Chapter

Introductory Chapter: DNA Repair in Human Cells - A Daily Challenge

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1. Introduction

The faithful repair of DNA is a challenge that human cells have to fight every day to maintain genomic stability. The type and frequency of DNA lesions are related to both endogenous and exogenous sources of DNA damage. In addition to normal metabolism, which is responsible for a great number of DNA lesions (approximately 70,000 per cell) [1, 2], environmental agents (i.e., ionizing radiation, UV light, and chemicals) contribute to enhance such number. The capacity of cells to faithfully repair their proper DNA is the primary goal to safeguard the genome integrity. To this purpose, eukaryotic cells have evolved accurate repair systems to overcome the different lesions induced by both external and internal sources of DNA damage. A lot of information is now available for most repair systems, and in the last decades, a lot of efforts have been made in the comprehension of the role of DNA repair proteins, in relation to the type of damage and the effectiveness of repair carried out by different complexes. Besides the molecular role of proteins in such pathways, several other important factors can affect the efficiency of DNA repair, including epigenetics, chromatin structure, mitochondrial function, and aging.

Epigenetics regulate gene function through posttranslational modifications of histones, DNA methylation noncoding RNAs, and when DNA is damaged, epigenetic alterations can occur at sites of lesions. Epigenetic alterations that occur during DNA repair are mostly transient, being the original epigenetic marker restored. However, sometimes, epigenetic alterations can persist after DNA repair as a sort of "scars" [3]. What is the role of such epigenetic markers left after repair? Epigenetic modifications occur either in normal cells or in cancer cells, representing a further element for cancerogenesis in this last case. Numerous studies reported gene expression changes in human cancers and found signature for specific type of tumors. Each cancer has its own genetic and epigenetic profile, which increases the difficulty to comprehend the process of tumorigenicity. In this regard, the response to each tumor to different DNA-damaging agents is related to the characteristics of its genetic and epigenetic landscape.

The structure of chromatin around DNA damage changes significantly to promote DNA repair proteins accessibility. During DNA repair, the structure of chromatin is modified as a consequence of new histone incorporation, replacement, and modification. The coordination of DNA repair protein interactions is a critical process which needs to be fully elucidated, also in relation to the specific DNA-damaging agent.

Mitochondria, with their own DNA, are organelles that are on the rise for several reasons, including the repair of their proper DNA, the mtDNA. Mitochondrial DNA is different from the nuclear one, being circular, without histones, and present in multiple copies. The repair of mtDNA relies on the activity of proteins encoded by

nuclear DNA, and the efficiency of repair is crucial for the maintenance of mtDNA integrity. What happens when the mitochondrial genome is affected by improper DNA repair and mutations arise? To address this question, studies should take into account that the multiplicity of mtDNA genomes inside the same cell originates a coexistence of mutant and wild-type genomes [4].

Notably, the accumulation of DNA damages during the cell lifespan threatens the fidelity of repair. According to the candidate hallmarks of aging in mammalian cells, recently reviewed by Lopez-Otin et al. [4], it appears evident how the process of DNA repair is tightly linked to genomic instability, cellular senescence, epigenetic alterations, and mitochondrial dysfunction. In humans, alterations in nuclear DNA repair are present in several syndromes characterized by premature aging, and epigenetic modifications in histones and histone-modifying enzymes affect chromatin structure in an age-related manner. Several studies attempted to elucidate the linkage between mitochondria dysfunction and aging. Indeed, when the mitochondrial function is impaired, the result is an increase of oxidative stress that triggers a cascade of toxic effects on cellular environment.

Finally, the connection between DNA repair process and angiogenesis is another open research field. Angiogenesis is a physiological process that allows the regeneration of blood vessels following injuries. However, angiogenesis is extremely harmful in pathological conditions, such as in tumoral tissues, characterized by the uncontrolled growth of new blood vessels. Mutations or alterations in genes involved in the cellular response to DNA damage can affect the angiogenic response.

Many questions are still open and further investigations are needed to shed light on the whole mechanism of DNA repair, either nuclear or mitochondrial. To this purpose, the present book offers a collection of chapters dedicated to the interplay between DNA repair and epigenetics under physiological and pathological conditions, aging, mitochondrial function, angiogenesis, and the contribution of base excision repair process to oxidative damage, giving a contribution to cancer biology and clinical management. **Figure 1** shows some of the principal aspects discussed in this book.

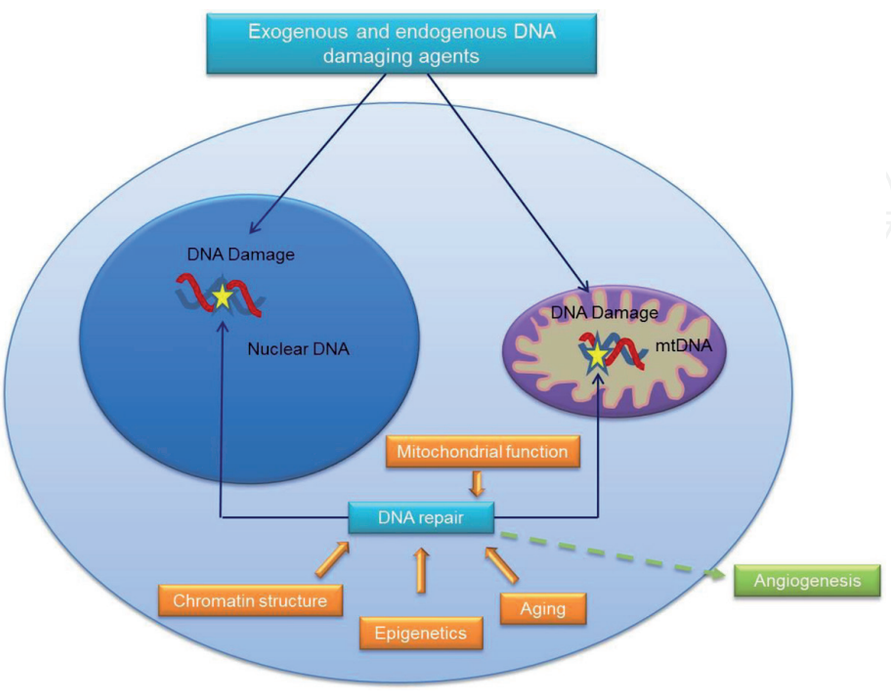

Figure 1.
Example of intrinsic factors affecting the repair of DNA damage induced by exogenous and endogenous sources in nucleus and mitochondria of eukaryotic cells.

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