

Complex Interplay between Oxidative Stress and Inflammatory signaling in Development of Neurodegenerative Diseases and Cancer

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Abstract

Introduction

Oxidative stress (OS) and inflammation are closely related with cancer progression and neurodegenerative diseases. Excess ROS generated either oxidize biomolecules or triggers the signaling cascade thereby activating inflammation. The activation of inflammation causes immune cells to secrete cytokines and chemokines which recruits various immune cells to the site of infection or oxidative stress. This interrelation between oxidative stress and inflammation in cancer and neurodegenerative diseases is discussed in the article.

Methods

The role of oxidative stress and inflammation in cancer progression and neurodegenerative disease related literature were collected to obtain data. A narrative review was constructed after obtaining all the relevant information to provide a detailed note on it.

Results

In cancer, OS and inflammation aids in various oncogenic metabolic events including proliferation, differentiation, angiogenesis, migration, invasion, metabolic changes and evading programmed cell death. The disproportion between reactive oxygen species (ROS) and antioxidants in the body is termed as OS which damages the macromolecules (nucleic acids, lipids and proteins). It leads to dysfunction in biological signaling cascade. Prolonged oxidative stress triggers inflammation by stimulating transcription factors (NF- κ B, p53, HIF-1 α , PPAR- γ , Nrf2, AP-1) which altered expression of various other genes and proteins such as growth factors, tumor suppressor genes, oncogenes, pro-inflammatory cytokines etc., triggering cancer cells survival. In neurodegenerative diseases, both OS and inflammation activates astrocytes and microglia, which in turn altered energy metabolism, proteostasis and redox signaling in brain by activating various protein kinases.

Conclusion

The present review article delineates the complex interplay between OS and inflammation in some cancers (Colorectal, breast and lung cancer) and neurodegenerative diseases (Alzheimer's and Parkinson's disease).

1. Introduction

The interplay between oxidation and reduction is invariably pivotal for cellular signalling 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 the 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, signal transduction, etc. 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 predominant in the cells to have potential impact on the rate of mutagenesis [4, 5]. ROS include hydrogen peroxide (H_2O_2), superoxide anion (O_2^-), hydroxyl radical (OH^\cdot), ozone (O_3) and singlet oxygen (1O_2) [6]. All these molecules were regarded deleterious for nucleic acids, lipids and proteins in the beginning. It was then studied that they play 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 endoplasmic reticulum, generation of ROS takes place as a result of protein oxidation [7].

Increase in OS and aerobic respiration are two main attributes of cancer [8]. There is a constant pressure to sustain the balance between ROS and oxidative-stress responses. They demand unlimited energy for their deviant proliferation [9]. They are greatly linked with different types of cancer progression. For instance, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), hepatocellular carcinoma etc. [10, 11]. Many of the oncogenic cellular pathways and genes are evidenced to be combined with oxidative stress responses and epigenetic regulations [12]. 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 [13]. ROS and reactive nitrogen intermediates (RNI) mediate genetic damages causing inflammatory bowel disease (IBD), closely related with colorectal cancer development [14]. Malignancies of breast cancer are delineated by indicative levels of estrogen, being a major one for ROS generation. It initiates proteins intricately 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 involves hypoxia-inducible factors, and endoplasmic reticulum stress responses [15]. Studies on brain pathology suggested an inverse interconnection between hypoxia and OS on the prospects of cancer and neurodegenerative diseases, for instance, sensitivity of nonmalignant glial cells and glioblastoma cancer cells to low oxygen [16]. ROS production has a direct control over the mechanism Epithelial–mesenchymal transition (EMT), that further enables tumor progression by allowing the cancer cells to colonize remote locations [17].

2. Free Radicals- A Bridge Between Inflammation And Cancer

Cancer risks higher when inflammation persists longer than usual. The free radical intermediates derived from nitrogen (RNI) and oxygen (ROI) induces inflammatory cells to the damaged sites of tissues which ends up with cancer progression [18]. Mitochondria, cytochrome P450, peroxisomes and apoplast are the sole production centers of ROI and RNI that stimulates signals for intracellular transduction pathways, cell cycle and metabolism in favorable conditions [19]. Under unfavorable conditions, oxidative stress as well as nitrosative stress implicates the extracellular pathways related to metabolic stress. It reacts with biomolecules in the body to alternate the intra and intercellular equilibrium eventually ruling to cell death [20]. 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 tumor. Interleukins-6 (IL-6), a multifunctional cytokine, levels up during the exposure to an inflammatory stimulus. In BALB/c mice *in-vivo*, prostaglandin (PGE₂) 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* [21]. 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 (Figure 1). It is stated that a toxic radical from nitrogen species namely peroxyxynitrate too stimulates the prostaglandin synthesis [22, 23]. At lower concentrations, the lipid oxidizes to form aldehydes and lipid peroxides acts as a signal transducer of ROI promoting 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 leads to increased oxidative stress [24].

3. Mitochondria Integrate Ros Signaling And Cancer

Mitochondria, a double-membraned organelle composed of matrix, outer and inner mitochondrial membrane (OMM & IMM) with a middle intermembrane space region (IMS). OMM is the first barrier providing permeability of Ca²⁺ 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 [25]. A tight diffusion barrier called IMM, is specialized for the transportation of larger molecules which was allowed by a translocase namely translocases of the inner membrane (TIM) smaller molecules (carbon dioxide, water, oxygen) whereas, the movement of [26]. IMS involves in regulating mitochondrial respiration, transport of protein, lipid equilibrium and exchange of ions whereas matrix involves in diverse metabolic pathways as it contains a circular double-stranded DNA without histones namely mitochondrial DNA (mtDNA) [27].

mtDNA is known for its effective DNA repair mechanism and encodes 13 components for mitochondrial electron transport chain (mtETC) [28], which is composed of 4 complexes. Among those, NADH-CoQ reductase (Complex I) and cytochrome C reductase (complex III) are the major area for the superoxide (O₂⁻) generation [29], which is a byproduct of oxidative phosphorylation (OXPHOS) bioenergetic

metabolism. Superoxide dismutase converts it to H_2O_2 [30]. It leads to loss in mtDNA integrity, reduction in mtDNA copy number and acquires mutations which contribute for various diseases [31]. In addition, the modulation of mtROS production is due to the alterations in Ca^{2+} dynamics and transfer of lipids from endoplasmic reticulum to mitochondria [29]. mtROS together with ATP, cardiolipin, mitochondrial Ca^{2+} are transported to extracellular milieu or cytosol to stimulate the mito-inflammation through enhancing the levels of pro-inflammatory cytokines [32, 33]. It promotes oxidative damage to various organelles and triggers the production of nuclear factor- κ B (NF- κ B), hypoxia-inducible factor 1 (HIF-1) and activator protein-1 (AP-1) that provokes pro-inflammatory cytokines initiation namely Interleukin-6 (IL-6) and Interleukin-8 (IL-8) [34, 35]. The alteration in OXPHOS activity increases the mtROS due to the oxidative damage in mtDNA discharged from matrix interceding impaired mitophagy. These mtROS and mtDNA are identified by the 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 [36, 37].

In cancer, during the initiation and promotion stage, mtROS stimulate oxidation in mtDNA and causes damage. It increases mutation and structural changes in mtDNA with certain effects on expression and signalling in genes [38]. All these favours the apoptotic evasion in the advancement stage of cancer. It aids not only in the genomic instability but also influences the inflammatory cytokines of tumour cells and activates several transcription factors that modifies the energy of cancer cells [37]. In 1930s, Otto Warburg was the first to state that cancer is caused by mitochondrial dysfunction. Cancer cells adopt aerobic glycolysis to produce energy instead of OXPHOS in mitochondria which is called as Warburg switch [39]. A study stated that tumour progression is inhibited by preventing the lactate conversion from pyruvate by lactate dehydrogenase [40]. By stimulating the metabolism in mitochondria by OXPHOS, cancer cells proliferation is arrested [41]. 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 [42]. All these findings state that cancer cells undergo Warburg effect that affects cellular events and increase in mtROS production. The pro-inflammatory cytokines increase the ROS production in mitochondria which enhances cancer progression (Figure 2).

4. Inflammation And Oxidative Stress In Pathogenesis Of Diseases

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 tumour neovascularization, invasion in tumour-associated basement membrane, angiogenesis and metastasis. ROS, an effector molecule participates in host defence or acts as chemo-attractants volunteering leukocytes to wounded site, thereby prompting inflammatory reaction in tissue injured area. There are various cancer and diseases that are caused by oxidative stress followed by inflammation.

4.1 Colorectal cancer

Colorectal cancer (CRC) is a perplexing multistage disease that has numerous mutations in oncogene as well as tumor suppressor genes such as p53, adenomatous polyposis coli (APC) and K-ras mutations [43]. was found widely in western countries with the highest mortality rates of 70-80% that occurs intermittently while the rest 20-30% of the cases develop through inherited factors. These uncommon CRC cases leads to obesity, physical inactivity, changes in environmental as well as lifestyle factors of the individual etc [44, 45]. 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 [46]. In daughter cells, these DNA damages cannot be repaired and leads to mutation that could also result in cell cycle arrest, transcription activation, genomic instability closely linked with the initiation of carcinogenesis in colon [47]. 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 [48]. However, recent evidences stated that the ROS generation has a considerable role in cancer development [49]. The chronic inflammation in the intestine may leads to colon carcinogenesis in both type of IBD patients with Crohn's disease (CD) and ulcerative colitis (UC) [50] (Figure 3).

UC, a chronic inflammation is represented with large number of inflammatory cell infiltrations such as neutrophils, lymphocytes, plasma cells etc. These infiltrated cells are largely to generate higher levels of ROS, thereby stimulating OS and various protein degrading enzymes. These ROS and proteolytic enzymes cause severe damages to cells, which in turn inflame inflammatory damage, which subsequently enters into intestinal mucosal necrosis and ulceration, thereby, leading it to colon [51–53].

JAK/STAT protein acts as diagnostic as well as prognostic marker that has a vital play in the development and prolonged survival of CRC that is profoundly seen during lymph node metastasis and tumor infiltration depth [54]. The oxidative modifications of Cys253 residue, dimerizes and translocate STAT3 to nucleus by signalling activation [55]. There are various other passages involved in CRC such as MAPK, Wnt/ β -catenin and Notch signalling, PI3K/AKT. MAPK induces phosphorylation and activation of downstream genes including Ras through S-glutathionylation on Cys118 residue that generates higher ROS levels leading to CRC [56]. Wnt/ β -catenin and Notch signalling are modulated by NOX as they are redox-sensitive and are involved in proliferation, migration and differentiation of CRC [57]. PI3K/AKT was intimately linked to CRC where it has a contact between redox balanced oncogenic signalling 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 [58]. 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 such as IL-10, TIR8 (also called single immunoglobulin IL-1R molecule, SIGIRR), TGF- β , cyclooxygenase-2 (COX-2) and others like innate

immune cells and signalling molecules like toll-like receptors 4 (TLR4), MyD88 and important transcription factor named NF- κ B [48].

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 [47]. In human with colorectal cancer, it was observed that the patients had high RS levels and malondialdehyde (MDA), a product obtained from lipid peroxidation and decline in the sodium dismutase (SOD) and glutathione (GSH) levels [59]. MDA that acts as a marker for OS enhance the CRC aggression and advancement [60].

4.2 Breast cancer

Breast cancer (BC) is one of the most common cause 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 [44, 61]. Chronic inflammation promotes various cellular related changes that initiates ROS production and enhances cell proliferation [62]. OS has a considerable play in breast cancer associated with dysfunctional adiposity and produces higher levels of ROS through various metabolic ways in obese and type 2 diabetes inmates [63, 64]. Chronic inflammation is a type of cytokine-activated oxidative stress that initiates carcinogenesis in breast by producing instability in genome which takes it into malignant transformation where high frequency of DNA damage is linked with metastatic cancer cells increasing the growth and tumorigenic potential [65–67].

Gain in weight and obesity are of significant factor in post-menopausal women to predict the estrogen-dependent breast cancer (EDBC) [68]. Adipokines secreted from adipose tissue along with inflammatory cytokines and polypeptides are involved in EDBC initiation [69]. In overweight and obese women, concentration of leptin, TNF- α and IL-6 correlates with body mass index (BMI) and directly promotes carcinogenesis and all these are found in estrogen receptor (ER+) patients [70] (Figure 4).

Recent insights provide evidences that various pro-inflammatory cytokine (COX-2, IL1-b, IL-8, TNF- α) expression are convoluted in pathogenesis of BC [71]. These pro-inflammatory cytokine does not directly promote carcinogenesis through obesity related factors either it activates by insulin resistance or by the modification of aromatase activity in adipose tissue [72, 73]. Also, breast cancer development is associated with higher COX-2 levels and ROS production with increased levels of estrogen [74]. It has been stated that IL-8 simulated secretion aids in both invasion and angiogenesis enhancing tumor growth by causing disturbance to immune system [75]. IL-6, an inflammatory cytokine is involved directly in the stimulation of NF- κ B/STAT3 and induces insulin resistance [76, 77]. This insulin resistance will downregulate the insulin-like growth factor (IGF) binding proteins that enhances the IGF-1 bioavailability and initiates tumor development in breast [78]. Additionally, necrosis, inflammation and immune response in tumor cells are related with TNF- α [79]. Frequent cases of worsenning BC, higher expression of TNF- α and IL1-b activates epithelial to mesenchymal transition and stimulates movement and adhesion [80]. ROS derived from IL1-b increases malignancy in breast cancer patients by improving cell proliferation and differentiation [81].

Because of weight gain, insulin resistance, IGF-1, inflammatory and metabolic changes, induces oxidative stress which damages nucleic acids, proteins, lipids, in turn activates Akt/PI3K/mTOR signalling which acts as a major pathway in promoting tumour growth, progression and modulating the receptor function of estrogen which is strictly associated with lipid, glucose metabolism for energy and regulation of autophagy [82–86]. The endocrine resistance mechanism is found in ER and PI3K/Akt/mTOR signalling 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 blockade stimulates anti-tumor activity in breast cancer models [87, 88].

Doxorubicin is an anthracycline used in BC treatment generates ROS by disrupting replication mechanism of DNA by binding to topoisomerase II leading to DNA damage [89]. Another drug called Paclitaxel stabilizes microtubules by modifying cell division causing cell mortality [90]. Both these drugs cause oxidative stress and 50% cytotoxic chemotherapy treatment develop resistance to breast cancer [91]. In BC patients, status of oxidative stress is reported by putative markers derived from lipid peroxidation process namely malondialdehyde, 8-F2-isoprostanes and 4-hydroxinoenal [92].

4.3 Lung cancer

Lung cancer (LC) is the top most killer cancer that is highly invasive, found both in men and women in United States of America (US) that causes higher mortality per year than the other next four highest deadliest cancer such as colon, breast, pancreas and prostate cancer death [93] according to International Agency for Research on Cancer. There are numerous types of lung cancers include adenocarcinoma, squamous cell carcinoma, SCLC and NSCLC [94].

Researches witnessed that tobacco inhaling contributes as an important risk factor where active smoking is dangerous while passive smoking causes some extend to LC (Doll and Hill, 1950). Smoking, an important factor causes pulmonary inflammation that activates macrophages, decreases neutrophils clearance and initiates oxidative stress [95, 96]. Along with smoking, there are various factors contributes 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, Cr, ionizing radiation like α , 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 that attributes for lung cancer when the individual had long term exposure to these carcinogens [97]. All the above-mentioned extrinsic factors after long term exposure initially promotes oxidative stress followed by chronic inflammation. Inmates with lung cancer, there is a huge level of OS and inflammation in bronchial epithelium [98].

LC development involves various stages namely initiation, promotion and development [99]. In the first stage of initiation, inflammation causes direct damage to DNA causing mutation or erratic effect stimulated by 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 re

oncogenes induced by ROS generated from inflammatory cells. Also, higher expression of c-Jun was witnessed in LC individuals [100] (Figure 5).

A variety of TF such as NF- κ B, AP-1 (activator protein), p53 (tumor suppressor gene), HIF-1 α , PPAR- γ (peroxisome proliferator-activated receptor gamma), Wnt/ β -catenin, Nrf2 (nuclear factor erythroid 2-related factor 2) are triggered by OS having a considerable role in initiation and promotion of LC [101, 102]. All these TF overexpresses various other genes namely genes of growth factor, inflammatory cytokines, cell-cycle regulatory molecules and anti-inflammatory molecules. Thereby, OS stimulated inflammatory pathways transforms normal cell to tumor cell, enhancing its durability, proliferation, differentiation, angiogenesis, chemoresistance and radioresistance. Therefore, OS, chronic inflammation and LC are closely related [103–105].

4.4 Alzheimer's disease

Alzheimer's disease (AD) is a complex neurodegenerative disease. It is often linked with aged-dementia and extensive neuronal loss in hippocampus, amygdala, enterorhinal and neocortex regions which is separated into familial AD (FAD) and sporadic forms [106, 107]. Various genes involved with the accretion of fibrillar proteins. Example: extra-cellular amyloid β (A β) plaques and neurofibrillary tangles (NFTs) have been identified and it leads to death after 3-9 years of diagnosis. These genes are a direct causative forms during the early-onset of the disease. Example: Amyloid precursor protein (APP) gene (chromosome 21) and presenilin (PS) genes 1 and 2 (chromosomes 14 and 1). Mutations identified on the APP, PS1 or PS2 genes result in amyloidogenesis means, the increased production of β -amyloid peptide [108]. The symptoms are dysfunction ranging from slow to progressive cognitive skills, decline in memory, language disturbances and physical disabilities [109].

Besides the pathological expression in AD, diseased brain evidences are reported caused as substantial damage due to brain atrophy, chronic inflammation, oxidative stress, extracellular and intracellular deposition of A β and NFTs respectively leading to neurodegeneration [110]. When the natural antioxidant, glutathione level becomes low and the neural membranes contain a higher ratio of polyunsaturated fatty acids, the neurons become extremely vulnerable to free radicals and the brain metabolism will require a considerable amount of oxygen [111]. Studies from both dead and live patients, along with transgenic mouse models, shows insights of the bridge between ROS, inflammation and AD. Several surrogate markers of ROS-mediated injury are found to be greatly enlarged in the brain and cerebrospinal fluid of AD patients. A few, such markers mentioned are 1) LPO - malondialdehyde, 4-hydroxynonenal, F2-isoprostanes 2) protein oxidation - protein carbonyls, nitrotyrosine 3) DNA oxidation - 8-hydroxy-2'-deoxyguanosine, respectively [112]. Insulin regulates appetite, glucose level and homeostasis of lipid in hypothalamus of the brain. So, when insulin signaling and transport of glucose is disrupted, it predominantly causes AD [113, 114] (Figure 6).

TREM2 gene associated with sporadic AD codes for cell surface protein. The knockdown of this gene brings cognitive impairment followed by the high levels of pro-inflammatory cytokines such as IL-6 and TNF- α , and decline in anti-inflammatory cytokines namely IL-10 in senescence-accelerated mouse prone-

8 (SAMP8) brain model [115]. An adaptor protein named DAP12 associates with TREM2 that serves as an important factor for survival, proliferation, chemotaxis and phagocytosis of microglia in mice [116]. Microglia- predominant immune cells, involved in the homeostasis of central nervous system (CNS) during stress, disease, trauma and pathology and also attributed to the remodeling of neuronal circuits [117–119]. Either these immune cells exert neuroprotection by the phagocytic mechanism on A β , subsequently the loss in function exacerbate amyloidosis followed by inflammation, synaptic loss and further leads to neuronal loss [120, 121], or the inability of the microglial to clear A β fails, it activates pro-inflammatory passage leading to inflammation and OS in AD [122, 123].

ROS generated in the neurons interacts with any of the biomolecule causing oxidative stress to proteins. It breaks down the metabolism process, proteostasis and redox motion in the brain by stimulating various stress-related protein kinases namely JNK, mitogen activated protein kinase (p38) and ERK1/2 or brings about oxidative modifications in redox-sensitive transcription factors [124, 125]. ROS generated from two sources serves as a major donor to the AD pathophysiology includes transition metals like Fe and Cu acts as a ligand to A β and also mitochondrial dysfunction.

In addition, ROS from activated microglia induces inflammatory response in the brain of AD patients where NOX has a considerable play role in AD [126, 127]. The upregulation of microglial NOX2 is triggered from multiple sources like A β 42. Along with NOX2 derived ROS, proinflammatory cytokines, chemokines further activate microglia and causes neuronal damage through linking inflammation and oxidative damage in the pathogenesis of AD [128].

4.5 Parkinson's disease

Parkinson's disease (PD) is recognized by the cumulative neurodegeneration of pigmented nigrostriatal dopaminergic neurons (DA) and Lewy bodies formation, which are eosinophilic inclusions comprising intracytoplasmic aggregates of α -synuclein. The clinical manifestations of PD have both motor and non-motor signs. The major motor indications of PD are akinesia (complication in starting voluntary actions), bradykinesia (leisure down of movements) and extrapyramidal rigidity (muscle groups become stiffer) [129].

The general factors behind neuronal degeneration are environmental toxins, genetic factors and oxidative stress. OS is linked with PD progression in highly oxidative conditions that generally prevail in DA. Mitochondrial dysfunction is also documented in PD. For instance, respiratory enzyme in complex-I was suppressed by the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) causing PD. Moreover, tetrahydrobiopterin, an endogenous compound inhibits mitochondrial complexes I and IV, causing malfunction in the electron transport chain, oxidative stress and conclusively has PD symptoms [130]. In the pathogenesis of PD, increasing recognition of neuroinflammation to have a possible role are witnessed. They are shown to be stimulated by the vulnerability to infectious particles with pro-inflammatory characteristics [131] (Figure 7).

DA loss was witnessed due to oxidative stress that progresses to PD [132]. These unstable neurons oxidize to form quinone and H_2O_2 in the brain of PD patients simultaneously reacting with oxygen or iron forming hydroxyl radical (OH^-). Dopaminergic neurotoxicity is caused by the interaction of DA quinone synthesized from catechin epoxidation of dopamine and cysteine residues where DA is inactivated by the removal of sulfhydryl groups, interferes with dysfunction of mitochondria and protein functions is inhibited [133, 134]. Sulfhydryl groups in the proteins react with DA metabolites and form adducts which damages the intracellular thiol group, aids with the advancement of PD [135]. Also, OS causes a disproportionate in the build-up of ROS bringing mitochondrial dysfunction [136]. Recent evidence suggested that rotenone (ROT) is another major risk factors in the PD pathophysiology [137].

Neuronal inflammation is mainly due to the microglia stimulation. Various studies stated that in PD patients with microglial overactivation, neuronal cell death was observed in substantia nigra [138, 139]. In addition, stimulated microglia are found in other regions of brain namely basal ganglia and pontine [140]. This microglia in activated form are composed of two different cells having opposite functions. The polarized microglia are of two extremes namely M1 pro-inflammatory (classically activated) and M2 anti-inflammatory (alternately activated) phenotypes [141]. M1 is morphologically altered and discharges numerous inflammatory components (TNF- α , IT-1, IL-6 and nitric oxide (NO)) leading to DA neuronal loss in PD patients [142]. M2 synthesizes anti-inflammatory cytokines (IL-4, IL-13, IL-10, TGF) via phagocytic effects that reduces inflammation and repairs the inflammatory response thereby microglia-mediated neuroinflammation plays both as positive and negative response in PD progression [143, 144]. Oxidative stress and neuroinflammation plays major role in PD through microglia-mediated neurotoxicity using two mechanisms. NOX activation induces the generation of huge extracellular ROS and also increases ROS intracellularly in microglia. This microglia-mediated OS stimulates pro-inflammatory genes generation [145].

Table 1
Oxidative stress and inflammation in certain disease and cancer and its mechanism

S. No	Diseases	Mechanism	Reference
1.	Alzheimer's disease	T2DM is due to resistance in insulin level playing a considerable part in Alzheimer's disease. Chronic inflammation and OS combined with T2DM enhances the build-up of A β protein and tangles in neurons along with mitochondrial dysfunction leading to the formation of AD.	[145]
2.	Parkinson's disease	Exogenous and endogenous factors induce OS in the brain. While, neuroinflammation is due to the deposition of huge amount of proinflammatory factors through blood brain barrier. Recent studies reported that lipopolysaccharides induce chronic inflammation along with rotenone-induced ROS to stimulate the damage and create a progressive loss in dopamine neurons that leads to formation of Lewy bodies and α -synuclein accumulation causing PD.	[146]
3.	Prion disease	It is transmissible neurodegenerative disease that is incurable caused by misfolding of cellular protein (PrP ^{sc}). Higher oxidative stress level, initiates the normal prion protein (PrP ^c) conversion to infectious prion protein (PrP ^{sc}). Along with PrP ^{sc} , metal ions like Cu and Fe interacts in the progression of prion disease. PrP ^{sc} accumulation in neurons enhances inflammation causing loss of function in neurons and leads to neuronal death.	[147]
4.	Colorectal cancer	One mechanism in the pathogenesis of colon cancer, ulcerative colitis. It is a chronic inflammation caused by variety of infiltrated cells which generate ROS stimulating oxidative stress. These stress damages nucleic acids, followed by inflammatory damage and subsequently causes necrosis and ulceration in intestine, leading to the formation of colon carcinogenesis.	[148, 149]
5.	Breast cancer	Various pro-inflammatory cytokines activate breast cancer by activating insulin resistance and modifying aromatase activity in adipose tissue. In addition, cytokines IL-1 β generates ROS and enhances cell proliferation and differentiation in breast cancer cells.	[150]
6.	Lung cancer	Chronic inflammation is stimulated by various external factors namely viruses, bacteria, smoke, pollution etc. This type of inflammation induces ROS and affects the hepatocytes, leading to the initiation and progression of LC.	[151]
7.	Bladder cancer	Overproduction of ROS enhances proinflammatory cytokines (IL-6, TNF- α) promoting proliferation in cancer cells. Also, cytokines enhance ROS generation thereby, forming a cyclic phenomenon. Additionally, JAK/STAT-3 pathway closely related with malignant transformation of urothelial cells that progresses bladder cancer.	[152]
8.	Gastric cancer	In gastric cancer, inflammation and OS are linked with <i>H. pylori</i> that damages DNA. This DNA damage induced progression of gastric cancer from normal infection stage.	[153]

5. 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, diabetes and many more [154]. Generally, when ROS levels are increased it damages DNA followed by a signalling cascade stimulated by other TFs and inflammatory cytokines eventually leading to chronic inflammation [155]. 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, obesity combined inflammatory diseases [156].

Cancer is an abnormal growth of cells that intracellularly maintains deleterious level of ROS to enhance oxidative stress and creates a tumor microenvironment with the help of inflammatory cells [157]. Cancer cells adapt to high levels of ROS by modifying sulphur metabolism, NADPH production and antioxidant activity [158].

Neurodegenerative disorders are gradual loss of particular liable group of neurons due to metabolic or toxic diseases. It is classified into three types namely early clinical features (eg: motor neuron disease, dementia), anatomic neurodegeneration (eg: extrapyramidal disorders, frontotemporal degenerations) or principal molecular abnormality [159]. Recent evidence witnessed that genetic alterations, cellular changes and circuit dysregulation in brain leads to cognitive hallmarks of neurodegenerative diseases [160].

Accumulation of oxidants are 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 cell to tissue injured site and eliminate the foreign substances. But prolonged inflammation activates various immune cells along with pro-inflammatory and anti-inflammatory cytokines, chemokines, prostaglandins, cyclooxygenase and ROS as well as nitric oxide causes OS leading to the enhancement and progression of diseased state [161, 162]. Therefore, prolonged inflammation along with oxidative stress alters normal cell metabolism and signalling pathways that enhances cancer and other pathological neurodegenerative disease. Both inflammation and oxidative stress are complex events which concludes with the cancer as well as neurodegenerative disease progression and the cellular mechanism still remains subtle.

6. Conclusion

This review mainly focusses on the role of oxidative stress and inflammation and their complex interplay in cancer and neurodegenerative disease. Numerous pathways have a considerable play in linking oxidative stress and inflammation in various cancers and neurodegenerative diseases. Either oxidative stress appears first or inflammation occurs. Both the oxidative stress and inflammation occurs one after other, which take part in pathogenesis of disease.

Declarations

Data Availability

Not Applicable.

Author contributions

All authors contributed to the study conception and design. The first draft of the manuscript was written by LCP. KMS, CK and RRR provided critical revisions of the work. All authors read and approved the final manuscript.

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Compliance with ethical standards

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Conflicts of interest

The authors declare they have no conflicts of interest.

Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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Figures

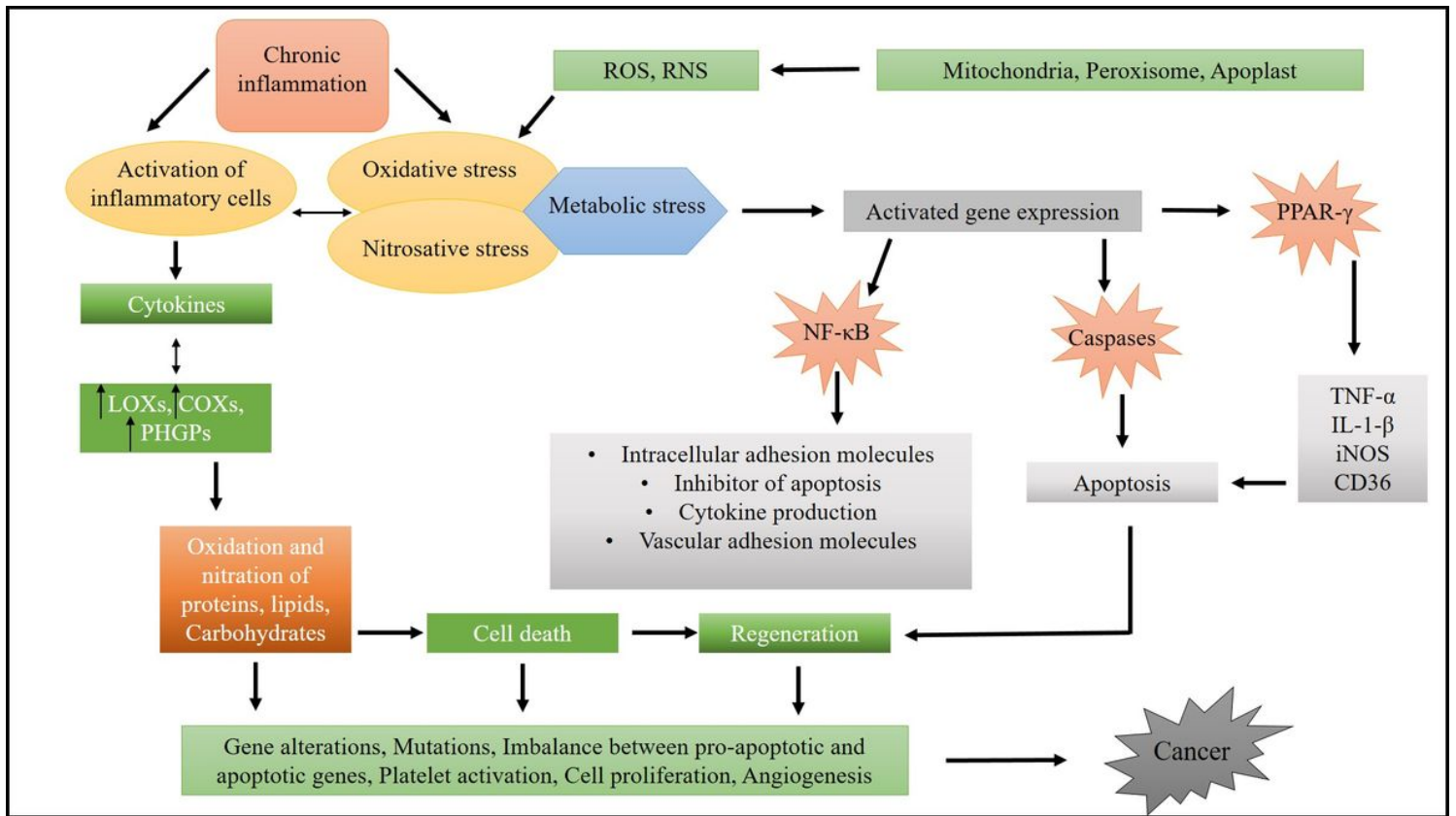


Figure 1

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 induces 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 environment that simultaneously leading to regeneration, cell death and eventually causing cancer through gene alterations, mutations, proliferation, angiogenesis etc.

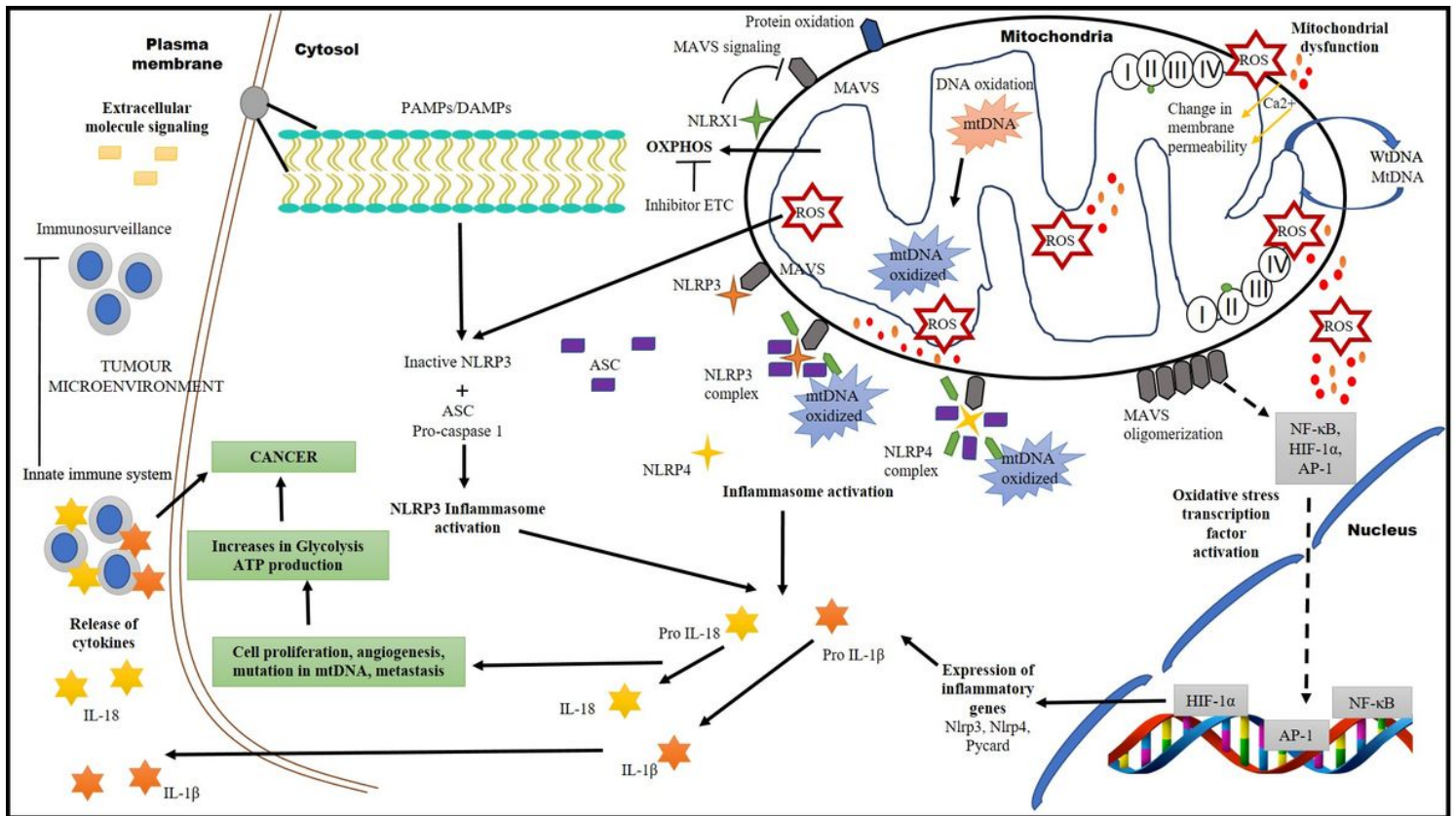


Figure 2

mtROS leads to Mito-inflammation that induces cancer. In mitochondria, excess releases of ROS oxidize mitochondrial DNA and also excess calcium in mitochondria changes membrane permeability thereby causing mutation in mtDNA and brings about dysfunction in mitochondria. Inflammasome activation is 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 expresses 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 plasma membrane on interaction with ROS and ASC Pro-caspase 1 also form NLRP3 inflammasome complex. All the three mechanisms, simultaneously activates IL-18 and IL-1β that enhances proliferation, angiogenesis, metastasis and DNA mutation that increases glycolysis and ATP production causing cancer. In tumor microenvironment, immunosurveillance takes place by innate immune system which is inhibited due to the proliferation of cancer cells.

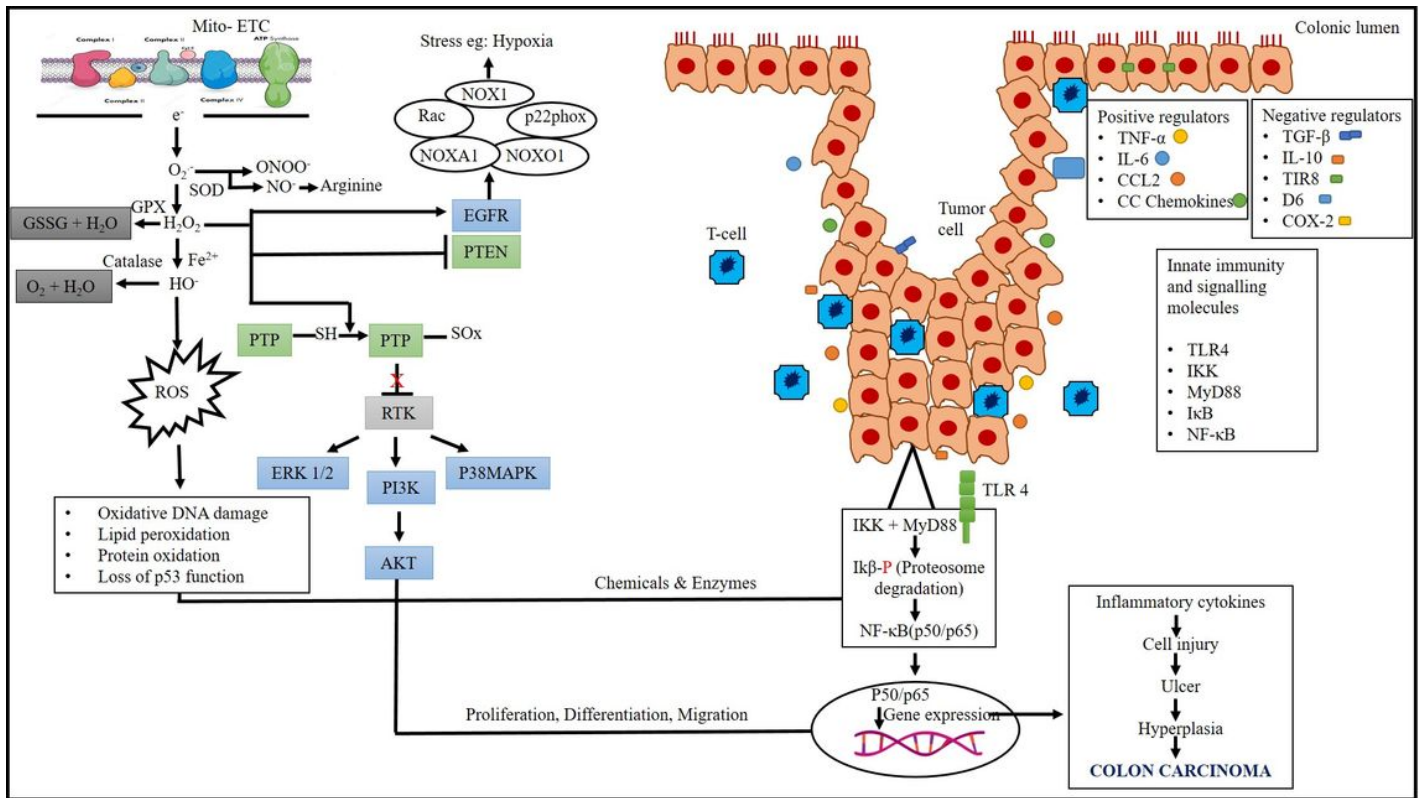


Figure 3

Colorectal cancer initiation & progression by inflammation and oxidative stress. Colon cancer is caused excessive ROS production and inflammation leading to abnormal cell proliferation. ROS (O_2^- , H_2O_2 , OH^-) 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) which main role is to inhibit transmembrane protein receptor (RTK). H_2O_2 will inhibit the role of PTP and activates Ras-dependent ERK $\frac{1}{2}$, Phosphatidylinositol 3-kinase (PI3K) and p38 mitogen-activated protein kinases (P38MAPK) inducing Akt transforming (AKT) causing excessive proliferation, differentiation and movement of CRC. It also induces epidermal growth factor (EGFR), in turn activates NADPH oxidase organizer 1 (NOX1), NADPH oxidase activator 1 (NOXA1), human neutrophil cytochrome b light chain (p22phox), NADPH oxidase 1 (NOX1), 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 innate immune system and signalling molecules activates IKK with MyD88. This will induce $I\kappa B$ which on phosphorylation degrades proteins and activates NF- κB . All the pathways meet in phosphorylation of NF- κB (p50/p65) which produces inflammatory cytokines that making cell injured and causing ulcer that leads to a condition called hyperplasia eventually leading to cancer.

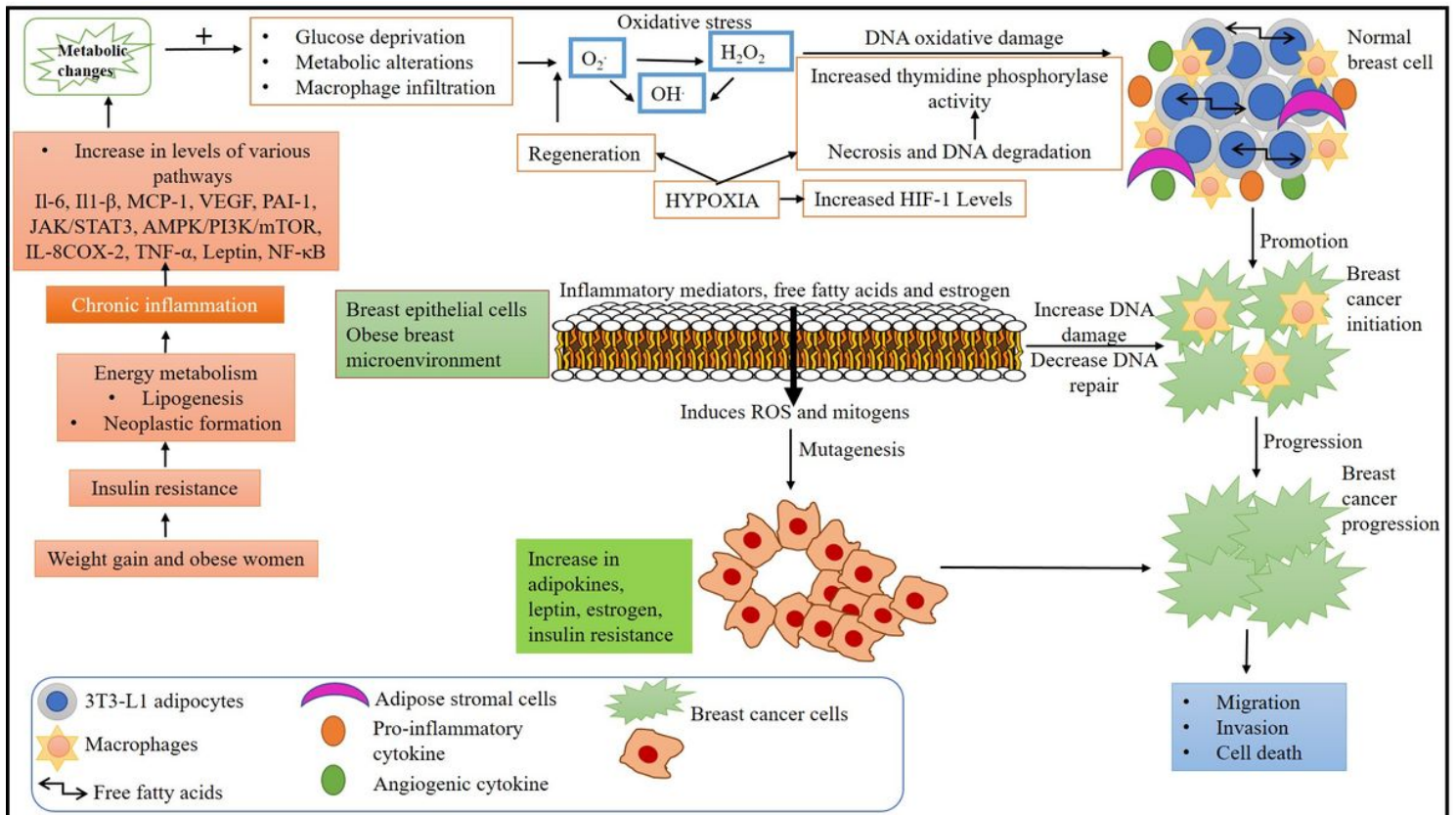


Figure 4

Breast cancer initiation & 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- κ B, IL-8, COX-2, AMPK/PI3K, VEGF etc.) linking metabolic changes in the body. These changes along with glucose deprivation and macrophage infiltrations generates 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 increases DNA damage and decreases DNA repair that promotes breast cancer. Also, these inflammatory mediators induce ROS and mitogens that increases adipokines, leptin, estrogen levels and insulin resistance. Inflammatory mediators along with ROS aids in the progression of BC causing intrusion and cell death.

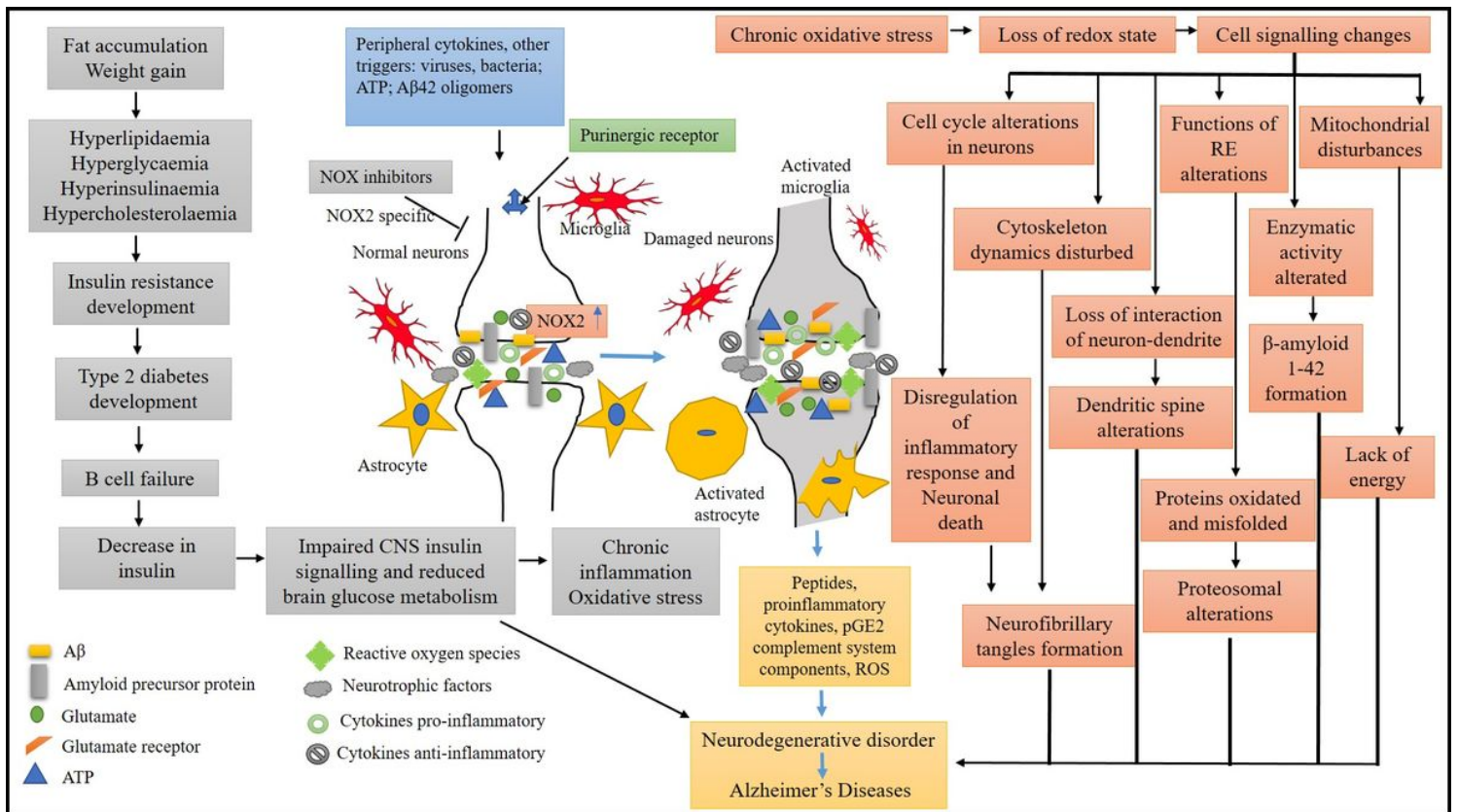


Figure 5

Lung cancer initiation & progression by inflammation and oxidative stress. Exposure to cigarette smoke, particulate matter, carcinogenic metals, ionizing radiations, silica dusts, diesel fumes, dioxins, polychlorinated compounds cause oxidative stress. Oxidative stress increases lipid peroxidation (LPO), ROS and decreases sodium dismutase (SOD), 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 induces 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.

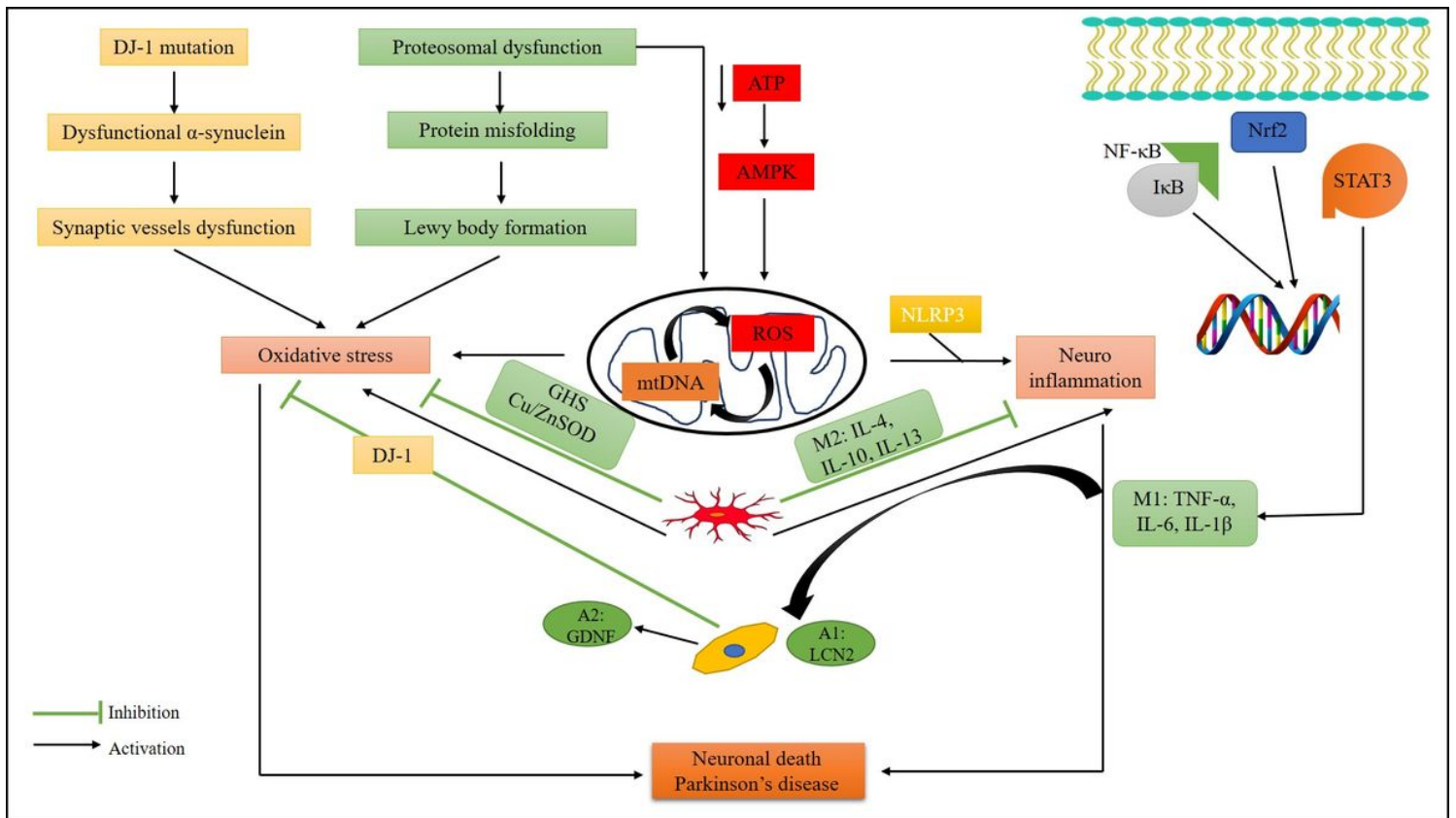


Figure 6

Alzheimer's disease initiation & progression by inflammation and oxidative stress. Fat accumulation, weight gain, viruses, bacteria, ATP, A β 42 oligomers, inflammation and chronic OS has an important part in Alzheimer's disease progression. First, accumulation of fat gains weight causing resistance in insulin level and developing T2DM. This causes failure in B cell thereby decreases in insulin production reducing glucose metabolism in brain. Decrease in metabolism increases chronic inflammation and oxidative stress. Second, peripheral cytokines, ATP, viruses, bacteria, A β 42 oligomers increases NOX2 in normal neurons and activates microglia and astrocyte that damages neurons. Damaged neurons contain higher levels of pro-inflammatory, anti-inflammatory cytokines, neurotrophic factors, ROS, ATP, glutamate, its receptors, A β which increases inflammation and ROS in neurons. Third, due to chronic OS results in loss of redox environment brings cell signalling changes. These changes alter cell cycle causing dysregulation in inflammatory response and neuronal death, alters enzymatic activity leads to the formation of β -amyloid 1-42, disturbances in cytoskeleton dynamics causing neurofibrillary tangles, mitochondrial dysfunction leads to energy loss, alteration in RE functions leading to protein oxidation and misfolding and loss in neuron-dendrite interaction eventually leading to AD.

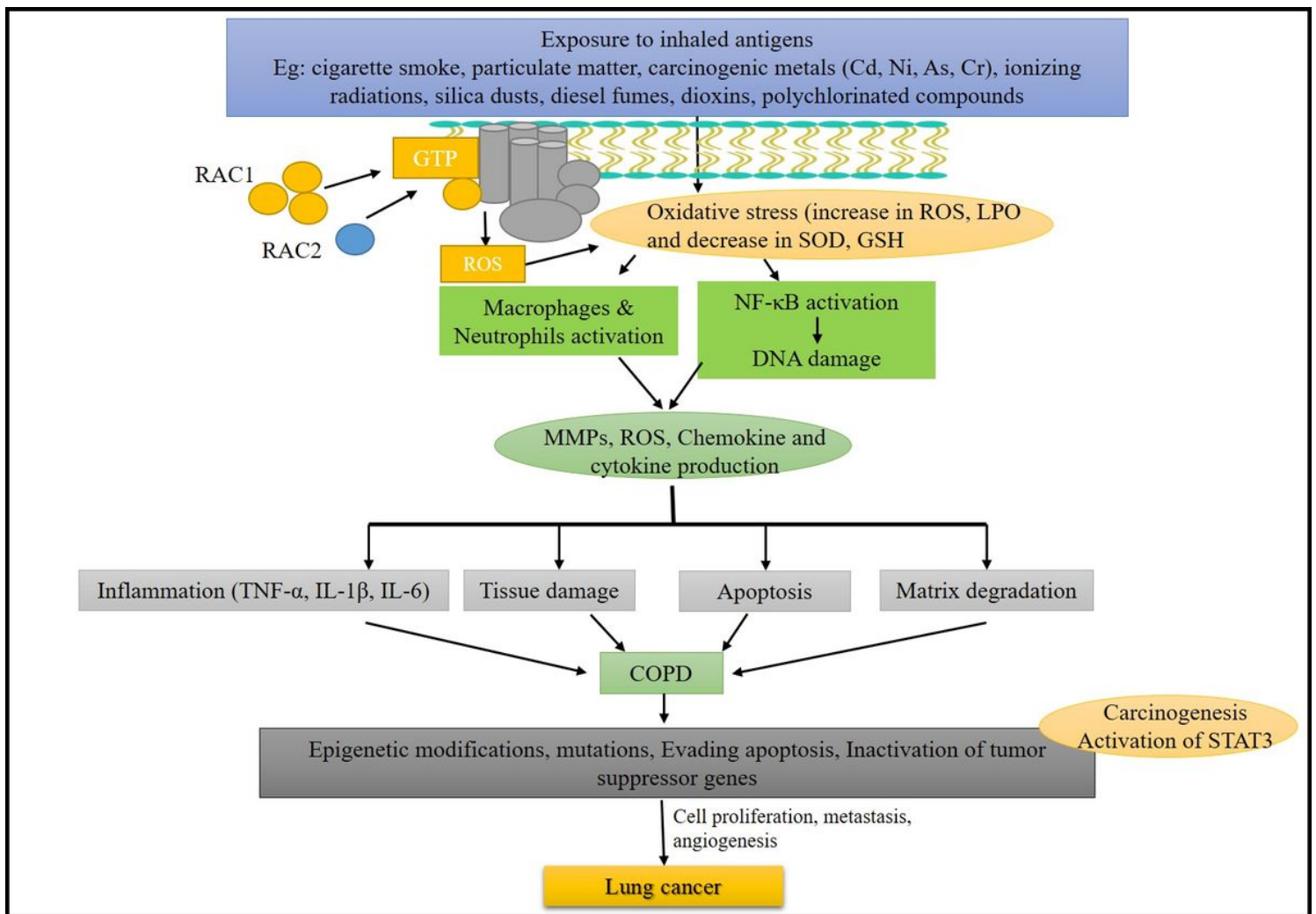


Figure 7

Parkinson's disease initiation & progression by inflammation and oxidative stress. OS is caused by mutation in DJ-1 and proteosomal dysfunction. It brings synaptic vessel dysfunction and lewy body formation respectively causing OS. Prolonged expose to ROS leads to mtDNA alterations enhancing oxidative stress. Also, dysfunction in mitochondria triggers the innate immune response activating the NLRP3 inflammasome complex through the production of cytokines. NF-κB, Nrf2 and STAT3 are the three crucial signalling pathway which has an important role in PD process. NF-κB combines with IκB, an inhibitory protein that enters the nucleus and mediates inflammation. Nrf2 is activated and entered the nucleus that also stimulates inflammatory response. Finally, STAT3 is stimulated and enhances the proinflammatory response of microglia. Microglia is the inflammation marker which is polarized to form M1/M2 phenotype having both pro- as well as anti-inflammatory effects. Microglia will not only induce oxidative stress but will also inhibit oxidative stress through activating GSH and Cu/ZnSOD. Additionally, astrocyte overexpressed DJ-1 exerts antioxidative stress which induced A1 astrocytes to polarize to A2 phenotype and produce GDNF which enhances neuron growth. Both OS and inflammation exerts their synergistic way in advancement of PD.