

# Dimensions of DNA Damage Recognition are Key Events in Inducing Complementary Multi-Pathway Repair Response in Potentiating Tumor Therapeutic Resistance

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## Abstract

Dimensional resolution of malignant transformation events in cells is a putative reflection of susceptibility hot spots in DNA biology of response to genomic damage. It is further to such understanding that repair processes are potentially a vast array of complementary pathways that significantly promote the resistance to therapeutic attempts at cancerous lesion ablation. Sufficient promotional repair of single-strand and double-strand breaks may subsequently compromise susceptibility to therapy once cell replication is initiated. The toxic nature of abasic sites is a prime example for a need for selective phase susceptibility during the cell cycling of tumor cells to engineered or natural chemotherapeutic agents or to ionizing radiation.

**Keywords:** Dimensions; DNA damage; Lethality

## Introduction

Dynamics of synthetic lethality constitute a truly viable dimensional concern within such diverse modifications as post-translational products of protein modification. The incremental evolutionary course of such dimensions contributes to the particularly powerful and diverse identities and consequences of transcription factor binding biology to the cellular DNA.

RNA integrity is one specific field of anticipatory evolution with regard, in particular, to oxidative injury of tumor cells within a persistently hypoxic micro-environment. The equilibrating involvement of further contributory factors underlies APE1 (AP abasic site apurinic/aprimidinic endonuclease1) functionality and dysfunctionality. These enhance hypersensitivity of tumor cells to the effects of various chemotherapeutic agents and also to ionizing radiation. BER (base excision repair) activation at cisplatin inter-strand crosslinks modulates cisplatin cytotoxicity via specific UNG, APE1 and Pol beta polymerase functions [1].

## Interactivities and Complementarity

The combination of dysfunctional lack of two or multiple enzyme entities in synthetic lethality is sufficiently advanced in clinical effect to warrant the complex participation of multiple repair pathways. These constitute genetic instability and thus subsequently potent apoptotic response of tumor cells. Group participation of dimensional repair of damaged DNA constitutes an active propensity to DNA-protein and DNA-transcription factor binding series of modalities. These compare favorably with the extensively versatile spectrum of potential post-translational modifications of proteins. Dictated evolutionary identity profiles reflect an inherent series of processivity potentials that attribute to the formerly susceptible hot spots in malignant transformation of individual and groups of cells with genomic

instability. Oxidatively damaged DNA bases are substrates for both BER and APE1-initiated nucleotide incision repair [2].

## Post-Translational Modifications

Ubiquitination, deamination, alkylation and oxidation of DNA are processes that indicate a recognized focus profile for damage-recognition within the DNA molecules. Co-application of bacterial ghosts strengthens the immunogenic component of oxaliplatin anticancer response and thus constitutes a promising natural immunoadjuvant to chemotherapy in advanced stages of colorectal carcinoma [3].

The further participation of acetylation, phosphorylation, nitrosation, ubiquitination and enzymatic deletion of the N-termini of APE1 involves dynamic interaction as ongoing excision of damaged bases and of endonuclease cleansing of the abasic sites (AP sites) within nicked or gaped DNA strands. Basic sites are frequent DNA lesions, due to spontaneous base hydrolysis or as intermediates of base excision repair [4]. It is further to evolutionary response to DNA damage in terms of such enzymes as glycosylases that the further dimensional reconstitution of the DNA strands and DNA helix proves amenable to processes of resistance of DNA molecules to administered chemotherapy and ionizing radiation under hypoxic conditions.

## Dimensional Evolution of Repair

Interactivity is inherently constitutive attribute to the dimensional evolution of DNA damage and constitutes a range of complementary actions implicating multiple repair and metabolic pathways affecting degrees of genomic stability and instability. Human DNA repair mechanisms must be precisely modulated in order to prevent genomic instability in urothelial bladder carcinoma [5].

Exogenous and endogenous damage agents cause single- and double-strand breaks, inter and intrastrand cross-links, basic sites and modified DNA nucleases. DNA lesions can be cytotoxic or mutagenic

due to abnormal gene expression or apoptosis. DNA glycosylases initiate BER excision of the nuclease followed by processing by APE1 that generates a nick in the DNA backbone [6].

The combination of base damage and Homologous Recombination pathways as seen with PARP1 deficiencies and BRCA1 and/or BRCA2 mutation allows for a further complex but promising micro-environmental conditioning that renders cells susceptible to apoptosis. P53 and other suppressor gene components may render such susceptibility as hypersensitivity profiles leading to tumor cell death.

Incremental evolutionary attributes allow a damage response of cells and altered permissive dimensions that would implicate feedback response in its own right, as seen with APE1 dysfunction.

### Processivity

Effective measures of complementary repair pathways in cells presenting double-strand DNA breaks, and also base damage, allow permissive processes of DNA repair within environments particularly activating oxidative injury and repair. These occur in ubiquitous conditions of hypoxic stimulation of Hypoxia-Inducible Factor- $\alpha$ 1.

The anti-tumor effects of Notch inhibition, in general, reverse malignant transformation via differentiation-inducing therapeutic effect [7].

Several mechanisms of resistance underscore the complex nature of oestrogen receptor signaling, with many connections to other essential signaling pathways in breast cancer cells [8].

Oxidative damage of DNA can be both blocking and miscoding with resulting mutations and/or apoptosis. Oxidized nucleases may be repaired by both BER and Nucleotide incision repair; these two pathways overlap [9].

Further interactivities of a global genomic nature indicate a realization of events that permit the progression of DNA repair. This is in a manner that is highly specific for phases of therapeutic resistance in tumor cells exposed to single or multiple chemotherapeutic agents, and also to ionizing radiation. Multiple polymorphisms affecting many DNA repair pathways are related to early age at diagnosis and TP53 mutations in patients with breast carcinoma [10].

### RNA Biologic Susceptibility

RNA is particularly susceptible to oxidative injury in terms of its lack of hydrogen bonding. It further evolves in terms of consequent damaged protein translation pathways.

Indeed, it is due to RNA as a particularly susceptible focus in tumor cells, in general, that promising targets in tumor genomics would permissively impact pre-replicative and also replicative tumor cells.

Both the repair endonuclease functionality and the redox potentiality of APE1 include the performance of dual dysfunctional profiles in synthetic lethality of tumor cells showing both deficiency of APE1 and of BRCA1/2.

The powerful lethality issues in such cells indicate the progression of modified interactivity of multiple repair pathways. This reconstitutes tumor cells as essentially complementary profiles of wild-type cells, both in genomic and RNA profile dimensions. Targeting carnitine palmitoyl transferase 1A that mediates fatty acid oxidation sensitizes nasopharyngeal carcinoma to radiotherapy [11].

### Nucleobase Deamination

Protein post-translational modifications and the constitutively evolving deamination of bases of nucleotides are potent variables within multiple participation of many repair pathways affecting genomic stability.

Damage to nucleotide bases may be monofunctional or multifunctional in inducing a damage response based largely on functionality or dysfunctionality of damage-recognizing systems. These may be projected by either micro-modifications of the DNA structure or as helix-distorting DNA injuries. Such events occur especially in genomic instability and replication fork collapse.

### Enzymatic and Non-Enzymatic Systems

Both enzymatic and non-enzymatic component systems of response to oxidative injury to the DNA include also parallel systems of response in the presence of messenger and ribosomal (rRNA and tRNA) modification. This is seen especially in oxidative stress of cells and tumor cells. Indeed, further contributory evidence of ongoing processivity of such damage is key to understanding the persistent evolutionary development of malignancy in transformed cells. In terms, therefore, of constitutive recognition of, and response to, cell injury within genomes, there further is compounding complementary response of the multiple repair pathways. This is evidenced by replacement of Homologous Recombination by Non-Homologous End-joining strand repair.

Anticancer chemoprevention is a major strategy in colorectal cancer and most therapeutic agents, in such patients, induce DNA-alkylation damage that is repairable by the BER pathway [12].

Complex interactions between oxidative stress, antioxidant potential and efficiency of multiple DNA repair pathways determine inter-individual susceptibility to gastric carcinoma [13].

Essential non-sequence repair of damaged DNA calls into operative exposure the thymine opposite to the damaged bases especially in oxidative injury to the genome.

Reactivity issues of constitutively damaged bases such as those due to deamination is a specific target for ongoing biology of response. Such complementary pathways of repair constitute genomic integrity as related especially to helix distortion.

APE1 is essential in DNA repair via base excision and has been considered a druggable oncotherapeutic target in such lesions as glioblastoma [14].

### Nucleolus and Nuclear Export Systems

The nucleolus and the nuclear export systems together with ribosomal biogenesis machinery are specifically implicated in terms of modifications in post-translational changes in proteins. They acquire significant roles in the induced processivity of DNA damage and of genomic instability. Oxidative damage also implicates dysfunction of mitochondria and an added dimension of susceptibility of RNA that is unsupported by systems of DNA histone architecture.

Ubiquitination effects of APE1 in particular vary between increased stability in cases of mono-ubiquitination and of induced cell death in cases of poly-ubiquitination. Pronounced collaborative inducements are also reflected by the vast array of protein interactions with DNA

and by transcription factor binding as proposed by promoter sites and also subsequent protein processivity.

APE1 is also a redox factor maintaining transcription factors in an active, reduced state and these may include HIF-1 $\alpha$ , p53, NF kappaB and AP-1(Fos/Jun) [15].

## Concluding Remarks

Multiple gaps in the understanding of significant post-translational modifications of proteins. Especially in view of the reversibility of many of these protein modifications, these do not allow for a systematic approach to therapy of cancerous lesions. High frequencies of inherited DNA sequence variations or polymorphisms are common in humans. Their involvement as combined polymorphic genes for cancer susceptibility is under intense investigation [16]. Indeed, the recognition of DNA damage is a vitally significant system in inducing complementary pathways in the potential repair of such DNA damage. This would integrally promote the sequential repair of damaged bases as either short-patch or long-patch repair of such bases.

However, it is becoming more and more evident that single-locus effects do not account for complex multifactorial disease like cancer [17]. In view of the dimensions of exposure to potentially evolving lesions to the DNA, the specific attributes of DNA repair are indicative of an evolving predisposition that originates usually in the S and G2 phases of the cell cycle.

Failure to completely repair DNA lesions such as 2-deoxyribonolactone may complicate the repair process by forming a protein-DNA crosslink [18]. In overall terms, it appears that biomarker investigations do not provide consistent observations to understand functions of the variant genes in carcinogenesis [19].

Wild-type APE1 protein binds tightly to DNA containing a one-nucleotide gap but not to DNA with a nick. This indicates that substrate recognition by APE1 implicates a space bracketed by duplex DNA rather than mere flexibility of the DNA helix [20].

Protein arginine methyltransferase 8 gene enhances the colon cancer stem cell function by up regulating the pluripotency transcription factor [21].

Paradoxically, an understanding of mechanics in acquired therapeutic resistance of tumor cells to single or combined chemotherapeutic regimens and to ionizing radiation as under hypoxic conditions would allow for an understanding of permissive attributes of complementarity. Many repair systems induce DNA damage resolution in transforming malignant cells. Proteomics aids to the discovery and expansion of protein-protein interaction networks. These are key mechanisms to delineate molecular mechanisms in physiology and physiopathology, and also to infer protein function in a guilt-by-association fashion [22].

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