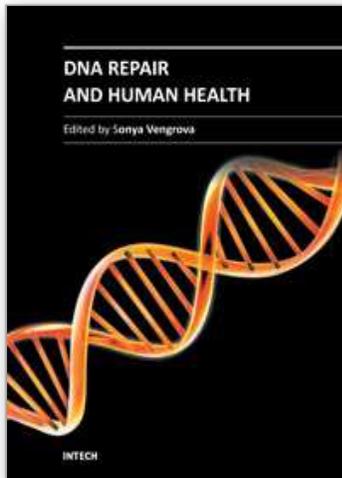
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Over the past decades, great advances have been made in understanding the cellular DNA repair pathways. At the same time, a wealth of descriptive knowledge of human diseases has been accumulated. Now, the basic research of the mechanisms of DNA repair 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.

How to reference

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