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The Role of DNA Repair Enzymes in Maintaining Genome Stability

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Introduction

Endogenous metabolic processes and exogenous environmental factors always test the integrity of the genome of the organism, and it is estimated that there is two million DNA damaging events per cell per day [1]. These myriads insults may cause a wide range of DNA lesions, including subtle base modifications to disastrous double-strand breaks, all of which are very dangerous to the genomic stability when they are not repaired [2], [3]. Single cell in a human being may experience approximately 105 events of DNA-damaging per day, which would lead to the culmination of approximately 1016 to 1018 repair events per day in an entire organism to counter all these endogenous lesions [4]. This sustained attack demands complex and high robust network of DNA repair that has evolved to detect, signal, and repair different forms of DNA damage, to protect genetic data and cellular homeostasis [5]. These repair pathways are highly complex since unrepaired or poorly repaired lesions can impair DNA replication and transcription, or induce mutation and aberrant chromosomes that can jeopardize cell viability and the health of the organism [6]. Because of this, the defects of such critical repair systems are strongly linked to a variety of human pathologies, including developmental defects, accelerated aging syndromes, and the predisposition to a number of cancers [7], [8]. In response to the detrimental effects of the DNA damage, organisms acquired complex repair networks and eliminate the chemical modification or aberrant base structures, and restore the genome to the original state [9]. These complex repair processes have again been subdivided into a number of generalized primary pathways that have been adapted to a certain type of DNA lesion with an unbelievable level of specificity: base excision repair, nucleotide excision repair, mismatch repair and different forms of double-strand break repair [1]. Such pathways are highly regulated and highly diverse containing a high concentration of DNA repair enzymes that perform the recognition and reparation of different DNA damage forms to ensure that the integrity of our genomes remains intact in the face of unceasing barrage of insults [10]. The mechanisms of repair would be paramount in avoiding the accumulation of DNA damage, which when unchecked may result in transcriptional errors, dysregulation of proteins and eventually, serious pathological mechanisms [6], [11]. Nevertheless, persistent exposure to environmental carcinogens may overpower these advanced systems resulting in the development of mutations known to be characteristic of most types of cancer [1]. Effective sensing and repair of the DNA damage by the cells is essential in maintaining genomic stability and preventing the disease [12]. A complex association of DNA repair, DNA damage response pathways, and cell cycle checkpoints are all aimed at ensuring the precise transmission of genetic information on the generations and protection against oncogenesis and neurodegeneration [9], [13].

Literature Review

The effectiveness of these repair systems is supported by the fact that a variety of the mechanisms of DNA repair, which include base excision repair, mismatch repair, nucleotide excision repair, homologous recombination and non-homologous end joining are precisely coordinated to target particular forms of DNA lesions [14], [15]. An example is that base excision repair mainly fixes small chemical modifications in bases that may cause miscoding and subsequent mutagenesis whereas nucleotide excision repair plays an important role in fixing bulky lesions, helix-distorting damage, like those caused by ultraviolet radiation [16], [17]. Homologous re-combination and non-homologous end joining are considered important path-ways in cases of double-strand breaks, with homologous recombination offering a high-fidelity repair mechanism using a homologous template, and more rapid and error-prone alternative is provided by non-homologous end joining [18], [19]. Besides these key repair pathways, there are additional repair systems, including the mismatch repair, which are

important in correcting the errors added during replication of the DNA, such as base mismatch, small insertions, and deletions, which promote the fidelity of DNA synthesis [20]. These various DNA repair pathways exist independently and cooperatively to form a broad system of DNA damage response that includes in excess of 200 proteins that sense, signal and repair DNA lesions continuously to sustain genomic stability [6]. The unrepaired DNA lesions may then accumulate resulting in genomic instability, a characteristic of cancer progression and development when those DNA repair mechanisms are lost or surpassed [21]. The result of this instability is common to cause an increased rate of mutation, rearrangement of the chromosomes, and aneuploidy, which lead to the malignant phenotype and disease pathogenesis [22]. These adverse effects are mitigated by activating robust DNA damage response path-ways in cells, which temporarily halt cell cycle progression and activate relevant DNA repair mechanisms in order to resolve the damage [5]. Lack of these complex repair systems is becoming a major consideration in disease etiology especially in carcinogenesis in which they promote genetic aberrations that characterize tumor initiation and progression [23]. In fact, dysregulation of many DNA repair path-ways, like nucleotide excision repair, mismatch repair, base excision repair, homologous recombination repair, non-homologous end joining, and others, plays an important part in development and progression of breast cancer, not only in resistance to therapy but also in the possibility of new treatment [5], [24]. One such case is the case of the double strand breaks, which are one of the worst types of DNA damage which can severely disrupt genomic integrity and are highly linked to oncogenesis [25].

Methodology

This part discusses how the identification, synthesis and critical analysis of the literature which is accessible on the different functions of the DNA repair enzymes in genome stability can be conducted in a systematic method and the implication which they have in the pathogenesis of the diseases. The research design was an exhaustive review of the literature, available in the scientific databases so that it could have a comprehensive and profound comprehension of the topic. The search strategy entailed the utilization of certain keywords that were relied on the DNA repair pathways, enzymes, genomic instability, and the relevant diseases to ensure that a large number of peer reviewed articles and proceedings (reviews and book chapters) were obtained. This cautious approach was instrumental in extracting pertinent information about the molecular events that occur in the repair of DNA, the various enzymatic machineries, the pathological effects of the respective dysfunction [6]. The discussion below was directed towards classifying the literature available in context to the particular DNA repair pathway of interest, and the type of enzymes of interest, and, therefore, to making a methodical assessment of the functional component of this enzyme in the mechanism of genomic integrity maintenance. Moreover, the methodological rigor also involved the critical assessment of experimental designs and interpretation of data as a component of the obtained studies and their contribution to the current knowledge of the DNA repair mechanisms and clinical value [26]. This systematic review will be used to develop the existing data on the mechanistic foundation of DNA repair pathways and the enzymatic components, and in this regard, these mechanisms will be uncovered to reveal their major roles in maintaining genomic integrity in the response to endogenous and exogenous genotoxic agents [20]. The impact of the impaired DNA repair was also studied in-depth in this study and it points into the profound influence it has on the functionality of cells, disease progression and the response to therapy particularly in the case of cancer [27]. This review thus integrates the information presented in other publications to highlight the role of depletion of DNA repair processes in genomic instability, which is a known characteristic of cancer, and how the knowledge of these pathways can inform new therapeutic approaches [26], [28]. It is true that the complex balance between DNA damage and repair plays important parts in cellular homeostasis and it is common when the balance is disturbed that the DNA lesions begin to accumulate, leading to the loss of cellular survival and advancement of the diseases [29].

Results

The next section provides the most critical results of the extensive literature review, based on the particular functions of different DNA repair enzymes in preserving the genomic stability and their

direct implications to both the disease pathogenesis and therapeutic intervention [1], [30]. A substantial part of the literature also underlines the fact that the defects of DNA repair mechanisms are intrinsically connected with cancer development since a reduced ability to repair the damage in DNA results in the higher rate of mutation and genomic instability, contributing to the development of oncogenesis [31]. As an example, the base excision repair pathway, a primary defense against the most widespread DNA lesions, is essential in preventing diseases like cancer as it continuously repair the base lesions and single strand breaks in DNA as a result of endogenous and exogenous mutagens [4]. An example is X-ray repair cross-complementary gene family, which encodes proteins that are significant in single-strand break and base damaged repair, and dysfunctions in this family are often correlated with the development of tumors [32]. Defects in another important pathway, namely mismatch repair, have been proven directly involved in the etiology of urogenital cancers, and this demonstrates the pervasive role of impaired DNA repair in multiple cancer types [32], [33]. Germline mutations in DNA mismatch repair genes, including hMLH1, which are implicated in inherited non-polyposis colon cancer, whereas somatic mutations in other MMR genes that play a role in sporadic colorectal and gastric cancers [26]. Further, DNA repair deficiencies, particularly in the instance of the double strand break, have been broadly related to a variety of pathologies and a lot of literature has been devoted to the homologous recombination as an important repair of the double strand break [34]. The primary role of DNA repair mechanisms that include mismatch repair and base excision repair in genomic integrity is further justified by direct association with human diseases including xeroderma pigmentosum and hereditary non-polyposis colon cancer caused by defective nucleotide excision repair and MMR respectively [34], [35]. The overall disease spectrum associated with these forms of repair deficiencies does not necessarily involve specific cancers, but also neurodegenerative disorders, ocular and cochlear disease and myocardial infarction, which is typically considered collectively as oxidative-stress-related diseases [36].

Discussion

This section gives a summary of the amount of information regarding the DNA repair enzymes and critically evaluates the multitask aspects they have in the context of genomic integrity maintenance and the significant implications of their failure in the etiology and the progression of numerous human pathologies. Nevertheless the complex relation between the damage to the DNA and the complex cellular repair system is actually a core component of cellular homeostasis that determines cell fate and health of organisms [37]. The constant exposure of DNA with endogenous and exogenous genotoxic agents imposes a very strong repair in order to correct the potential mutations and maintain genomic stability [38], [39]. Five of the large repair path-ways include nucleotide excision repair, base excision repair, mismatch repair, repair of a double-strand break, and direct reversion repair and address the various forms of DNA damage, although collectively ensure the fidelity of the genetic code [40]. Dysfunctions in these pathways are most often related to several human diseases, the most frequent of them being cancer, but neurodegenerative disorders and premature aging syndromes are the phenomena that were reported to be of the primary significance in the prevention and progression of the diseases [41], [42]. The result of impaired DNA repair, particularly the repair of a double-strand break, is often exhibited as altered DNA damage response, causing higher mutation rates and genomic aberrations, the hallmarks of high cancer risk and other diseases, including severe combined immunodeficiency [43]. Moreover, the complicated regulatory networks of these pathways, often including ubiquitination and ubiquitin-like modifiers are important in the mechanism of organizing cellular response to DNA damages, and in regulating genomic integrity [44]. Specifically, the role of SUMOylation, ubiquitination, and Neddylation in the regulation of nucleotide excision repair, Fanconi Anemia pathway and double-strand break repair, and the pervasive involvement of post-translational modifications in the regulation of DNA repair have been demonstrated [45]. The intricacy of these control mechanisms highlights the cellular dedication to ensure genomic fidelity, and the disastrous results of the impact of a failure in such pathways [46].

Conclusions

The relevance of DNA repair enzyme is thus paramount in preserving the genomic integrity, and most fundamental of biological processes, including clinical practice [47]. Additional study of the exact mechanisms and regulatory networks regulating these enzymes will unlock new treatment possibilities of many human diseases, such as cancer and age-associated disorders [8], [48]. Future studies may attempt to explore the exact spatiotemporal regulation of DNA repair protein complexes and their dynamic interactions with chromatin architecture to better understand the pathways involved in efficient DNA damage recognition and repair. Additionally, emerging technologies in advanced imaging methods and single-molecule technologies would be able to offer new evidence on real time dynamics of repair enzyme recruitment and activity at lesion sites [49], [50]. The investigation of personalized medicine technologies, based on the unique DNA repair ability, is also a promising way of personalizing therapeutic interventions and predictive diagnostics in the diseases of the DNA repair deficiency. Also, further insight into crosstalk between repair pathways and their complex post-translational modifications would provide new therapeutic targets, which would potentially make resistant tumors sensitive to existing therapy [27], [51]. These combined efforts of ubiquitination and SUMOylation, have been instrumental in controlling DNA damage response, and defects in those systems are often related to different human diseases, like cancer and accelerated aging [45], [52]. It is still an important field of study to elucidate mechanisms by which those modifications strictly regulate DNA repair pathways, their effects on protein-protein interactions, and chromatin dynamics [45]. This sustained effort is bound to inevitably bring in, never before, the opportunities of researching further on the secrets of our genomic DNA structure integrity and harmonization of its functions, clinical disease prevention and therapeutic choice, more so, further enhancement of precise cancer treatment [48]. Particularly, the aspect of future research is that future studies will assist in clearing up the unique changes and regulatory mechanisms occurring during telomere maintenance and repair and result in the emergence of novel approaches of targeting telomeres without inducing undesired genomic DNA repair pathways [53]. The findings will develop a more profound knowledge on the stability of the genome and provision of new opportunities of therapeutic interventions in aging diseases and cancer [54].

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