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Review

Tumor-promoting inflammation in lung cancer: A literature review

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ABSTRACT

Tumor-promoting inflammation is an inflammation that occurs because tumor cells cause necrosis of healthy cells which releases cell contents into the environment, triggering the release of proinflammatory mediators. There are intrinsic and outside factors of tumor-promoting inflammation. Intrinsic factors are genetically related, while extrinsic factors are due to mediators and inflammatory cells. The primary inflammatory mediators in the tumorigenesis process include NF-kB, STAT3, HIF-1, and TNF-α. in contrast, the inflammatory cells that play a role are TAM, a collection of tumor-associated leukocytes. Bacteria is also one of the extrinsic factors that can cause tumors because of the chronic inflammation it causes.

1. Introduction

Lung cancer is one of the leading causes of death from cancer. The incidence of lung cancer ranks second after breast cancer. According to data from global cancer data, lung cancer causes 13.8% of all cancer deaths. Based on gender, most lung cancer is suffered by men (10.2%) [1,2]. The mechanism of cancer occurrence in general (carcinogenesis) is initiation, promotion, and progression. Initiation is the initial stage of neoplasia. Carcinogenic substances induce normal cells, so mutations occur in these cells. The mutated DNA will increase into a cancer cell. The next stage is promotion, which is a stage where the process of mutated normal cells is enhanced by the presence of proinflammatory cytokines and the unique expression pattern of each individual's genes. The last stage is progression, where after normal cells are mutated and increased in the promotion process, these cells will invade surrounding tissues, increase intake to defend cancer cells themselves and prevent cancer cells from apoptosis, and carry out foreign invasion or metastasis both lymphogenously and hematogenous [3].

The progression of a normal cell to a cancer cell has been summarized in a conceptual diagram that briefly explains the formation of cancer cells, consisting of ten components known as the Hallmark of Cancer (Fig. 1). One component of the Hallmark of Cancer is tumor-promoting inflammation [4]. Inflammation is one of the protective responses in eliminating harmful substances and restoring tissue responses in a homeostasis state [5]. Inflammation caused by tumors generally occurs continuously (non-resolving inflammation). Data in several previous studies showed that 25% of the causes of tumors with chronic inflammatory characteristics were chronic infections [6,7].

In this literature review, we discussed one of the Hallmarks of Cancer, tumor-promoting inflammation including, the definition, causes, and mechanisms of tumor-promoting inflammation.

1.1. Definition of tumor-promoting inflammation

Tumor-promoting inflammation is inflammation that occurs because tumor cells cause the necrosis of healthy cells. This results in the release of beneficial cell contents into the interstitial tissue, triggering proinflammatory signals. This state will remain to continue as long as tumor cells grow [5,8,9].

1.2. Etiology and types of tumor-promoting inflammation

Various types of inflammation based on the cause, mechanism, intensity, and outcome can lead to cancer development. The inflammatory process associated with tumor development can be seen in Fig. 2 [10].

1.3. Chronic inflammation due to infection

Persistent infections caused by parasites, bacteria, viruses, and physical and/or chemical stimuli can lead to inflammation [11]. Risk factors for cancer are increased in patients with persistent infection, for example, persistent infection with *Helicobacter pylori* causing gastric adenocarcinoma and persistent infection with *Epstein-Barr* virus causing nasopharyngeal carcinoma [5].

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1.4. Inflammation due to environmental exposure and diet

Environmental exposures can also cause chronic inflammation. Cigarette exposure can lead to an increased risk of lung cancer. Inhalation of asbestos and silica particles causes inflammation through the effect of interleukin-1β (IL-1β; Fig. 3), which can trigger tumorigenesis. Diets containing carcinogenic substances will initiate p53 gene mutations, preventing the mutated cells from apoptosis thereby triggering tumor cell formation. Obesity can also cause chronic inflammation which increases the risk of hepatocellular carcinoma by 1.6 times [10].

1.5. Therapy-induced inflammation

Therapy such as radiation and chemotherapy can cause of cancer cells and surrounding tissue necrosis, triggering an inflammatory reaction. Therapy-induced inflammation is still controversial because, apart from provoking tumor development, it can also trigger an antitumor immune response [10].

1.6. Tumor-associated inflammation

In some circumstances, the malignant process can live independently because it can create blood flow for nutrients and oxygen requirements. The proliferation of tumor cells and several oncogenes cause cell necrosis in the tumor nucleus and release proinflammatory mediators such as IL-1 and HMGB1 (High Mobility Group Box-1; Fig. 4). This inflammatory response in tumors triggers neoangiogenesis, genome instability, immunosuppression, metastasis, and tumor development [10].

1.7. Tumorigenesis

The interaction of tumors with the immune system is thought to occur in three stages: elimination, equilibrium, and escape. In Elimination, the immune system reacts by destroying tumor cells that are still developing. In Equilibrium, the immune system controls tumor cells that expand in surrounding tissues and metastasize. In Escape, tumor cells begin to form self-defence (resistance) in immune cells, for example, by changing the expression and function of HLA (Human Leukocyte Antigen) on the surface of tumor cells [12].

1.8. Association between tumorigenesis and immune system

1.8.1. Association between tumor-promoting inflammation and innate immune system

Tumor-Associated Macrophage (TAM) is the most significant component in the inflammatory process. Tumor cells infiltrate macrophage cells, inhibiting antitumors from adaptive immune cells by inducing T cells and releasing immunosuppressive modulating agents [9,12,13].

1.8.2. Association between tumor-promoting inflammation and adaptive immune system

T cells affect the adaptive immune system, including inducing and recruiting T cells to develop tumor cells, stimulating both mature and immature dendritic cells to stimulate cytokine immunosuppressive substances, especially IL-10 and TGF-β, and inhibiting dendritic cell maturation [12,14]. Treg cells from lung tumor patients impede the proliferation of T cells. Treg cells are produced in large numbers to provide an immunosuppressive effect and promote tumor growth in the area around the tumor [12,15].

One of the causes of tumors due to inflammation is TNF-α, a proinflammatory cytokine that plays a role in the tumor-promoting inflammation process through the involvement of ROS (Reactive Oxygen Species) and RNS (Reactive Nitrogen Species). This mechanism is related to the production of ROS and RNS during inflammation, for example, in *Helicobacter pylori* infection that secretes the Tip-α protein (TNF-α-Inducing Protein). This causes interactions on the surface of gastric cells through a receptor called nucleolin. This binding induces the release of proinflammatory cytokines and produces NF-κB. This is associated with neoplasia of the epithelial-mesenchymal tissue in the stomach. In metastatic cancer, the freedom and increase of TNF-α cause widespread metastases. For example, in Lewis lung carcinoma

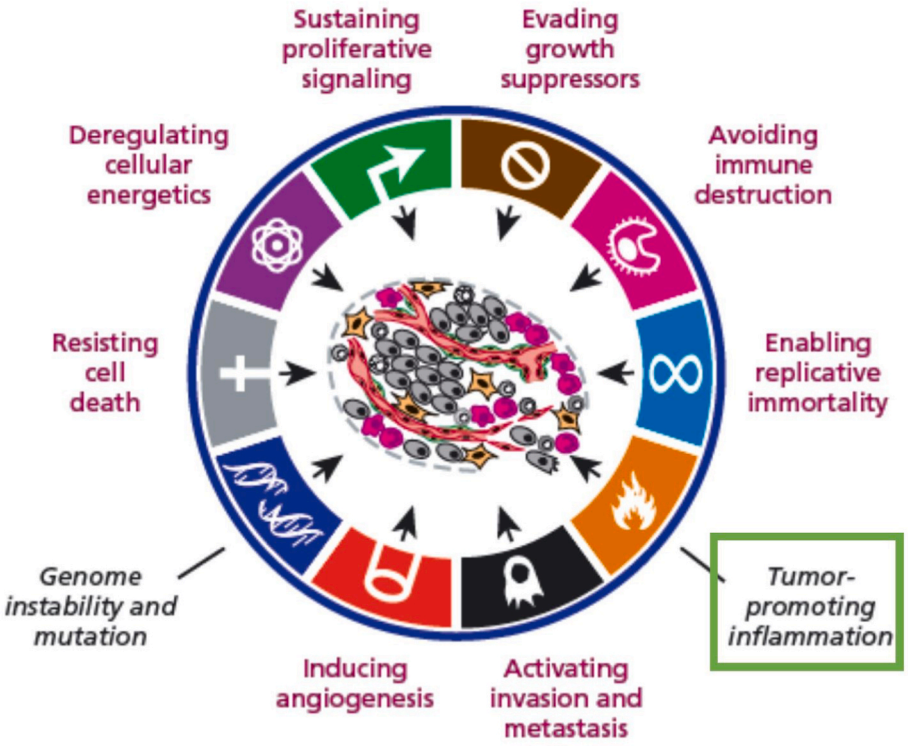

Fig. 1. Hallmark's cancer scheme [4].

(epidermoid), IL-6 and TNF-α are found to be elevated [15,16].

In obese patients, the accumulation of hypertrophy and hyperplastic adipocytes leads to the arrival of macrophages. Inflammation begins with increased production of IL-6, TNF-α, and Plasminogen Activating Inhibitor (PAI-1). Adipocytes then undergo angiogenesis and remodeling as well as chronic hyperinsulinemia and increase in Hypoxia Inducible Factor (HIF-1), TGF-β, Matrix Metalloproteinase (MMP). This leads to tumor development due to inflammation [17].

Fig. 5 describes the relationship between chronic inflammation and carcinogenesis/tumorigenesis influenced by intrinsic and extrinsic factors. Intrinsic factors are genetically related, while mediators and inflammatory cells cause outside factor. The primary inflammatory mediators in the tumorigenesis process are NF-κB, STAT3 (Signal Transducer and Activator of Transcription 3), HIF-1, and TNF-α. In contrast, the inflammatory cells that play roles are TAM (Tumor-Associated Macrophages), a collection of tumor-related leukocytes. Macrophages secrete IL-1, IL-6, and TNF-α, resulting in chronic inflammation that stimulates carcinogenesis. This inflammation stimulates the proliferation of lymphoblasts into B cells. B cells are thought to play an essential role in solid tumor formation. Excessive B cell proliferation (Fig. 6) leads to angiogenesis, hyperproliferation, and chronic inflammation [18,19]. The results of the TAM molecular-based examination stimulated the release of the transcription factors NF-κB and HIF-1. These two factors play an essential role in tumor metastasis and the rapid progression of tumors, particularly NF-κB, which can enhance tumor cell activation, growth, and resistance to apoptotic signals [18,20].

Bacteria is also one of the extrinsic factors that can cause tumors due to chronic inflammation, for example, in patients with intestinal

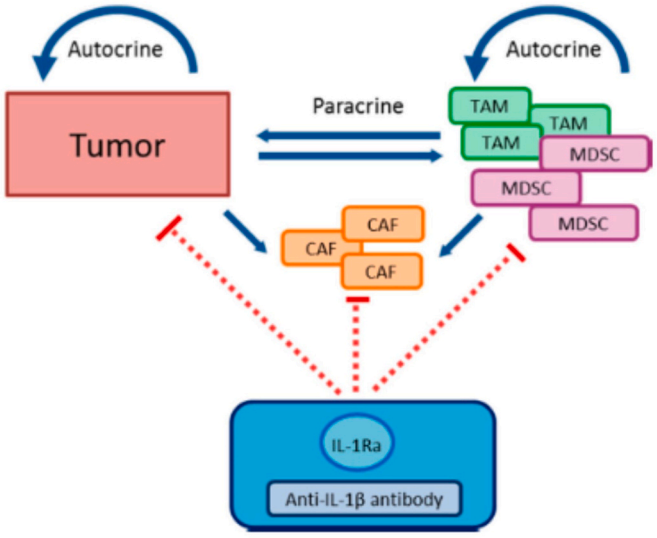

Fig. 3. Impact of IL-1 on the tumor environment. IL-1β is expressed by cancer cells and exerts a valid effect on the management of growth-associated susceptible cell populations such as TAM (tumor-associated macrophage) and MDSC (myeloid-derived suppressor cells) that produce IL-1β. Both cell populations are formed from tumor-derived soluble factors. IL-1β exerts both autocrine and paracrine tumorigenic effects. IL-1β exerts an expanding effect on fibroblast development and angiogenesis. CAF (carcinoma–associated fibroblasts) is the term for this group of fibroblasts formation. This cell population increases the production of interleukin-1 (IL-1) [32].

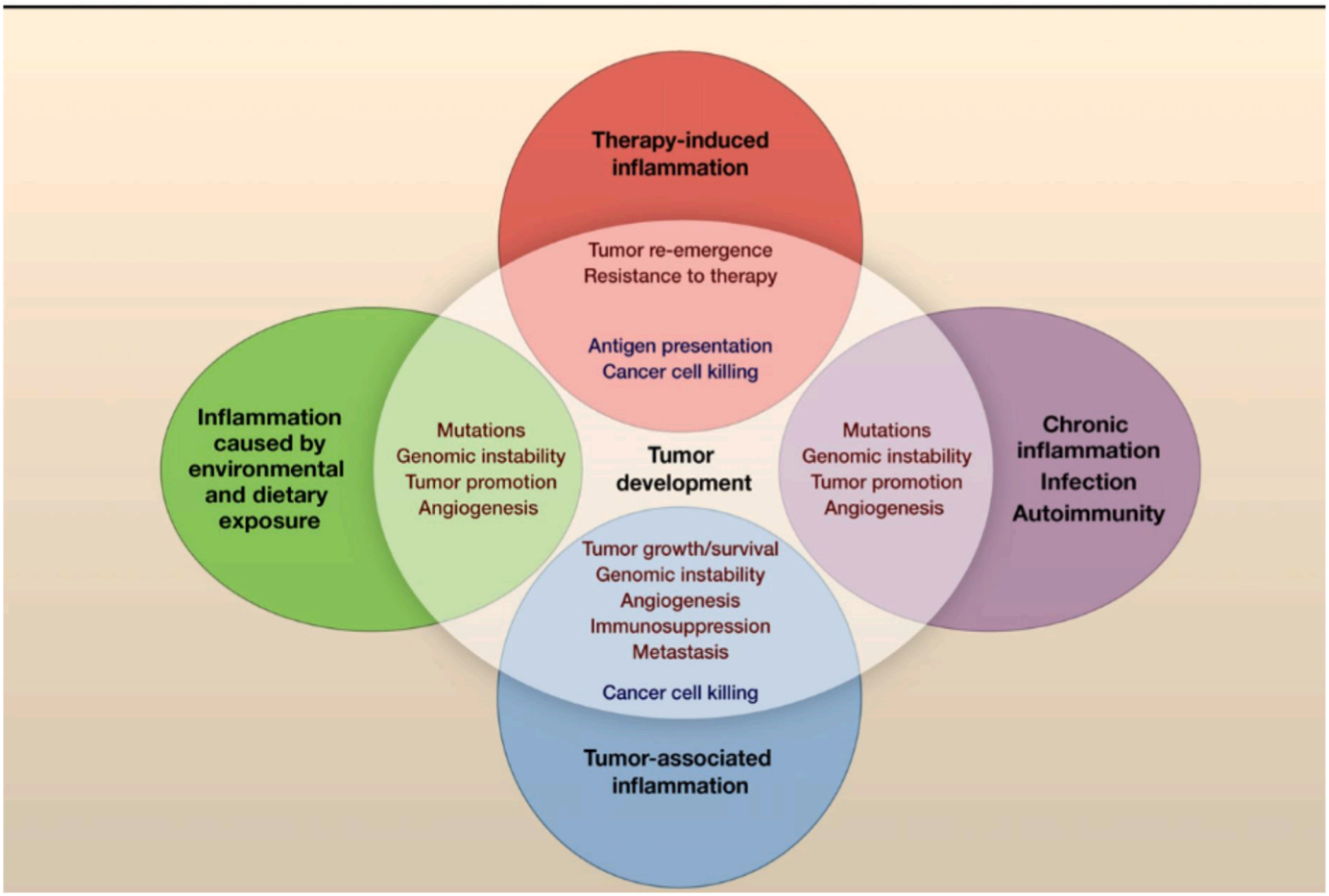

Fig. 2. Types of inflammation in tumorigenesis and cancer [10].

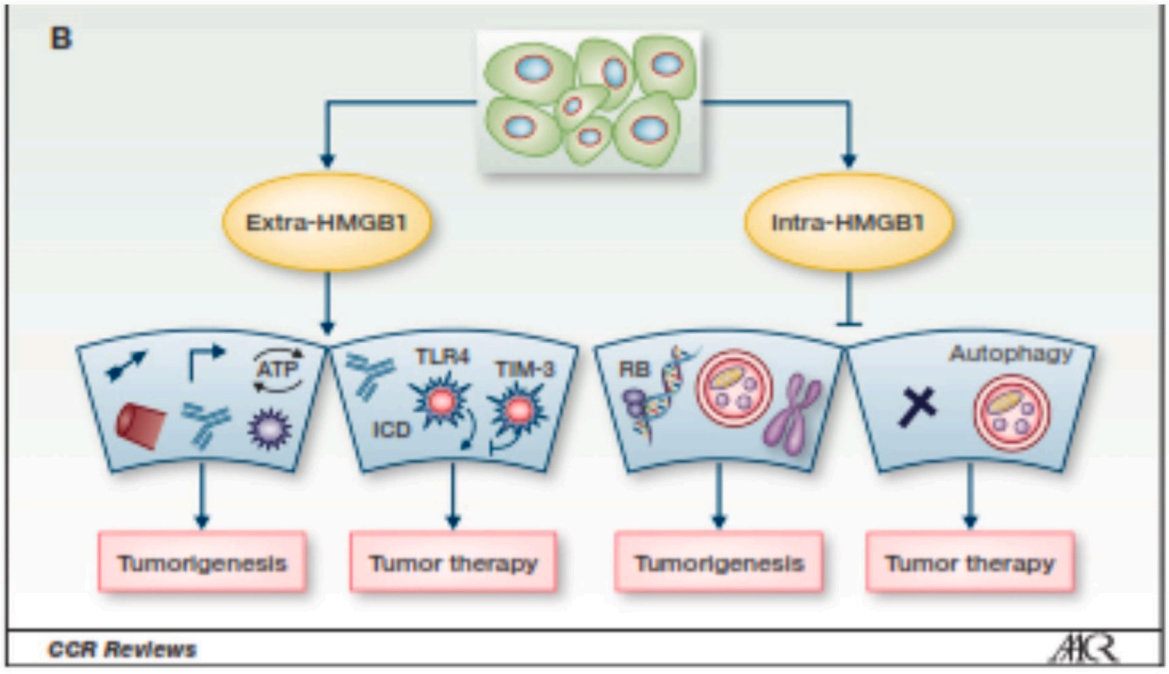

Fig. 4. The role of HMGB-1 in tumorigenesis and tumor therapy is still under study. HMGB-1 can be found in intra and extracellular cells. Extracellular HMGB-1 plays a role in proliferation, inflammation, energy metabolism, and angiogenesis, and inhibits anti-cancer immunity, thereby causing immunity during radiotherapy or chemotherapy. HMGB-1 binds to TLR-4 (Toll-Like Receptor-4), giving an anti-tumor effect, and HMGB-1 binds to TIM-3 (T-Cell Immunoglobulin Mucin-3), giving an immune inhibition effect on anti-tumor cells dendritic. Intracellular HMGB-1 exerts an unstable impact on the genome and enhances the development of the Rb-gene (retinoblastoma) in tumorigenesis. Decreased HMGB-1 causes suppression of autophagocytes and enhances the effect of anticancer therapy in regulating autophagocytosis [33].

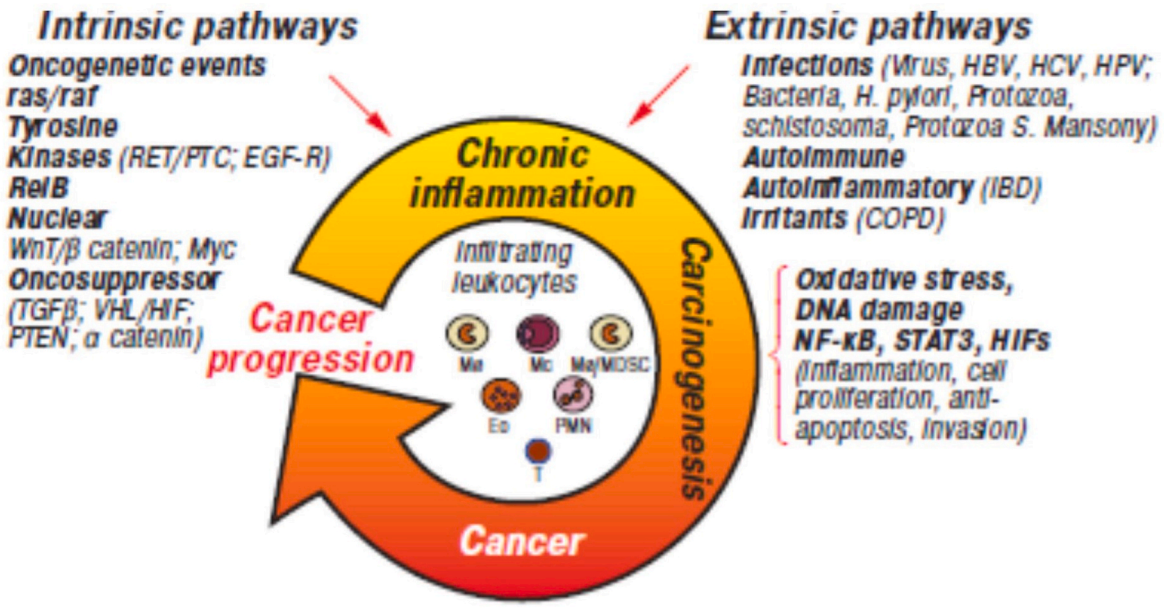

Fig. 5. Schematic of intrinsic and extrinsic pathways of chronic inflammation and carcinogenesis [18].

mucosal infections. Research show that Interferon Gamma (IFN-γ) levels are decreased due to a chronic inflammatory response that produces IL-18. This results in dysregulation of bacteria in the intestine, and then the growth of bacteria in the intestine increase and causes chronic inflammation. the mucosal surface undergoes necrosis will produce IL-6 that stimulates the occurrence of epithelial cell neoplasia. IL-6 has the transcription factor STAT3, which, together with NF-κB, induces epithelial-mesenchymal transition (EMT) to downregulate the expression of epithelial cell differentiation markers. Homeostasis is regulated by NLCR-4 (NOD-like Receptors), activates of ASC protein (apoptosis-associated speck-like protein containing a CARD) through Caspase I activates the proliferation of immature cells and apoptosis of mature cells. This concept resembles chronic inflammation leading to lung and skin tumors (Fig. 7) [21,22].

The type of cancer therapy related to tumor-promoting inflammation is immunotherapy. This immunotherapy is associated with IL-10 in the

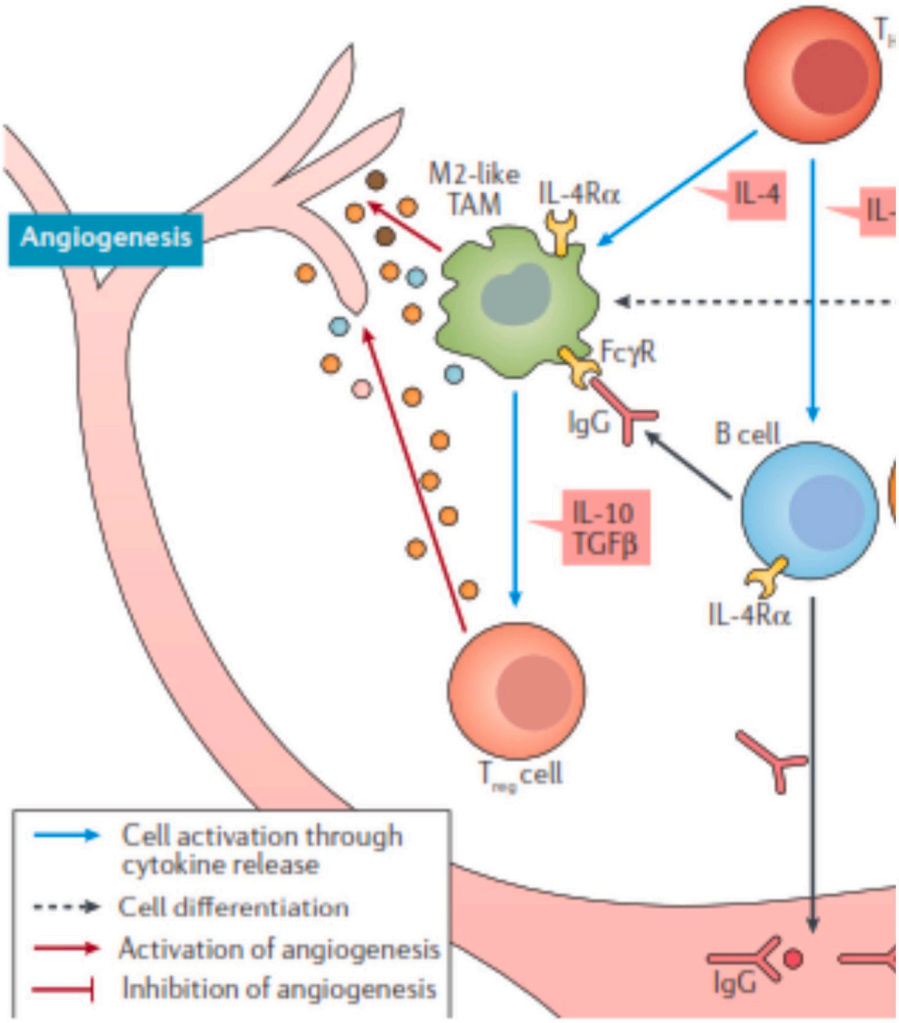

Fig. 6. B cells proliferate by secreting IgG, which speeds up the process of angiogenesis. (Immunoglobulin-G) which binds to TAM. On the other hand, IgG produced by B-cells that do not attach to TAM inhibits angiogenesis [34].

form of PEG-IL-10 (Pegylated IL-10), which induces IFN-γ expression-dependent tumor growth and development. However, in the experiment by Emmerich et al., injection of PEG- IL-10 in mice with breast cancer stimulates $CD8^+$ T cells and eliminates lung metastases. PEG-IL-10 then protects effect against these tumors and provides memory for $CD8^+$ T cells [23,24].

1.9. Role of inflammation in lung cancer

The incidence of lung cancer can be caused by asbestos, silica agents, and cigarette smoke. The immune system cannot eliminate these three agents, so chronic inflammation will persist. Cigarette smoke is an agent with a complex structure. The components in cigarettes are paraneoplastic agents, including nitrosamines, peroxides, and other potent oxidants. This gradual inflammation will result in tumor development, migration, tumor growth, and differentiation of normal cells into various forms of tumor cells. Tumor cells that have been formed can escape from the patient's immune system by expressing PDL-1 (Programmed Cell-Death-1 Ligand) so that tumor cells look like normal cells. These modulators are usually desctibed in 40%–50% of NSCLC cells [25–27].

There are many stages in the growth and development of tumors. In the early stages, the inflammation will directly affect DNA damage, mutation, or trigger DNA damage by activating cytochrome p-450 oxidase or flavin monooxidase, which produces ROS (Reactive Oxygen Species), causing damage to proteins and DNA. In the second stage, a promotion phase causes tumor cells to divide and form focal lesions, which invade the surrounding tissue over time. In the final step, malignant tumor cells mature both genetically and phenotypically. One of the promotional factors that cause tumor cells to experience excessive/abnormal proliferation is EGFR (Epidermal Growth Factor Receptor). It is a transmembrane factor with intrinsic tyrosine kinase activity that triggers instability of cell genes and DNA mismatches at several nucleotide levels in lung cancer cells [25–27].

In inflammation, a protein called MMP recruits inflammatory cells in damaged tissue. MMP has been suggested to play an essential role in cancer, COPD (Chronic Obstructive Pulmonary Disease), and ALI (Acute Lung Injury). MMP acts by amplifying pro-inflammatory cytokines into active cytokines. For example, MMP can activate insoluble TNF-α into soluble TNF-α. MMP-9 also controls the IL-12-dependent proliferation of T lymphocytes [25–28].

The relationship between COPD and the occurrence of lung cancer related to tumor-promoting inflammation is the presence of ROS and reactive nitrogen in cigarettes, both of which are abbreviated as RNOS. These free radicals, such as RNOS, cause normal cells to accumulate in a zone and damage the cell's DNA. DNA mutations also occur at the level of point mutation, SSB (single-strand breaks), and DSB (double-strand breaks). RNOS also triggers cancer cell growth and progression by activating intracellular signals and inflammatory cell proliferation to increase the mitotic process. In addition, RNOS enhances the

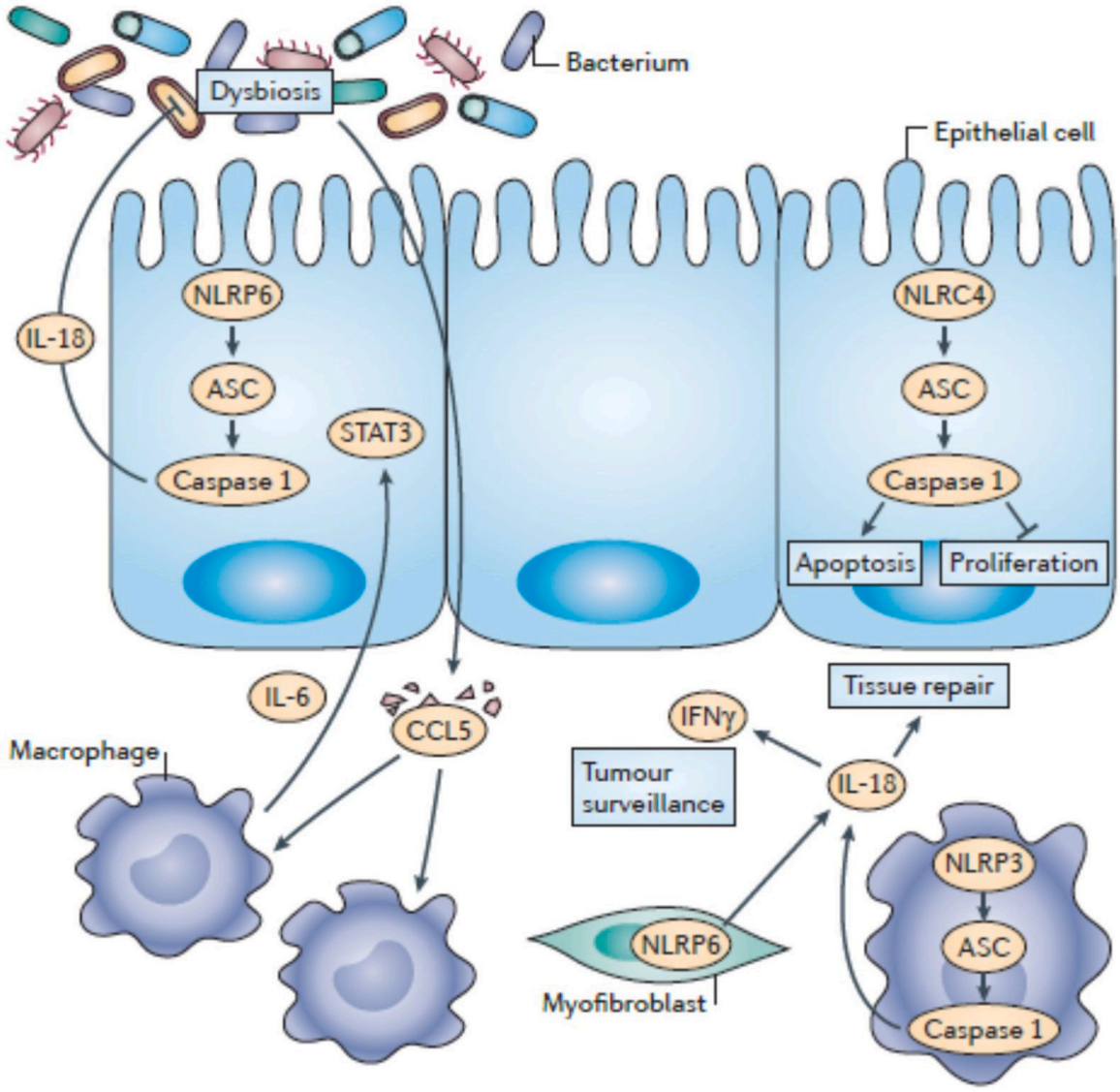

Fig. 7. Effect of inflammation on carcinogenesis [21].

angiogenesis process for the nutrition of the tumor cells themselves. RNOS can change the protein structure of a cell, both its function and modification of amino acids [29,30].

Chronic inflammation from smoking at the genetic level results in telomeres shorten at the ends of chromosomes. This causes premature cell aging. Hayflick limit is a state of cells entering into aging due to chronic inflammation and cell damage or entering the phase of cell mutation towards cancer. The mutated cancer cells can pass this stage of cell aging by inactivating Rb (Retinoblastoma Protein) and the tumor suppressor protein p53 so that these cells continue to replicate (Fig. 8) [29,31].

A limitation of our study is that the material on tumor-promoting inflammation in lung cancer is minimal. Current tumor-promoting inflammation is mostly general tumor and unspecific. Future research is expected to reveal the role of tumor-promoting inflammation in lung cancer (primary and metastases). Studies in this field are beneficial for preventive lung health in the future.

1.10. Summary

Chronic inflammation is one of the process that might become lung cancer in the future. Tumor-promoting inflammation occurs because tumor cells destroy healthy cells releasing cell contents into the environment, and triggering the release of proinflammatory mediators. There are intrinsic and outside factors that play roles in tumor-promoting inflammation. Intrinsic factors are genetically related, while extrinsic factors are due to mediators and inflammatory cells. The primary inflammatory mediators in the tumorigenesis process include NF-κB, STAT3, HIF-1, and TNF-α. In contrast, the inflammatory cells that play a role are TAM, a collection of tumor-associated leukocytes. The extrinsic factors that cause tumors due to chronic inflammation are chronic infection, such as bacterial and viral infection, the exposure to environment and diet, and therapy-induced inflammation.

Ethical approval

Not applicable.

Sources of funding

None.

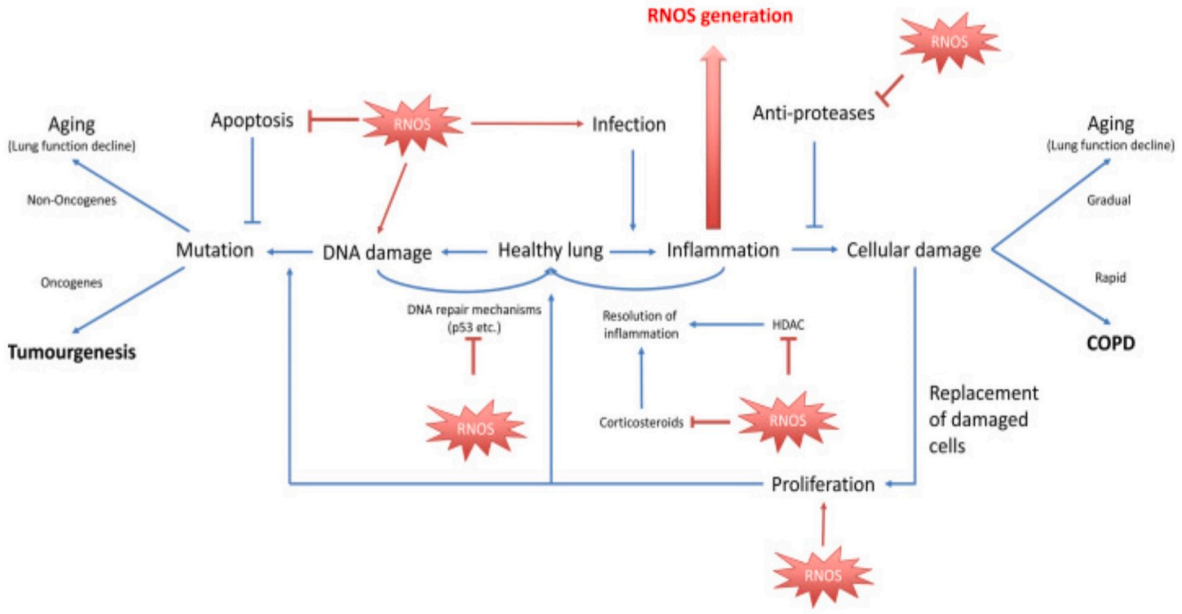

Fig. 8. Effects of RNOS on COPD and its association to lung tumors [29].

Author contribution

All authors contributed toward data analysis, drafting and revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Registration of research studies

Name of the registry:
Unique Identifying number or registration ID:
Hyperlink to your specific registration (must be publicly accessible and will be checked)

Guarantor

Farah Fatma Wati is the person in charge of the publication of our manuscript.

Consent

Not applicable.

Declaration of competing interest

Gemilang Khusnurrokhman and Farah Fatma Wati declare that they have no conflict of interest.

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