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Review Paper

Investigating the Bidirectional Influence of Genetic Damage, Genetic Repair Mechanisms and Inflammation in Lung Injuries

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ABSTRACT

The respiratory system is continually exposed to various harmful agents, which is why DNA repair is required. This comprises injury, inflammation, and other contents that are toxic and can cause damage to its genes. To eliminate the impact of DNA damage and restore cellular function, three pathways of repair are induced as follows: base excision repair, nucleotide excision repair (NER), and double-strand break pathway. However, such healing responses can be downregulated by long-term or severe injuries resulting in decreased recovery ability and predisposition to various diseases, such as lung cancer, chronic obstructive pulmonary disease (COPD), and fibrosis of the lungs. The generation of reactive oxygen species (ROS) during inflammation alters DNA and damages tissues. Despite this, inflammation will affect the initiation of tissue repair as well as DNA damage through the creation of ROS in this intricate process that occurs partly through innate immune responses and cytokine signaling. Cytotoxic processes hamper these fixing pathways of damaged genetic materials by inhibiting enzymes involved in DNA reparations and genes linked to repairs, thereby enhancing the risks of mutagenesis, carcinogenesis, and progressive diseases. Hence, the relationship between DNA repair and inflammatory reactions is crucial for lung health. It plays a major role in the pathophysiology of illnesses, such as cancer, COPD, fibrosis, and asthma. Inflammation and DNA damage are positively associated because they form a positive feedback loop that promotes disease and tissue pathology progression. DNA injury activates inflammation because immune cells are attracted to the site of injury, which in turn produces more oxidant molecules damaging the DNA. The evaluation of this relationship may help find approaches for reducing DNA damage, protecting genomic integrity, and preventing the progression of respiratory diseases.

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Introduction

One of the most admirable aspects of the human body is its ability and capacity to mend, fix, and protect the body's DNA. These protecting systems are useful because they aid in repairing tissues damaged through disease or injury [1]. However, the healing processes are more significant for the repair of the lungs due to constant assaults by the environment through poisons, pollutants, infections, and inflammatory diseases [2].

Damage to lung cell DNA might result from distortion in the balance of homeostasis in lung tissue which can be caused by various injuries, such as acute trauma, chronic inflammation, or toxic chemicals [3]. Despite this, damage may take many different forms, such as the modification of chemical properties of DNA bases and the division of the DNA strands into single or double-strand breaks [4]. When this damage is not remedied it causes changes and destruction of cells, which in turn causes lung diseases inclusive of cancer, fibrosis, chronic obstructive pulmonary disease (COPD), and so on [5].

When the lungs are harmed, the body creates a variety of repair processes that serve to reduce the negative consequences of DNA breakage and return the cell to its normal functional state [6]. The processes of such repairs are carried through a sophisticated network of proteins and enzymes that all have a specific role to play in recognizing the breakages, signaling, and repairing the broken DNA [1].

Among the main systems, the base excision repair (BER) system is a principal mechanism for DNA repair. BER refers to the recovery of individual DNA base damage caused by genotoxins, alkylating agents, and reactive oxygen species (ROS), all of which are common in the lung environment [7]. The process is carried out in several steps, including the recognition of the damaged base by DNA glycosylases which then excise the damaged base from the DNA strand, other enzymes are then brought in to complete the repair process by forming a nick on the DNA strand [8].

In addition to BER, there is another major repair process that occurs in the lungs and it is called nucleotide excision repair (NER). NER mainly deals with gross DNA damage that is caused by ultraviolet or certain chemicals that bend the DNA helix and disrupt cellular functions [9]. NER operates through two sub-pathways, namely the global genome repair which directs DNA repair throughout the genome, and transcription-coupled repair which targets the parts of the DNA, is actively transcribing [10]. It plays an important role in avoiding mutations and maintaining the stability of the lungs' cells by repairing and replacing the damaged segments of DNA [11].

Additionally, the DNA double-strand break-repairing process is also incised for repairing more pathetic forms of DNA damage like that which is caused by ionizing radiation and certain sorts of chemotherapeutic agents [12]. Non-homologous end joining and homologous recombination repair pathways are utilized by double-strand break repair to carry out the re-ligation of the resulting DNA ends and the accurate reestablishment of the DNA sequence. These mechanisms are even more relevant to securing the genome stability and avoiding the chromosomal changes that underlie the malignant transformation of the lung cells [13].

Even though the DNA repair equipment that is polymerized in the lungs of humans is very efficient at preserving genomic stability, there is a possibility that their ability may be overburdened under situations of chronic or severe injury, thereby resulting in a compromises DNA repair and predisposition to diseases [2]. Thus, aging, chronic inflammation, and exposure to carcinogens decrease the effectiveness of DNA repair and cause lung diseases associated with genomic instability and aberrant cell proliferation [14].

This research has the specific objective of elucidating the relationship between the mechanisms of DNA repair and inflammation in lung injuries. As such, we seek to improve the investigation of how sustained inflammation disrupts the DNA repair mechanisms in the lungs and results in dangerous consequences, such as accumulation of genomic instability, which is known to significantly increase the likelihood of development of lung cancer, COPD, and pulmonary fibrosis.

Lung inflammation

Pulmonary inflammation is a multistep and multifaceted process that is prompted by a systemic immune reaction to numerous forms and manners of tissue damage, such as infections and exposures to environmental irritants [15]. It is an essential part of the body protection system and the mechanism of a small-scale removal of dangerous elements while eliminating debris and tissue's subsequent restoration. Nonetheless, there are negative consequences connected with dysregulated or chronic inflammation, which may become a cause of tissue injury, compromised pulmonary function, or chronic respiratory disorders [16].

The induction of inflammation in the lung marks one of the most critical moments in the defense of the body against various insults and threats ranging from infections to toxic environmental stimuli [17]. This is an elaborate series of cellular and molecular activities that lead to the activation of the immunologic system and the call for the inflammation cells at the site of the injury or the infections [18].

Innate immune cells, such as macrophages, and dendritic cells besides epithelial cells of the lungs contain receptors, for example, toll-like receptors, nucleotide-binding oligomerization domain-like receptors, and retinoic acid-inducible gene-I-like receptors [19]. These receptors can recognize conserved molecular patterns (PAMPs) linked to pathogens or endogenous molecules released from damaged tissues (DAMPs). Recognition and binding of PAMPs or DAMPs to their respective receptors initiate intracellular signaling processes by activation of transcription factors like nuclear factor kappa B (NF-κB) and interferon regulatory factors family. This leads to the synthesis of pro-inflammatory cytokines, chemokines as well as other mediators to direct the inflammation process [20, 21].

Tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-17 (IL-17), and interleukin-8 (IL-8) are some of the cytokines that play a crucial role in the commencement of inflammation in the lung. These cytokines are synthesized by immune cells and epithelial cells following activation of the mentioned receptors and act as powerful inducers of inflammation by causing vasodilatation, increased capillary permeability, and activation of other immune cells to the site of tissue injury [22]. Chemokines are chemoattractant cytokines of the inflammatory response involved in the delivery and transportation of leukocytes to the site of inflammation. Monocyte chemoattractant protein-1 and interleukin-8 are also chemical attractants that are released from resident cells in lung tissue and direct the movement of neutrophils, monocytes, and lymphocytes to the area of infection or inflammation [23].

Neutrophils are the first cells that move during inflammation in the lung. They are quickly drafted out to the site of infection or injury by chemotactic stimuli. They are responsible for ingesting and killing the invaders with the help of toxic substances, such as ROS, and proteolytic enzymes. However, excessive activation of neutrophils becomes detrimental to the lungs and aggravates the development of inflammatory lung diseases [24].

Alveolar macrophages are long-lived and specialized cells of the alveolar lining of the lung and carry out processes, such as phagocytosis of microbes or debris, as well as synthesis of pro-inflammatory cytokines and migration of inflammatory cells. Based on the nature of stimuli and signals received by macrophages' exposure to lipopolysaccharide, macrophages can undergo culture-induced change and become either pro-inflammatory or anti-inflammatory [25].

Antigen-presenting cells are specialized in presenting antigens to T cells and thus initiating adaptive immune response, dendritic cells are part of these cells. In the lung, the dendritic cells sample inhaled antigen and transport themselves to the nearby lymph nodes to activate the naive T cell and initiate the above-mentioned antigen-specific immune responses [26].

The resolution of inflammation in the lung

Resolution of inflammation in the lung is a complex and tightly controlled sequence of events aimed at returning the lung tissue to normalcy after successful resolution of the insult/hypersensitivity/trauma. Accordingly, although inflammation is rather an essential element of the immune response, chronic or adaptive inflammation has destructive effects on the tissues and is involved in the development of chronic respiratory diseases. The resolution phase includes the inhibition of the inflammatory response signals and the promotion of resolution mediators that enable the clearance of inflammatory cells and waste products and the initiation of tissue repair [27].

Therefore, lipoxin, resolvin, protectin, and maresin referred to as specialized pro-resolving lipid mediators, specialized pro-resolving mediators (SPMs), are critical in the termination of inflammation in the lung. These bioactive lipid molecules are produced from polyunsaturated fatty acids including, arachidonic acid, eicosapentaenoic acid, and docosahexaenoic acid through lipoxygenase and cyclooxygenase activities [28].

SPM mediates potent anti-inflammatory and pro-resolving actions through inhibition of neutrophil infiltration, enhancement of macrophage phagocytosis of apoptotic cells and debris, and facilitation of clearance of inflammatory exudates. SPMs also enhance tissue repair and regeneration, mediated through regulations of growth factors, extracellular matrix proteins, and angiogenic factors production [29].

NF-κB is one of the key transcription factors that drive the expression of pro-inflammatory genes during the

sensing phase following inflammatory stimuli. However, at the resolution phase, there are several mechanisms for the repression of its activation: Phosphorylation of inhibitor of κB family proteins, leading to their degradation; enhancement of anti-inflammatory signaling pathways, such as the PI3K-Akt pathway; and negative feedback mechanisms through the expression of A20 and IκBζ, which further repress its activity [30].

Pro-inflammatory cytokines, which include TNF-α, IL-1β, and IL-6, are downregulated at some point in the resolution of inflammation, leading to the dampening of inflammatory signaling cascades and the attenuation of immune cellular activation. This is mediated by way of the movement of SPMs, as well as anti-inflammatory cytokines together with IL-10 and transforming growth factor-beta (TGF-β) [31].

Efferocytosis is the technique with the aid of which phagocytes, consisting of macrophages and dendritic cells, engulf and clear apoptotic cells and cell particles. During the resolution of inflammation, efferocytosis is superior through the upregulation of phagocytic receptors inclusive of Mer tyrosine kinase (MerTK) and the activation of signaling pathways that sell the recognition and engulfment of apoptotic cells [32].

Inflammatory exudates, consisting of fluid, proteins, and cell debris, are cleared from the lung tissue through lymphatic drainage and macrophage-mediated phagocytosis. The resolution of irritation is facilitated by the discount in vascular permeability and the recovery of lymphatic function, making an allowance for the removal of inflammatory exudates from the tissue [33].

Following the resolution of inflammation, tissue restoration, and regeneration are initiated to repair the structural integrity and function of the lung tissue. This includes the reworking of the extracellular matrix through the deposition of collagen, elastin, and other matrix proteins, in addition to the activation of fibroblasts and myofibroblasts [34, 35].

Angiogenesis, the formation of new blood vessels from pre-existing vasculature, performs a critical role in tissue restoration and regeneration using restoring blood flow and oxygen delivery to the injured tissue. During the resolution of inflammation, pro-angiogenic factors which include vascular endothelial growth factor and fibroblast growth factor imply the proliferation and migration of endothelial cells, to form new blood vessels [36].

The effect of lung inflammation on DNA damage

While inflammation is a vital issue of the immune reaction, dysregulated or chronic inflammation can contribute to DNA damage, genomic instability, and respiratory disorders [37, 38].

Inflammatory cells consisting of neutrophils, macrophages, and eosinophils generate ROS and reactive nitrogen species (RNS) as part of their antimicrobial protection mechanisms [39]. These noticeably reactive molecules, together with superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), nitric oxide (NO), and peroxynitrite ($ONOO^-$), can cause oxidative damage to DNA by way of inducing base changes, DNA strand breaks, and DNA-protein cross-links [40].

ROS and RNS can oxidize DNA bases, main to the formation of mutagenic DNA lesions which include 8-oxoguanine (8-oxoG) and thymine glycol. Additionally, ROS/RNS-mediated DNA strand breaks can disrupt the integrity of the DNA double helix and impair DNA replication and transcription methods [41].

NF-κB is a key transcription issue involved in the control of pro-inflammatory gene expression. Long-act activation of NF-κB signaling, throughout chronic inflammation, can cause the upregulation of genes attributed to cellular proliferation, survival, and DNA damage, which includes cyclooxygenase-2, inducible nitric oxide synthase, and IL-6 [42].

Inflammatory signaling pathways can furthermore alter the DNA damage reaction (DDR) that is in regards to changes in the DNA repair proteins and cell cycle regulators. Abnormalities in DDR pathways can limit the chance of cells repairing DNA damage effectively, leading to genome instabilities [43].

Cytokines (TNF-α, IL-1β, IL 17 & IL -6) that are involved in inflammation also contribute to genotoxic stress through increased oxidative DNA damage, suppressed DNA repair mechanisms and cell cycle changes [44]. They can also promote the generation of DNA harming agents including ROS and RNS through activation of the inflammatory cells and release of plausible inflammatory mediators [45, 46]. IL-17 is an important mediator in pulmonary inflammation and is involved in the disease processes of numerous lung diseases. It triggers the production of ROS in different cells (e.g. epithelial cells or fibroblast cells). ROS can affect DNA directly by causing modifications in base, strand breakage, and cross-linking. IL-17 promotes several other pro-inflammatory cytokine

and chemokine derivatives such as IL-6 and TNF-α, granulocyte chemotactic protein, and neutrophil-activating protein. These mediators can also increase inflammatory events and DNA damage [46, 47].

The lung has an inflammatory microenvironment through cytokines and chemokines and increased ROS implying a pro-oxidative and genotoxic profile, which will further enhance DNA damage and carcinogenicity [48]. Oxidative DNA damage has been established to participate in the development of lung cancer, COPD, and pulmonary fibrosis [49].

Chronic inflammation may contribute to direct tumor development because the consecutive DNA damage and genome instability will create the environment for accumulating oncogenic changes and disturbance of the cell cycle regulation, apoptosis, and other pathways. For example, those inflammatory cytokines and chemokines that increase cancer can also stimulate epithelial-to-mesenchymal transition and metastasis and enhance tumor progression and dissemination [50]. According to Figure 1, lung inflammation leads to DNA damage.

The effect of lung inflammation on DNA repair

Pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6 can inhibit DNA repair pathways by modulating the expression and activity of DNA repair proteins. For instance, TNF-α has been demonstrated to decrease the levels of DNA repair proteins like DNA polymerase b (Polβ) and O6-methylguanine-DNA methyltransferase with consequent impaired repair of DNA injury provoked by alkylating agents and oxidative stress [51].

Many forms of inflammation are known to trigger DDR pathways and concomitantly activate cell cycle checkpoints and DNA repair processes as well [52]. Nevertheless, the constant activation of DDR pathways due to chronic inflammation poses a danger by overloading the cell's repair mechanisms with DNA damage and leading to genomic instability [53]. Meanwhile, changes in inflammation alter NER-related genes and proteins which affects the normal DNA repair process, mutagenesis, and tumorigenesis [54].

Neutrophils, macrophages, and eosinophils release large amounts of ROS and RNS that can inhibit the DNA repair process through oxidation of the enzymes required for DNA repair and dissolution of the DNA repair complexes [51]. ROS and RNS can directly inactivate DNA repair enzymes concerned with BER of DNA and other components of DNA repair systems. For example, oxidative damage of DNA glycosylases, such as 8-oxoguanine DNA glycosylase, OGG1 results in their lack of ability or less efficiency to recognize and degrade the damaged substrate DNA bases resulting in less effective repair of DNA lesions. ROS and RNS can alter the assembly of DNA repair complexes or the stability of the complexes by modifying protein-protein and protein-DNA interfaces. This disruption can cause a problem in the assembly of DNA repair proteins in the areas of DNA damage and also the initiation and process of DNA repair. ROS and RNS can also react with the active sites of DNA repair enzymes and compromise their functionality or cause their degradation. For instance, metallic residues in the DNA repair enzymes get oxidized and, in this state, they cannot compete in the repair of DNA damage [1].

The effect of lung inflammation on DNA repair-related genes

During inflammation, pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6 are discharged and can provoke some signaling cascades leading up or down-regulation of certain genes implicated in DNA repair [55]. For example, NFκB and AP-1 regulate DNA repair genes as they directly interact with the promoter area of DNA repair genes by either increasing or decreasing their expression [56].

The reactions showed that the inflammogens could change the accessibility of the promoters of DNA repair genes in the lung cells, which was attributed to an alteration in the epigenetic regulation of the genes. Histone modifications regarded as acetylation, methylation, and phosphorylation are known to modulate chromatin conformation and hence the rate of transcription of DNA repair-associated genes. Inflammation may also influence the DNA methylation patterns and result in various gene expression profiles regarding the DNA repair pathways [57].

Besides transcriptional regulation, post-transcriptional regulation in lung inflammation, such as micro ribonucleic acid (RNA) regulation and RNA-binding proteins can also affect the DNA repair genes. Specific micro RNA, that is the small non-coding RNA molecules, can influence the degradation or suppression of translation of the DNA repair genes' messenger RNA transcripts in the context of inflammation response. Likewise, there are RNA-binding proteins that could bind to messenger RNAs to affect their stability and localization, in the presence of inflammatory mediators [58-60]. Hypothetically, the lung inflammation and DNA repair are exhibited in the following corresponding diagram (Figure 2).

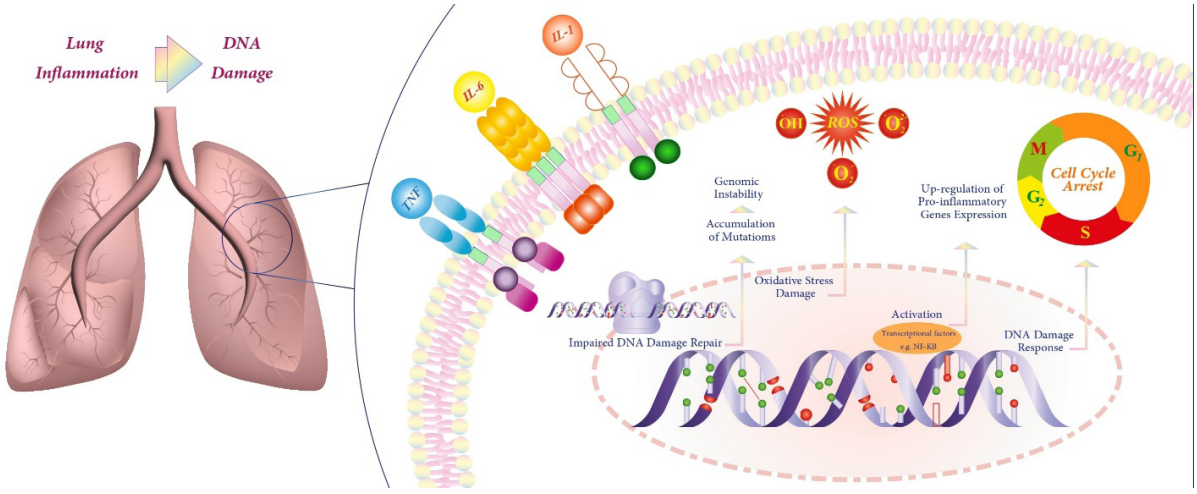

Figure 1. Schematic diagram of the effect of lung inflammation on DNA damage

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Effects of DNA damage and DNA repair pathways on lung inflammation

Pollutants, smoking, and infections in the lungs are some of the environmental stresses leading to DNA damage within the lung tissue, and this results in the manifestation of stresses with inflammation being the most common [61]. In the event of DNA damage and injury, a signaling occurs, which attracts immune cells hence the inflammation. DNA damage can be either chronic or acute and affects the repairing capability of the lungs leading to chronic inflammation and a higher risk of diseases like asthma, COPD, and pulmonary fibrosis [62].

Therefore, various types of DNA damage in the lung are regulated and handled using several essential DNA repair strategies. Since these repair pathways can be impaired, DNA damage continues to increase, which increases inflammation and the progression of the disease [63].

Genes involved in DNA repair play a critical role in managing lung inflammation. For example, *APEX1*/*XRCC1* is involved in base excision repair, and *XPC*/*ERCC1* is involved in the NER pathway. *BRCA1* and *BRCA2* genes have a basic vocation in repairing crossover breaks [64]. Decreased levels of such genes or their mutations can slow down the repair process,

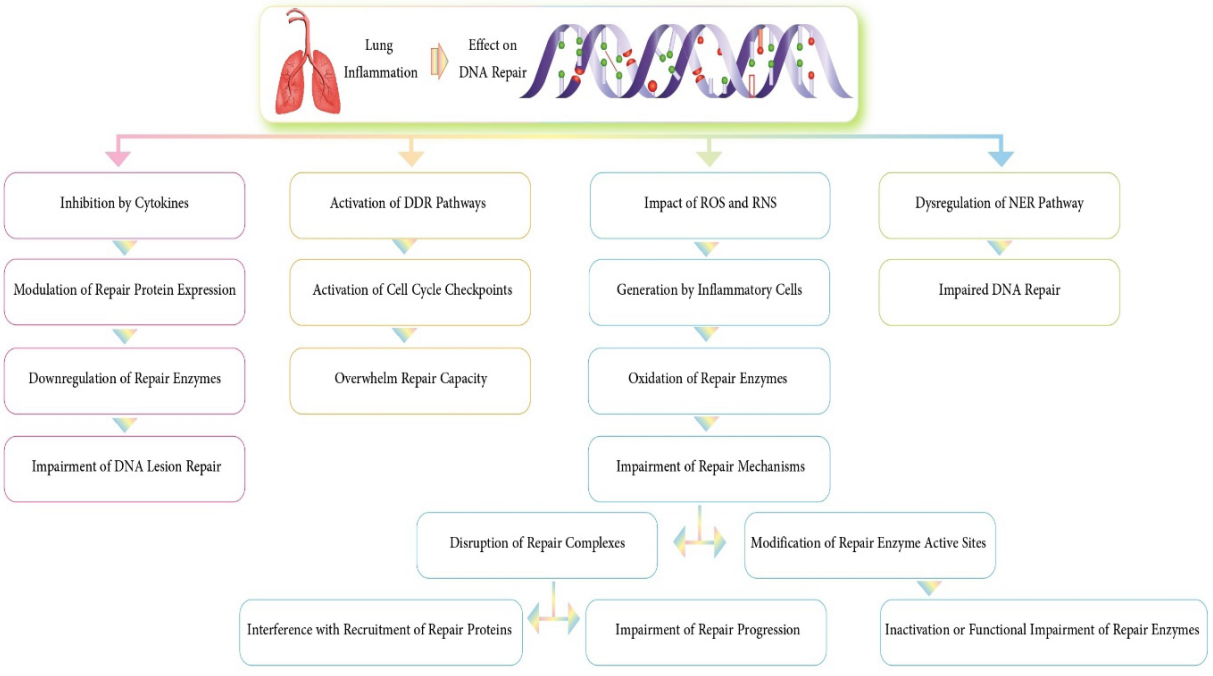

Figure 2. Schematic diagram of the effect of lung inflammation on DNA repair

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cause DNA damage, and sustained inflammation. This dysfunction can pave the way for the development and exacerbation of lung diseases since inflammation and genomic instability may persist [65].

Nonetheless, DNA repair plays an instrumental role in regulating inflammation and maintaining lung tissues' integrity. Chronic inflammation and other aspects of lung health are determined by alterations in DNA repair throughout one's lifetime for example, environmental and genetic influences can result in poor DNA repair and thus increased incidence of respiratory diseases [14].

Conclusion

Repair of DNA damage and inflammation is vital in preserving and instituting the health of the lungs as well as the etiology of respiratory disorders. Pulmonary tissue is at a continual risk of injury by acquired environmental pollutants, toxins, and pathogens, therefore it must utilize efficient repair molecules to address DNA damage. They include base excision repair, NER, and double-strand break repair which are critical in fixing different types of DNA damage that range from the alteration of baseline DNA to that of the double-stranded kind. Thus, in the presence of acute or chronic lung tissue injury, the effective cellular homeostasis is the failure of these repair mechanisms. This poor repair ability causes the utilization of damaged DNA and leads to instability of the human genome and hence the variation of diseases that are likely to develop such as lung cancer, COPD, and pulmonary fibrosis. Inflammation of the lungs caused by infections, toxins, and lung tissue injury is one of the most important factors that make this process chronic. Inflammation is protective in that it is useful in the removal of unwanted agents and in promoting tissue repair, but it creates reactive oxygen and nitrogen species that are capable of directly causing DNA damage. Chronic inflammation interferes with the DNA repair transactions and decreases the functional capacity of the repair enzymes and the expression of the repair-associated genes. TNF-α, IL-1β, IL-6, and IL-17 which are pro-inflammatory cytokines enhance this effect due to their role in the regulation of oxidative stress and genotoxicity. DNA damage and inflammation are more like two sides of the same coin, or in other words, a vicious cycle that feeds on itself and leads to the destruction of tissues and a faster pace of developing pathological processes. Inflammatory reactions occur due to DNA damage and there is aggregation of immune cells at the site of injury along with other files that produce more oxidants leading to more DNA damage. These describe a cycle of damage and inflammation where attempts are made at DNA repair and control of chronic inflammation via various therapies. Perhaps, it is even possible to halt the occurrence and development of respiratory diseases by lowering DNA damage and maintaining the genomes' integrity.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

Conceptualization and investigation: All authors; Writing the original draft: Marzieh Mojtahed, and Leila Nasiri; Review and editing, Hossein Hassanpour and Tahereh Jamali.

Conflicts of interest

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