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ORIGINAL ARTICLE

Regulatory Components of Oxidative Stress and Inflammation and Their Complex Interplay in Carcinogenesis

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Abstract
Cancer progression is closely linked to oxidative stress (OS) inflammation. OS is caused by an imbalance between the amount of reactive oxygen species produced and antioxidants present in the body. Excess ROS either oxidizes biomolecules or activates the signaling cascade, resulting in inflammation. Immune cells secrete cytokines and chemokines when inflammation is activated. These signaling molecules attract a wide range of immune cells to the site of infection or oxidative stress. Similarly, increased ROS production by immune cells at the inflamed site causes oxidative stress in the affected area. A review on the role of oxidative stress and inflammation in cancer-related literature was conducted to obtain data. All of the information gathered was focused on the current state of oxidative stress and inflammation in various cancers. After gathering all relevant information, a narrative review was created to provide a detailed note on oxidative stress and inflammation in cancer. Proliferation, differentiation, angiogenesis, migration, invasion, metabolic changes, and evasion of programmed cell death are all aided by OS and inflammation in cancer. Imbalance between reactive oxygen species (ROS) and antioxidants lead to oxidative stress that damages macromolecules (nucleic acids, lipids and proteins). It causes breakdown of the biological signaling cascade. Prolonged oxidative stress causes inflammation by activating transcription factors (NF-κB, p53, HIF-1α, PPAR-γ, Nrf2, AP-1) that alter the expression of many other genes and proteins, including growth factors, tumor-suppressor genes, oncogenes, and pro-inflammatory cytokines, resulting in cancer cell survival. The present review article examines the complex relationship between OS and inflammation in certain types of cancer (colorectal, breast, lung, bladder, and gastric cancer).

Keywords Oxidative stress · Inflammation · Transcription factors · Cancer · Cytokines

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Introduction

Oxidation and reduction are invariably pivotal for cellular signaling processes like proliferation, apoptosis, inflammation, and immune responses [1]. The maintenance of redox metabolism and its equilibrium relies on the interaction of oxygen and nitrogen species with biomolecules. An alteration in redox homeostasis is elucidative in the prognosis of various disease manifestations [2]. Oxidative metabolism as a result of aerobic respiration provokes the production of several compounds that are essential for molecular events, namely, gene expression, activation of enzymes, and signal transduction. However, cellular stress may increase the toxic levels of these compounds. The internal and external sources of oxidative stress are the detoxifying enzymes, radiation, and chemical compounds, respectively [3].

Reactive species are broadly classified into reactive oxygen species (ROS), reactive nitrogen species (RNS), reactive chloride species (RCS), and reactive sulfur species (RSS). Among these reactive species, ROS production is found to be more prevalent in the cells and has a potential impact on the rate of mutagenesis [4, 5]. ROS are oxygen-containing chemical metabolites. The disproportion in the antioxidant system increases ROS levels leading to oxidative stress. OS triggers the initiation and progression of various diseases such as hypertension, diabetes, and cancer [6]. ROS includes both free radical and non-free radical oxygen intermediates obtained from both endogenous and exogenous sources such as hydrogen peroxide (H_2O_2), superoxide anion (O_2^-), hydroxyl radical (OH^-), ozone (O_3), and singlet oxygen ($^1O_2$) [7, 8]. All these molecules were regarded deleterious for nucleic acids, lipids, and proteins in the beginning. It was then studied that they play a complex role in activating different physiological signaling cascades. These molecules are utilized in different metabolic pathways of mitochondria, endoplasmic reticulum, and peroxisomes. Mitochondria is the major reservoir of ROS where 2% of oxygen is estimated to form its superoxide. Peroxisomes host a number of free radical scavenging mechanisms via β-oxidation of fatty acids and catalase-mediated hydrogen peroxide decomposition. In the endoplasmic reticulum, generation of ROS takes place as a result of protein oxidation [9].

Increase in OS and aerobic respiration are two main attributes of cancer [10]. There is a constant pressure to sustain the balance between ROS and oxidative-stress responses. They demand unlimited energy for their deviant proliferation [11]. They are greatly linked with different types of cancer progression, for instance, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), and hepatocellular carcinoma [12, 13]. Many of the oncogenic cellular pathways and genes are evidenced to be combined with oxidative stress responses and epigenetic regulations [14]. For example, the signaling pathways of extracellular signal-regulated kinase (ERK), mitogen-activated protein kinase (MAPK), and JUN N-terminal kinase (JNK) that support tumor growth and survival are triggered by the oxygen species [15]. ROS and reactive nitrogen intermediates (RNI) mediate genetic damage causing inflammatory bowel disease (IBD), closely related to colorectal cancer development [16]. Malignancies in breast cancer are delineated by indicative levels of estrogen, a major factor in ROS generation. It initiates protein intricates in proliferation and anti-apoptotic pathways vulnerable to redox signaling.

Hypoxic conditions engage adaptive responses in both physiological and pathological conditions via diverse cellular pathways that involve hypoxia-inducible factors, and endoplasmic reticulum stress responses [17]. Studies on brain pathology suggested an inverse interconnection between hypoxia and OS on the prospects of cancer, for instance,

sensitivity of nonmalignant glial cells and glioblastoma cancer cells to low oxygen [18]. ROS production has a direct control over the mechanism of epithelial–mesenchymal transition (EMT), which further enables tumor progression by allowing the cancer cells to colonize remote locations [19]. Finally, the interrelation between oxidative stress and inflammation in cancer will be the focus of this review.

Free Radicals—a Bridge Between Inflammation and Cancer

Cancer risks are higher when inflammation persists longer than usual. The free radical intermediates derived from nitrogen (RNI) and oxygen (ROI) induce inflammatory cells to the damaged sites of tissues which end up with cancer progression [20], as depicted in Fig. 1. Mitochondria, cytochrome P450, peroxisomes, and apoplasts are the sole production centers of ROI and RNI that stimulate signals for intracellular transduction pathways, cell cycle, and metabolism in favorable conditions [21]. Under unfavorable conditions, oxidative stress and nitrosative stress implicate the extracellular pathways related to metabolic stress. It reacts with biomolecules in the body to alternate the intra- and intercellular equilibrium eventually leading to cell death [22]. Activation of protein kinase in non-phagocytic and phagocytic cells stimulates ROI and RNI production by proinflammatory cytokines and chemokines, which aids the growth and proliferation in neoplastic cells simultaneously with the production of autocrine growth factor in tumors. Interleukins-6 (IL-6), a multifunctional cytokine,

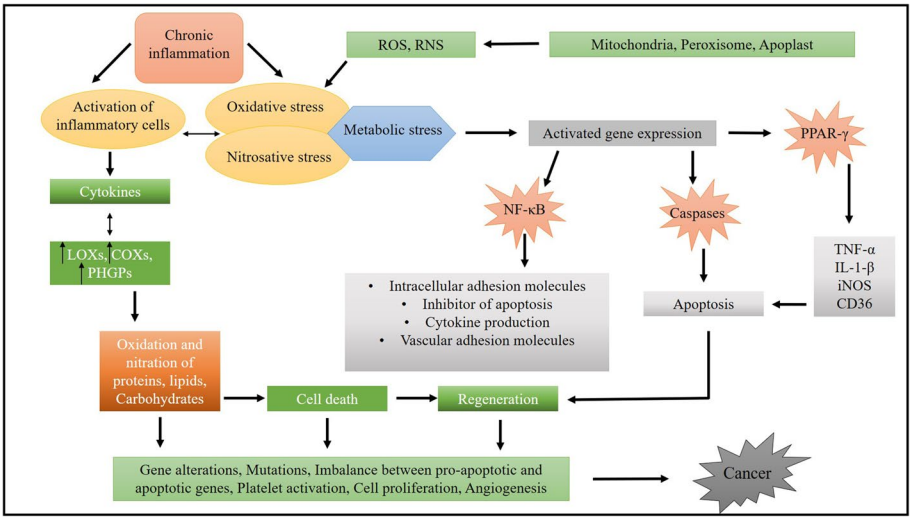

Fig. 1 The main steps involved in inflammation that leads to cancer via free radical stress. ROS/RNS causes oxidative stress and nitrosative stress, which is also activated by chronic inflammation that induces inflammatory cells and activates gene expression via various pathways such as NF-κB, caspases, PPAR-γ, IL-1β, TNF-α, iNOS, and CD36. In addition, the cytokines released from inflammatory cells induce oxidation and nitration of lipids, proteins, and carbohydrates. All these transcription factors along with cytokines stimulate apoptosis, thereby creating an imbalance between pro-apoptotic and apoptotic gene environments that simultaneously lead to regeneration and cell death and eventually causing cancer through gene alterations, mutations, proliferation, angiogenesis, etc.

level up during the exposure to an inflammatory stimulus. In BALB/c mice in vivo, prostaglandin (PGE_2) secretion from cyclooxygenase-2 (COX-2) elevated the level of IL-6 enhancing the growth of pristane-induced plasma cell tumors and also pristane elicited macrophages in vitro [23]. Prostaglandin derived from the oxidation of arachidonic acid and certain other cytokines raises the level of ROI and RNI production that adds up to the amplification of cancer. It is stated that a toxic radical from nitrogen species, namely, peroxynitrate, stimulates the prostaglandin synthesis [24, 25]. At lower concentrations, the lipid oxidizes to form aldehydes and lipid peroxides act as a signal transductor of ROI promoting the expression of genes and proliferation of cells, while at higher concentrations, these lipid peroxides easily interact with biomolecules to generate a wide range of inter- and intramolecular toxic covalent adducts that lead to increased oxidative stress [26].

Mitochondria Integrate ROS Signaling and Cancer

The mitochondrion is a double-membraned organelle composed of matrix, outer mitochondrial membrane (OMM), and inner mitochondrial membrane (IMM) with a middle intermembrane space region (IMS). The OMM is the first barrier providing permeability of Ca^{2+} through high expression of voltage-dependent anion-selective channel proteins (VDACs) thereby creating pores in OMM to mediate the flux of ions, nucleotides, and other metabolites [27]. A tight diffusion barrier called IMM is specialized for the transportation of larger molecules which is allowed by a translocase, namely, translocases of the inner membrane (TIM) smaller molecules (carbon dioxide, water, oxygen) [28]. IMS is involved in regulating mitochondrial respiration, transport of protein, lipid equilibrium, and exchange of ions whereas the matrix is involved in diverse metabolic pathways as it contains a circular double-stranded DNA without histones, namely, mitochondrial DNA (mtDNA) [29].

mtDNA is known for its effective DNA repair mechanism and encodes 13 components for the mitochondrial electron transport chain (mtETC) [30], which is composed of 4 complexes. Among those, NADH-CoQ reductase (complex I) and cytochrome C reductase (Complex III) are the major areas for superoxide ($O_2.^-$) generation [31], which is a by-product of oxidative phosphorylation (OXPHOS) bioenergetic metabolism. Superoxide dismutase converts it to H_2O_2 [32]. It leads to loss in mtDNA integrity and a reduction in mtDNA copy number, and acquires mutations which contribute to various diseases [33]. In addition, the modulation of mtROS production is due to alterations in Ca^{2+} dynamics and transfer of lipids from endoplasmic reticulum to mitochondria [31]. mtROS together with ATP, cardiolipin, and mitochondrial Ca^{2+} are transported to extracellular milieu or cytosol to stimulate the mito-inflammation through enhancing the levels of pro-inflammatory cytokines [34, 35]. It promotes oxidative damage to various organelles and triggers the production of nuclear factor-kappa B (NF-κB), hypoxia-inducible factor 1 (HIF-1), and activator protein-1 (AP-1) that provokes initiation of pro-inflammatory cytokines, namely, interleukin-6 (IL-6) and interleukin-8 (IL-8) [36, 37]. The alteration in OXPHOS activity increases mtROS due to the oxidative damage in mtDNA discharged from the matrix causing impairment in mitophagy. These mtROS and mtDNA are identified by pattern recognition receptors (PPRs) in the cytosol. They interact with other receptors to form the inflammasome complex in the cytosol, which then gets activated and induces cancer [38, 39].

In cancer, during the initiation and promotion stage, mtROS stimulate oxidation in mtDNA and cause damage. It increases mutations and structural changes in mtDNA with certain effects on expression and signaling in genes [40]. All these favor the apoptotic evasiveness in the advancement stage of cancer. It not only aids in genomic instability but also influences the inflammatory cytokines of tumor cells and activates several transcription factors that modify the energy of cancer cells [39]. The role of mtROS in cancer formation is presented in Fig. 2. In the 1930s, Otto Warburg was the first to state that cancer was caused by mitochondrial dysfunction. Cancer cells adopt aerobic glycolysis to produce energy instead of OXPHOS in mitochondria, which is called a Warburg switch [41]. A study stated that tumor progression is inhibited by preventing the lactate conversion from pyruvate by lactate dehydrogenase [42]. By stimulating the metabolism in mitochondria by OXPHOS, cancer cell proliferation is arrested [43]. In colorectal and lung cancers, a malignant potential increase in expression levels of glucose transporter (GLUT) proteins has been evidenced. All these data showed that the cancer cells accumulate more glucose for its metabolism [44]. All these findings state that cancer cells undergo a Warburg effect that affects cellular events and increases mtROS production. The pro-inflammatory cytokines increase ROS production in mitochondria, which enhances cancer progression.

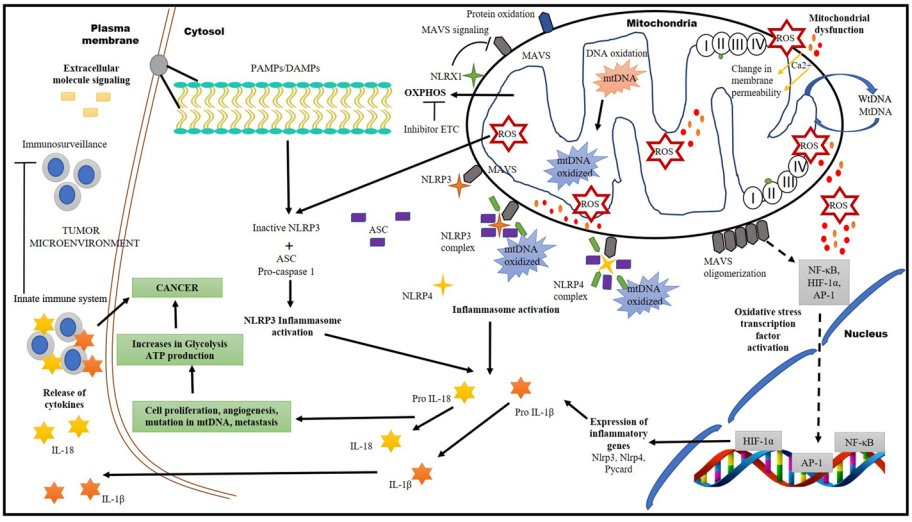

Fig. 2 mtROS leads to mito-inflammation that induces cancer. In mitochondria, excess releases of ROS oxidize mitochondrial DNA and excess calcium in mitochondria changes membrane permeability thereby causing mutation in mtDNA and bringing about dysfunction in mitochondria. Inflammasome activation consists of three mechanisms: first, mitochondrial anti-viral signaling protein (MAVS) oligomerizes via oxidative stress activating various TFs (NF-κB, HIF-1α, AP-1). All these TF express many other inflammatory genes (Nlrp3, Nlrp4, pycard). Secondly, NLR family pyrin domain containing 3 (NLRP3) receptors after interacting with oxidized mtDNA forms a complex with apoptosis-associated speck-like protein containing a CARD (ASC) and activates inflammasome. Thirdly, the inactive NLRP3 from the plasma membrane on interaction with ROS and ASC Pro-caspase 1 also forms the NLRP3 inflammasome complex. All three mechanisms simultaneously activate IL-18 and Il-1β that enhance proliferation, angiogenesis, metastasis, and DNA mutation that increase glycolysis and ATP production causing cancer. In the tumor microenvironment, immunosurveillance takes place by the innate immune system which is inhibited due to the proliferation of cancer cells

Inflammation and Oxidative Stress in Different Cancer Types

Inflammation contributes to carcinogenesis through various mechanisms such as instability in genome, changes in epigenetic events and consecutive irrelevant gene expression, increased differentiation of initiated cells, apoptotic resistance, aggressive tumor neovascularization, invasion in tumor-associated basement membrane, angiogenesis, and metastasis. ROS, an effector molecule, participates in host defense or acts as a chemo-attractant, volunteering leukocytes to the wounded site, thereby prompting inflammatory reaction in the tissue injured area. There are various cancers that are caused by the complex interplay between oxidative stress followed by inflammation.

Colorectal Cancer

Colorectal cancer (CRC) is a perplexing multistage disease that has numerous mutations in oncogenes as well as tumor-suppressor genes such as p53, adenomatous polyposis coli (APC) and K-ras mutations [45]. It was found widely in western countries with the highest mortality rates of 70–80%, which occur intermittently, while the rest 20–30% of the cases develop through inherited factors. These uncommon CRC cases lead to obesity, physical inactivity, and changes in environmental as well as lifestyle factors of the individual [46, 47]. In India, the CRC incidence rate was 5.8 per 100,000 people in 2004–2005, rising to 6.9 in 2012–2014 [48]. CRC incidence in younger adults was 3.5 (a 30% increase over a decade), while it was 22.9 (a 22% increase over a decade) in older adults [49]. The increase in DNA oxidation and metabolic rate in CRC is mainly due to the rapid division of epithelial cells where CRC originates and lines the bowel [50]. In daughter cells, this DNA damage cannot be impaired and lead to mutations that could also result in cell cycle arrest, transcription activation, and genomic instability closely linked with the initiation of carcinogenesis in the colon [51]. Though there is no history in the advancement of CRC after inflammatory bowel disease (IBD), there is a major factor that recent inflammation and cancer prototype are being in the epidemiological studies along with its high frequency rate in IBD patients [52]. However, recent evidence has stated that ROS generation has a considerable role in cancer development [53]. Chronic inflammation in the intestine may lead to colon carcinogenesis in both types of IBD patients with Crohn's disease (CD) and ulcerative colitis (UC) [54].

UC, chronic inflammation, is represented by large number of inflammatory cell infiltrations such as neutrophils, lymphocytes, and plasma cells. These infiltrated cells are largely able to generate higher levels of ROS, thereby stimulating OS and various protein-degrading enzymes. These ROS and proteolytic enzymes cause severe damage to cells, which in turn inflate inflammatory damage, which subsequently enters into intestinal mucosal necrosis and ulceration, thereby, leading it to colon [55–57].

JAK/STAT protein acts as a diagnostic as well as prognostic marker that plays a vital role in the development and prolonged survival of CRC that is profoundly seen during lymph node metastasis and tumor infiltration depth [58]. The oxidative modifications of the Cys253 residue dimerize and translocate STAT3 to the nucleus by signaling activation [59]. There are various other passages involved in CRC such as MAPK, Wnt/β-catenin, Notch signaling, and PI3K/AKT. MAPK induces phosphorylation and activation of downstream genes including Ras through S-glutathionylation on the Cys118 residue that generates higher ROS levels leading to CRC [60]. Wnt/β-catenin and Notch signaling are

modulated by NOX as they are redox-sensitive and are involved in proliferation, migration, and differentiation of CRC [61]. PI3K/AKT was intimately linked to CRC where it has a contact between redox-balanced oncogenic signaling and metabolic modification with CRC progression. An NADPH-generating enzyme called methylenetetrahydrofolate dehydrogenase (MTNFD2) was upregulated by c-Myc through KRAS downstream effectors facilitating CRC growth and metastasis that includes PI3K/AKT and ERK pathways [62]. There are two types of receptor molecules that are involved in colon carcinoma progression, namely, positive and negative regulators. Positive regulators include proinflammatory cytokines like IL-1, IL-6, TNF-α, and proinflammatory CC-chemokines. Negative regulators include IL-10 and TIR8 (also called single-immunoglobulin IL-1R molecule, SIGIRR), TGF-β, cyclooxygenase-2 (COX-2), and others like innate immune cells and signaling molecules like toll-like receptors 4 (TLR4), MyD88, and an important transcription factor named NF-κB [52].

In rat colonocytes, the lower crypt cells are prone to be very sensitive to hydrogen peroxide that causes severe damage than the differentiated surface cells. These cells are proliferating, which are the putative target cells of colon carcinogenesis [51]. In humans with colorectal cancer, it was observed that the patients had high RS levels and malondialdehyde (MDA), a product obtained from lipid peroxidation and a decline in the sodium dismutase (SOD) and glutathione (GSH) levels [63]. MDA that acts as a marker for OS enhances the CRC aggression and advancement [64]. The initiation and progression of cancer in colon is illustrated in Fig. 3.

Breast Cancer

Breast cancer (BC) is one of the most common causes of mortality in women. It is diagnosed by dysregulation in various molecular pathways, and the sensitivity differences in the treatment aids in the survival of the inmates [46, 65]. The incidence rate of BC was as high as 25.8 per 100,000 women, with a mortality rate of 12.7 per 100,000 women. Over the years (1984–2014), the age-adjusted incidence rate of breast carcinoma was found to be as high as 41 per 100,000 women in Delhi, followed by Chennai (37.9), Bangalore (34.4), and Thiruvananthapuram (33.7) districts [66]. Chronic inflammation promotes various cellular related changes that initiate ROS production and enhance cell proliferation [67]. OS plays a considerable role in breast cancer associated with dysfunctional adiposity and produces higher levels of ROS through various metabolic ways in obese and type 2 diabetes inmates [68, 69]. Chronic inflammation is a type of cytokine-activated oxidative stress that initiates carcinogenesis in breast by producing instability in the genome which takes it into malignant transformation where the high frequency of DNA damage is linked with metastatic cancer cells increasing the growth and tumorigenic potential [70–72].

Gain in weight and obesity are significant factors in post-menopausal women to predict estrogen-dependent breast cancer (EDBC) [73]. Adipokines secreted from adipose tissue along with inflammatory cytokines and polypeptides are involved in EDBC initiation [74]. In overweight and obese women, the concentration of leptin, TNF-α, and IL-6 correlates with the body mass index (BMI) and directly promotes carcinogenesis; all these are found in estrogen receptor (ER+) patients [75]. Initiation and progression of BC by various factors, including obesity and hypoxia are represented in Fig. 4.

Recent insights provide evidence that the expression of various pro-inflammatory cytokines (COX-2, IL1-b, IL-8, TNF-α) is convoluted in the pathogenesis of BC [76]. These pro-inflammatory cytokines do not directly promote carcinogenesis through

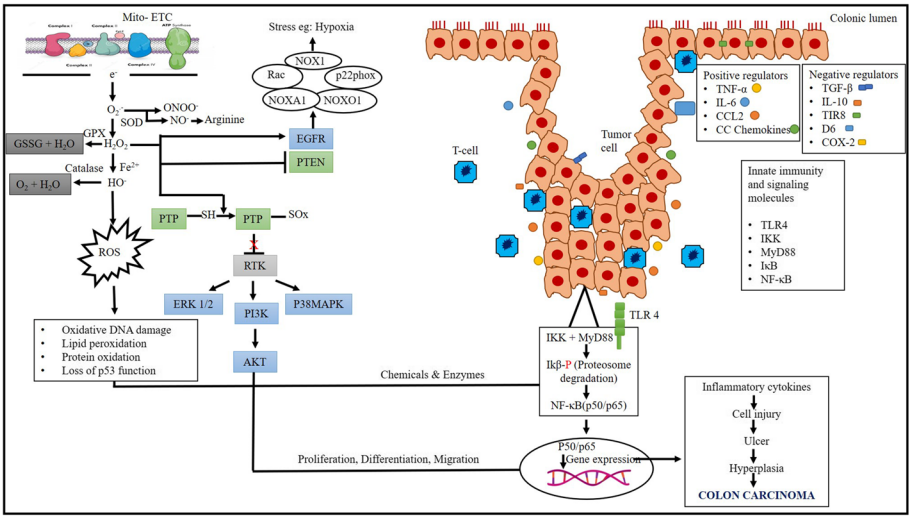

Fig. 3 Colorectal cancer initiation and progression by inflammation and oxidative stress. Colon cancer is caused by excessive ROS production and inflammation leading to abnormal cell proliferation. ROS ($O_2^{\cdot}$, H_2O_2, $OH^{\cdot}$). It is excessively generated from mitochondria leading to oxidation in DNA and protein, peroxidation in lipids, and loss of p53 function. H_2O_2 inhibits phosphatase and tensin homolog gene (PTEN). It also activates protein tyrosine phosphatase (PTP) whose main role is to inhibit the transmembrane protein receptor (RTK). H_2O_2 inhibits the role of PTP and activate Ras-dependent ERK ½, phosphatidylinositol 3-kinase (PI3K), and p38 mitogen-activated protein kinases (P38MAPK) inducing Ak stain transforming (AKT) causing excessive proliferation, differentiation, and movement of CRC. It also induces epidermal growth factor (EGFR), in turn activating NADPH oxidase organizer 1 (NOXO1), NADPH oxidase activator 1 (NOXO1), light chain of human neutrophil cytochrome b (p22phox), NADPH oxidase 1 (NOX1), and Ras-related C3 botulinum toxin substrate (Rac) causing hypoxia condition in colon cancer patients. In the lumen, both the positive and negative regulators along with the innate immune system and signaling molecules activate IKK with MyD88. This will induce IKβ which on phosphorylation degrades proteins and activates NF-κB. All the pathways meet in phosphorylation of NF-κB (p50/p65) which produces inflammatory cytokines making cells injured and causing ulcer that leads to a condition called hyperplasia eventually leading to cancer

obesity-related factors; it is activated either by insulin resistance or by the modification of aromatase activity in adipose tissue [77, 78]. Also, breast cancer development is associated with higher COX-2 levels and ROS production with increased levels of estrogen [79]. It has been stated that IL-8-simulated secretion aids in both invasion and angiogenesis, enhancing tumor growth by causing disturbance to the immune system [80]. Il-6, an inflammatory cytokine, is involved directly in the stimulation of NF-κB/STAT3 and induces insulin resistance [81, 82]. This insulin resistance will downregulate the insulin-like growth factor (IGF)–binding proteins that enhance IGF-1 bioavailability and initiate tumor development in breast [83]. Additionally, necrosis, inflammation, and immune response in tumor cells are related to TNF-α [84]. Frequent cases of worsening BC and a higher expression of TNF-α and IL1-b activate epithelial-to-mesenchymal transition and stimulate movement and adhesion [85]. ROS derived from IL1-b increases malignancy in breast cancer patients by improving cell proliferation and differentiation [86].

Because of weight gain, insulin resistance, IGF-1, and inflammatory and metabolic changes induce oxidative stress which damages nucleic acids, proteins, and lipids, which in turn activates Akt/PI3K/mTOR signaling which acts as a major pathway in promoting tumor growth and progression and modulating the receptor function of estrogen which

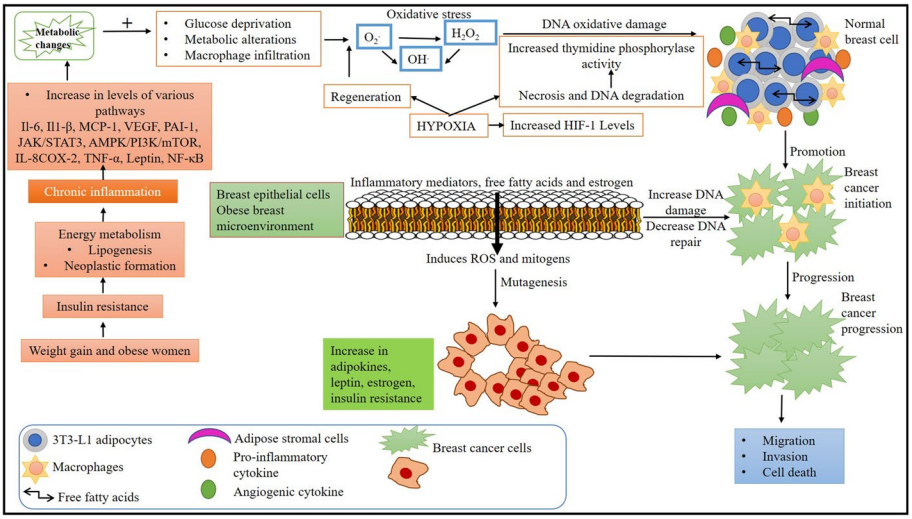

Fig. 4 Breast cancer initiation and progression by inflammation and oxidative stress. In obese women, weight gain roots to the progression of insulin resistance, thereby causing chronic inflammation and increases other pathway levels (IL-6, TNF-α, Leptin, NF-κB, IL-8, COX-2, AMPK/PI3K, VEGF, etc.) linking metabolic changes in the body. These changes along with glucose deprivation and macrophage infiltrations generate OS leading to DNA impairment in normal breast cells where increased HIF-1 levels are observed due to hypoxic stress. Hypoxia also increases necrosis and degradation in DNA, increasing the activity of thymidine phosphorylase in normal cells. All these changes promote the initiation of BC. In breast epithelial cells, inflammatory mediators, free fatty acids, and estrogen increase DNA damage and decrease DNA repair which promote breast cancer. Also, these inflammatory mediators induce ROS and mitogens that increase adipokines, leptin, estrogen levels, and insulin resistance. Inflammatory mediators along with ROS aid in the progression of BC causing intrusion and cell death

is strictly associated with lipid and glucose metabolism for energy and regulation of autophagy [87–91]. The endocrine resistance mechanism is found in ER and PI3K/Akt/mTOR signaling and in ER + MCF-7 cells; tamoxifen resistance is closely related with OS that increases JNK and c-Jun phosphorylation along with enhanced AP-1 activity. Both these resistance blockades stimulate anti-tumor activity in breast cancer models [92, 93].

Doxorubicin is an anthracycline used in BC treatment which generates ROS by disrupting the replication mechanism of DNA by binding to topoisomerase II, leading to DNA damage [94]. Another drug called paclitaxel stabilizes microtubules by modifying the cell division causing cell mortality [95]. Both these drugs cause oxidative stress, and 50% cytotoxic chemotherapy treatment develops resistance to breast cancer [96]. In BC patients, the status of oxidative stress is reported by putative markers derived from lipid peroxidation processes, namely, malondialdehyde, 8-F2-isoprostanes, and 4-hydroxinoenal [97].

Lung Cancer

Lung cancer (LC) is the top most killer cancer that is highly invasive, found in both men and women in the United States of America (US) and causing higher mortality per year than the other next four highest deadliest cancers such as colon, breast, pancreas, and prostate cancers [98] according to the International Agency for Research on Cancer. There

are numerous types of lung cancers, namely, adenocarcinoma, squamous cell carcinoma, SCLC, and NSCLC [99]. LC accounts for 6.9% of all new cancer cases and 9.3% of all cancer-related deaths in both sexes in India; it is the most commonly diagnosed cancer and cause of cancer-related mortality in men, with Mizoram having the highest-documented occurrences in both males and females (age-adjusted rate 28.3 and 28.7 per 100,000 population in males and females, respectively). In Delhi, Chennai, and Bengaluru, the time trends of lung cancer show a significant increase in both sexes. The prevalence and pattern of lung cancer vary by geographic region and ethnicity, and are heavily influenced by smoking [100].

Researchers witnessed that tobacco inhaling contributes as an important risk factor where active smoking is dangerous while passive smoking causes some extent to LC [101]. Smoking is an important factor which causes pulmonary inflammation which activates macrophages, decreases neutrophils clearance, and initiates oxidative stress [101, 102]. Along with smoking, there are various factors contributing to LC, such as ambient air pollution, especially particulate matter (PM), coal and waste burning, indoor air pollutants from non-ventilated kitchens, carcinogenic metals like Cd, Ni, As, and Cr, and ionizing radiation like α- and γ-rays. Other carcinogenic factors include industrial toxic exposures such as iron and steel founding, rubber production, diesel fumes and silica dusts, and organic chemicals with carcinogenic potential such as dioxins and polychlorinated compounds which are attributes for lung cancer when the individual had a long-term exposure to these carcinogens [103]. All the abovementioned extrinsic factors after long-term exposure initially promote oxidative stress followed by chronic inflammation. In inmates with lung cancer, there is a huge level of OS and inflammation in bronchial epithelium [104].

LC development involves various stages, namely, initiation, promotion, and development [105]. In the first stage of initiation, inflammation causes direct damage to DNA causing mutation or an erratic effect stimulated by a variety of enzymes generating ROS leading to DNA and protein damage. Secondly, during promotion of LC, oxidative stress initiates the formation of focal lesions causing invasive cancers. Progression is the last stage where malignant cells are formed from neoplastic clones. c-Jun and c-Fos are oncogenes induced by ROS generated from inflammatory cells. Also, a higher expression of c-Jun was witnessed in LC individuals [106], as illustrated in Fig. 5.

A variety of TFs such as NF-κB, AP-1 (activator protein), p53 (tumor-suppressor gene), HIF-1α, PPAR-γ (peroxisome proliferator-activated receptor gamma), Wbt/β-catenin, and Nrf2 (nuclear factor erythroid 2-related factor 2) are triggered by OS having a considerable role in the initiation and promotion of LC [107, 108]. All these TFs overexpress various other genes, namely, genes of growth factor, inflammatory cytokines, cell-cycle regulatory molecules, and anti-inflammatory molecules. Thereby, OS-stimulated inflammatory pathways transform normal cells into tumor cells, enhancing its durability, proliferation, differentiation, angiogenesis, chemoresistance, and radioresistance. Therefore, OS, chronic inflammation, and LC are closely related [4, 109, 110].

Bladder Cancer

Bladder cancer (BCa) is the fourth most common urinary malignancy ranking ninth among most of the common cancers worldwide [111]. BCa diagnosis is 3–4 times more common in men than in women [112]. In North and North-East India, the age-standardized rate (ASR) for BCa in women is 11.8 per 100,000 and 17.1 per 100,000, respectively. It is equivalent to high-incidence areas such as Bolivia (14) and Chile (9.3), and

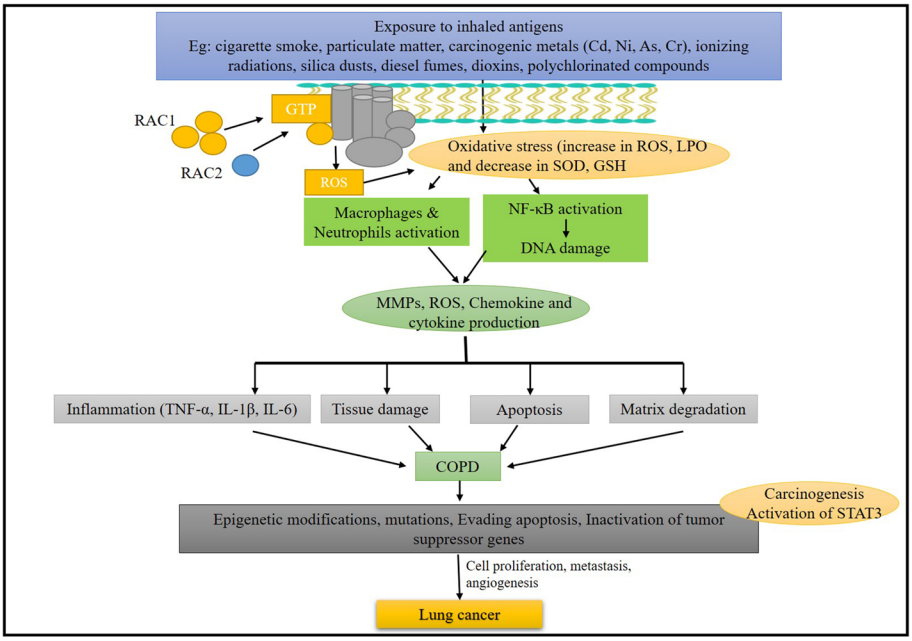

Fig. 5 Lung cancer initiation and progression by inflammation and oxidative stress. Exposure to cigarette smoke, particulate matter, carcinogenic metals, ionizing radiations, silica dusts, diesel fumes, dioxins, and polychlorinated compounds cause oxidative stress. Oxidative stress increases lipid peroxidation (LPO) and ROS and decreases sodium dismutase (SOD) and glutathione (GSH). It activates NF-κB and causes damage to DNA. DNA damage increases the production of matrix metalloproteins (MMPs), ROS, chemokines, and cytokines that induce inflammation, tissue injury, and apoptosis. It brings to a condition of chronic obstructive pulmonary disease (COPD). COPD inactivates tumor-suppressor genes, evades apoptosis, causes mutations, and brings epigenetic modifications. All these conditions enhance cell proliferation, metastasis, and angiogenesis, eventually causing lung cancer

it is higher than in other parts of Asia, including Thailand (7.4), South Korea (6.7), Nepal (6.7), and Bangladesh (5.1). The prevalence of both men and women in India has been steadily increasing. The average age-adjusted rate in women has risen from 6.2 in 2001–2004 to 10.4 in 2012–2014. This data comes from 30 population-based cancer registries across India that were established by the Indian Council of Medical Research (ICMR) [113]. Treatment becomes problematic due to the high cost, multicentric occurrence, and high recurrence rate of bladder cancer [114, 115]. For the past 1 year, platinum-based chemotherapy gave 5-year overall survival rates to patients with metastatic bladder cancer. It is essential to develop an important treatment strategy for bladder cancer to enhance survival rates, reduce adverse effects, and minimize recurrence rate [116].

Industrial as well as environmental chemical exposure (aromatic amines (benzidine and 2-naphthylamine used in the dye industry for the production of rubber, leather, and paints), polycyclic aromatic hydrocarbons) and smoking are the risk factors of bladder cancer [117, 118]. In rodents, one of the main components of tobacco, namely, N-nitrosodibutylamine (BBN), contributes as a stimulant for intracellular ROS-induced oxidative stress leading to DNA damage through adduct formation and DNA strand breaks,

modifies the base, and initiates BCa [119]. Therefore, tobacco smoking increases Bca three times more than non-smoking patients [120].

Malondialdehyde (MDA) is an indicator of lipid peroxidation product produced by arachidonic acid metabolism due to high levels of cyclooxygenase-2 (COX-2) [121]. BCa patients were observed with increased MDA levels in serum. In patients with BCa, COX-2 expression was found to be higher in comparison with normal urothelial individuals. Herewith, a higher COX-2 expression is directly involved in tumorigenesis in BCa [122]. The peroxidation of MDA and other membrane phospholipids might alter membrane permeability and its function. Further granulocyte adhesion was observed as a result of membrane dysfunction. In a viscous space, granulocyte adhesion activates xanthine oxidase and causes higher production of hydrogen peroxide. Also, ROS in these areas activates nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) causing proinflammatory cytokine production (TNF-α or IL-6) stimulating inflammation, thereby enhancing ROS overproduction [123]. Another biomarker is 8-iso-rostaglandin F2-α (8-iso-PGF2-α) reflecting the level of OS, which is formed through oxidation of arachidonic acid [124]. Another enzyme named inducible nitric oxide synthase (iNOS) is associated with oxidative stress generating nitric oxide (NO) [125]. In bladder cancer tissue, urine and serum samples of bladder cancer patients were observed with higher levels of NO [126]. Several studies showed that after surgical treatment in BCa individuals, there was a decrease in levels of NO [127]. The higher levels of NO in BCa are associated with increased expression of iNOS in bladder tumor tissue. Increased iNOS concentration correlated with the progression of advanced stages of bladder cancer [128].

A high number of macrophages and lymphocytes were observed in the inflammatory microenvironment [4]. These immune cells release tumor necrosis factor-alpha (TNF-α) and macrophage migration inhibitory factors with simultaneous provocation of DNA damage [129]. P53-dependent protective responses against cancer cells are impaired by macrophage migration inhibitory factors causing the development of oncogenic mutations [130]. Another pathway associated with macrophage migration inhibitory factor is the RB-E2F pathway. During normal conditions, Rb protein interacts with E2F and inhibits its function. Also, the RB-E2F complex prevents damaged DNA from replication. But higher levels of macrophage migration inhibitory factors correlated with chronic inflammation prevent Rb's inhibition of E2F and contributes to tumorigenesis progression and development [131]. Various cytokines such as IL-6, Il-11, IL-27, and interferons (IFN-α/β/γ) along with their receptors mediate the transformation of urothelial cells to the progression of BCa through JAK/STAT3 (Janus kinase/signal transducer and activator of transcription 3) pathway activation [132]. Silencing of STAT3 suppresses the proliferation of T24 bladder cancer cells [133–135]. Oxidative stress maintains the inflammatory environment promoting the proliferation of bladder cancer cells, as depicted in Fig. 6.

Gastric Cancer

Gastric cancer (GC) is the most common cancer and ranks fifth worldwide. It ranks third among cancer-related deaths. Approximately 18% of people with GC survived in the overall 5-year time period [136, 137]. The incidence of GC is found to be lower in India when compared to the rest of the world. The age-adjusted incidence rate among urban registries in India is 3.0–13.2, compared to the 4.1–95.5 globally. Mizoram has been reported to have the highest incidence of GC in India. The age-adjusted rate in males and females has been reported to be 50.6 and 23.2, respectively [138]. GC pathogenesis is a multifactorial

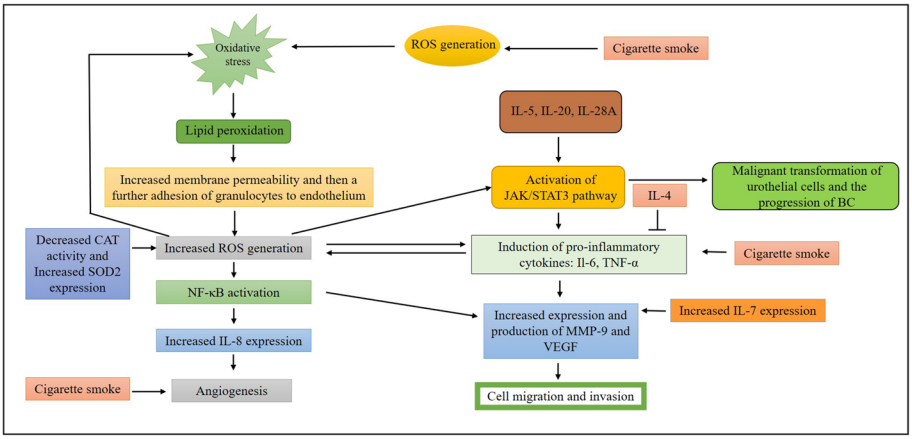

Fig. 6 Bladder cancer initiation and progression by inflammation and oxidative stress. Cigarette smoke induces oxidative stress causing lipid peroxidation that increases membrane permeability. Increase in membrane permeability enhances adhesion of granulocytes that further increase ROS, thereby activating NF-κB followed by increase in IL-8 expression leading to angiogenesis. ROS generation decreases catalase activity and increases sodium dismutase activity. Further, various cytokines activate JAK/STAT3 pathways inducing other pro-inflammatory cytokines. These increases MMP-9 and VEGF expression resulting in cancer cell migration and invasion. Cigarette smoke has direct contact in induction of pro-inflammatory cytokines as well as angiogenesis. The JAK/STAT3 pathway is involved in the transformation of a benign tumor to a malignant one of urothelial cells that progresses BC formation

disease that includes both environmental and genetic factors. Evidence has shown that ROS and inflammatory cytokines play a major role in GC carcinogenesis by inducing DNA damage and altering the function of tumor-suppressor genes [139, 140].

Various factors are involved in GC development, namely, hereditary, smoking, diet habits, environmental factors, and *H. pylori* infection [141]. OS played a major role in Hp-related GC. It is the main risk in GC pathogenesis, causing chronic atrophic gastritis and gastric ulcer followed by gastric cancer. Activation of spermine oxidase (SMOX) in gastric cells leads to induction of GC [142]. First-degree relatives of GC patients are more likely to develop the disease at a 2-to-threefold higher risk [143].

GC is a hazardous threat to the world due to its high prevalence and mortality. Several studies have shown that persons suffering from GC are observed with high levels of OS. Oxidative stress markers such as human oxoguanine glycosylase 1 (hOCG1), xanthine oxidase (XOD), and 8-hydroxy-2′-deoxyguanosine (8-OHdG) are deviant in GC [144, 145]. ROS acts as a signaling molecule triggering the important signaling pathways and promoting GC development. ROS, a secondary messenger, activates tyrosine kinases and MAPK, which leads to cell proliferation in GC [146]. It also targets the stimulation of protein kinase-B (Akt)/mammalian target of rapamycin (mTOR) signaling pathway to enhance cell proliferation in GC [147]. In GC invasion, ROS are more likely to initiate the activation of NF-κB [148].

Inflammation in gastric epithelial cells is known to be closely related to GC development and progression. Inflammation promotes cancer progression through several mechanisms. Some major pathways include activation of NF-κB and Stat3 and the inducement of cyclooxygenase-2/prostaglandin E2 (COX-2/PGE2) [149]. Along with these above mechanisms, innate immune response through the TLR/MyD88 pathway plays a considerable role in tumorigenesis [150]. Inflammation along with oncogene activation enhances

tumorigenesis, and Wnt signaling stimulation accumulates β-catenin facilitating growth of tumor cells. All these changes have been observed in over 50% of gastric cancer individuals [151]. Hp infection, hypoxia, and radiation trigger the cellular ROS followed by inflammation leading to the inhibition of anti-oncogenes, namely, p53 and activation of tumor-related signaling pathways contributing to GC development. The GC initiation and progression by oxidative stress and inflammation is presented in Fig. 7.

Discussion

Oxidative stress is a disproportionate between antioxidants and ROS present in the body. It results in hazardous conditions including cancer, atherosclerosis, neurological problems, perfusion, and diabetes [152]. Generally, the increase in ROS levels damages DNA followed by a signaling cascade stimulated by other TFs and inflammatory cytokines, eventually leading to chronic inflammation [153]. Inflammation is a response triggered by the body to various pathogens, alcohol exposure, toxic chemicals, etc. It is not a disease, rather it is a biological/cellular process which is closely linked with pathophysiology of various other diseases including insulin resistance, T2DM, cardiovascular diseases, and obesity combined with inflammatory diseases [5].

Cancer is an abnormal growth of cells that intracellularly maintains deleterious levels of ROS to enhance oxidative stress and creates a tumor microenvironment with the help of inflammatory cells [154]. Cancer cells adapt to high levels of ROS by modifying sulfur metabolism, NADPH production, and antioxidant activity [155].

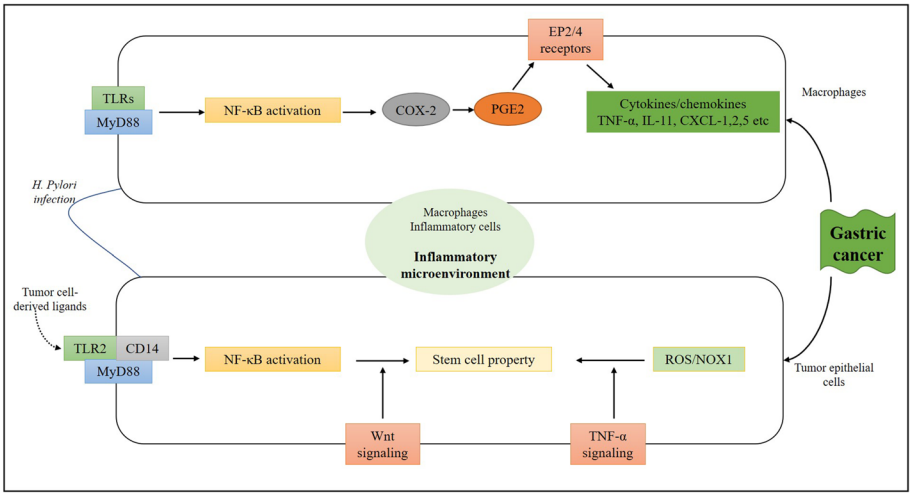

Fig. 7 Gastric cancer initiation and progression by inflammation and oxidative stress. *H. pylori* infection, ROS, and inflammation play a major role in gastric cancer progression. In macrophages, TLRs and MyD88 activate NF-κB that induces COX-2 and PGE2. This complex interacts with EP2/4 receptors and induces cytokines/chemokines such as TNF-α, IL-11, and CXCL-1,2,5. In tumor epithelial cells, tumor cell-derived ligands interact with the TLR2/CD14/MyD88 complex activating NF-κB. Also, the ROS produced in tumor epithelial cells along with NF-κB alters the stem cell property. Both these pathways end up in gastric cancer development and progression

Accumulation of oxidants is witnessed in the oncogenic conversion of normal cells, which is an important requirement for the cancer cells to survive along with the inflammatory mediator's aids in proliferation, differentiation, angiogenesis, metastasis, and invasiveness. Inflammation in the starting stage of a disease activates the immune cells and recruits the cells to the tissue injured site and eliminates the foreign substances. But prolonged inflammation activates various immune cells along with pro-inflammatory and anti-inflammatory cytokines, chemokines, prostaglandins, cyclooxygenase, and ROS and nitric oxide causes OS leading to the enhancement and progression of a diseased state [156, 157]. Therefore, prolonged inflammation along with oxidative stress alters normal cell metabolism and signaling pathways that enhance cancer. Both inflammation and oxidative stress are complex events which conclude with cancer progression, and the cellular mechanisms still remain subtle.

Colorectal cancer is a common cancer worldwide. Excessive ROS/RNS production causes OS, which damages DNA, resulting in cell cycle arrest, transcription factor induction, replication errors, and genomic instability, all of which are associated with colon carcinogenesis [158]. Excessive OS disrupts the extensive and persistent inflammatory response, as evidenced by the upregulation of pro-inflammatory mediators such as COX-2, PGE2, TNF-α, NF-κB, TGF-β, and IL-10. This will result in the development of inflammatory bowel disease (IBD) and as a result forms colon cancer [159].

Breast cancer is highly complex and commonly found in women. Almost 80% of stromal fibroblasts in BC develop an activated phenotype, which is manifested by the secretion of increased levels of growth factors (TNF-α, insulin-like growth factor (IGF), transforming growth factor beta (TGF-β)), cytokines, and metalloproteinases through NADPH oxidase (NOX) [160, 161]. They also produce hydrogen peroxide, which causes the subsequent generation of activated fibroblasts and tumorigenic changes in epithelial cells. When exposed to oxidative stress, the tumor stroma releases high-energy nutrients, which fuel cancer cells and aid in their growth and survival [162].

Lung cancer is initiated through excessive production of ROS and RNS, leading to oxidative stress and inflammation with high DNA damage. OS initiates and progresses cellular and mitochondrial DNA damage, membrane peroxidation, and oxidative damage to proteins. [163]. In turn, oxidative stress from chronic exposure initiates the synthesis of mediators of pulmonary inflammation (TNF-α, IL-1β, IL-6) in lung epithelial cells and contributes to the initiation of carcinogenic mechanisms [164]. These mechanisms are linked with a wide range of biochemical pathways of DNA and lipid membrane oxidative damage, macrophage stimulation, telomere shortening, modulation of gene expression, and activation of transcription factors (p53, NF-κB, Nrf2, AP-1) [165].

Bladder cancer is the most common cancer in people over the age of 65. Environmental and industrial chemicals cause DNA mutations in bladder epithelial cells by stimulating proinflammatory cytokines and proangiogenic factors (TNF-α, VEGF, MMP-9) [166]. These cytokines have an effect on angiogenesis by inhibiting apoptosis. Protein kinase B (AKT) also activates IL-6, which leads to cancer cell survival and apoptosis inhibition in BCa [134, 135, 167].

Gastric cancer is the world's third leading cause of cancer death. ROS levels are dramatically elevated in GC patients, causing genotoxicity and DNA damage. These modifications cause various genomic mutations and the onset of tumorigenesis [168]. It has also been observed that increased OS is associated with an increase in *H. pylori* infection and gastric adenocarcinoma. Infection with *H. pylori* produces ROS by activating several oxidant enzymes, including inducible nitric oxide synthase (iNOS) and NOX. These signaling pathways then activate other pathways, such as Wnt, mTOR and Ras, which initiates GC [169].

Conclusion

DNA damage-mediated oxidative stress activates a variety of inflammatory cytokines that are involved in initiation, promotion, and progression of cancer. Lipid peroxidation and mutagenic product accumulation in DNA contribute to carcinogenesis. Clinical evidence has witnessed that numerous pathways have a major role in linking oxidative stress and inflammation linked with overproduction of ROS is more likely associated with cancer progression. Both oxidative stress and inflammation occur one after the other, which takes part in the pathogenesis of disease.

Author Contribution Loganathan Chandramani Priya Dharshini — conceptualization, writing — original draft, Rajan Radha Rasmi — conceptualization, writing — review and editing; Chinnadurai Kathirvelan — conceptualization, writing — review and editing; Kalavathi Murugan Kumar — conceptualization, writing — review and editing; Kunnathur Murugesan Sakthivel — conceptualization, writing — review and editing.

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Declarations

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