Review Article

Oxidative Stress and Carbonyl Lesions in Ulcerative Colitis and Associated Colorectal Cancer

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Oxidative stress has long been known as a pathogenic factor of ulcerative colitis (UC) and colitis-associated colorectal cancer (CAC), but the effects of secondary carbonyl lesions receive less emphasis. In inflammatory conditions, reactive oxygen species (ROS), such as superoxide anion free radical ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($HO^{\bullet}$), are produced at high levels and accumulated to cause oxidative stress (OS). In oxidative status, accumulated ROS can cause protein dysfunction and DNA damage, leading to gene mutations and cell death. Accumulated ROS could also act as chemical messengers to activate signaling pathways, such as NF-κB and p38 MAPK, to affect cell proliferation, differentiation, and apoptosis. More importantly, electrophilic carbonyl compounds produced by lipid peroxidation may function as secondary pathogenic factors, causing further protein and membrane lesions. This may in turn exaggerate oxidative stress, forming a vicious cycle. Electrophilic carbonyls could also cause DNA mutations and breaks, driving malignant progression of UC. The secondary lesions caused by carbonyl compounds may be exceptionally important in the case of host carbonyl defensive system deficit, such as aldo-keto reductase 1B10 deficiency. This review article updates the current understanding of oxidative stress and carbonyl lesions in the development and progression of UC and CAC.

1. Introduction

Reactive oxygen species (ROS) refer to a class of special oxygen chemical forms or oxygen-containing compounds that have much higher chemical activity than the oxygen. Oxidative stress (OS) occurs if the generation of ROS exceeds the defensive capability of the antioxidant system in the cell [1]. As a largest endocrine and immune organ, the intestinal tract abundant with microorganisms is important in stress response, such as oxidative stress [2]. Superoxide anion free radical ($O_2^{\bullet-}$) and nitric oxide free radical ($NO^{\bullet}$) are two main endogenous reactive oxygen/nitrogen species (ROS/RNS), from which other reactive free radicals, such as hydrogen peroxide (H_2O_2), hydroxyl radical ($HO^{\bullet}$), and peroxynitrite anion ($ONOO^-$), are derived [3]. There are several sources of ROS in the digestive tract [4]. Luminal microbes produce a large amount of ROS; inside cells, superoxide anion, hydrogen peroxide, and hydroxyl radicals are produced as byproducts of mitochondrial respiration in aerobic metabolism and in cytochrome P450 detoxifying reactions; and in the process of chronic inflammation, a large amount of ROS is produced by neutrophil phagocytosis of bacteria, granular materials, or soluble irritants [5, 6].

In normal condition, intestinal ROS have bactericidal effects, participating in the intestinal defensive function. However, oxidative stress derived from excessive ROS production over the buffering capability of antioxidant defense in the host would cause lipid peroxidation, intestinal mucosal barrier damage, bacterial translocation, and inflammatory response [2, 7]. Ulcerative colitis (UC) is a type of chronic

inflammatory bowel disease (IBD) in which oxidative stress plays a critical role in its pathogenesis and malignant progression to colorectal cancer (CRC) [8, 9]. UC affects the distal colon and rectum but often extends to the proximal colon and eventually to the whole colon. Clinically, patients with UC usually experience an intermittent course for a lifetime and colectomy is the only curative option [10, 11]. A worse scenario of UC is the increased risk of developing colorectal cancer, so-called colitis-associated colorectal cancer (CAC) [12]. This review article focuses on the oxidative stress and secondary carbonyl (lipid peroxide) lesions in the pathogenesis of UC and CAC.

2. Oxidative Stress and Carbonyl Lesions in Ulcerative Colitis

UC is essentially an immune-inflammatory disease. Inflammation is a process that consists of a series of protective responses, such as immune cell infiltration and cytokine expression, to eliminate pathogens/insults and initiate damage repair of the tissue. Acute inflammation is the immediate response of the body to pathogens and characterized with recruitment of leukocytes, particularly granulocytes. Chronic inflammation is a prolonged inflammatory process and characterized by simultaneous damage and healing of tissues at the inflammatory spot, resulting in a progressive shift of cell types. Therefore, chronic inflammation often leads to progressive diseases in the host [13].

Ulcerative colitis (UC) is a chronic inflammation described with remission and reactivation [10]. In active phase, UC is characterized with diffusive inflammatory cell infiltration and small intestinal mucosal crypt abscesses. In the inflammatory colon, mucosa, submucosa, and lamina propria are often infiltrated with neutrophils, lymphocytes, plasma cells, and eosinophils [14]. The infiltrated neutrophils produce a large amount of ROS, triggering oxidative stress, and proteolytic enzymes. The proteolytic enzymes and ROS act on endothelial cells and cause cell injury and subsequent epithelial barrier permeability and luminal pathogen invasion, which in turn exaggerate inflammatory cell infiltration and inflammatory damage, eventually leading to intestinal mucosal necrosis and ulceration [15]. Meanwhile, epithelial regeneration starts to cover the ulcerative area under stimulation of mitogenic cytokines and prostaglandins produced in inflammatory response. In this circumstance, intestinal mucosal hyperemia, edema, and hyperplasia polyps may appear.

Etiopathology of UC is complicated, including bacterial or viral infection, changes of colon microbiota, excessive immune response, and oxidative stress injury [16, 17]. Host genetic factors also play an etiological role in the development and progression of UC. It has been reported that the chromosomal loci 3, 7, and 12 in humans are associated with individual sensitivity to inflammatory bowel disease, including UC [18]. Recent studies from our laboratory have demonstrated that aldo-keto reductase 1B10 (AKR1B10) is a potential etiopathogenic factor of UC and CAC [19]. Among these etiopathological factors, the abnormal immune

response is considered a key of UC. The normal colon mucosa plays an immune, endocrine, and barrier function. Injuries occurring in the intestinal mucosa insult its barrier function; increased intestinal mucosal permeability allows microbes and antigens to invade and excessively stimulate immune response, triggering intestinal inflammation. Excessive ROS are produced leading to oxidative stress during the inflammatory response, exaggerating inflammatory lesions in the pathogenesis of UC.

2.1. Redox in the Intestine. In the intestine, main ROS include hydroxyl free radical ($OH^{\bullet}$), superoxide anion radical ($O_2^{\bullet-}$), and hydrogen peroxide (H_2O_2) while superoxide dismutase (SOD), glutathione peroxidase (GSH-PX), and catalase (CAT) are main antioxidant enzymes [20]. Peroxisomes are important organelles in biological oxidation in cells and participate in production and clearance of free radicals. Peroxisomes are enriched with hydrogen peroxide enzymes, oxidases, and peroxidases [21, 22]. Oxidases catalyze β-oxidation of fatty acids for energetic metabolism, producing H_2O_2. H_2O_2 is in turn transformed into $OH^{\bullet}$ or other active free radicals [23]. In addition, xanthine oxidase and uric acid oxidase produce electronics in oxidative metabolic pathways [24, 25]. Hydrogen peroxide enzyme and SOD reduce H_2O_2 into H_2O. In the process of chronic intestinal inflammation, a large amount of ROS, such as $O_2^{\bullet-}$ and H_2O_2, is produced by neutrophils during phagocytosis. This phagocytic process activates nicotinamide adenine dinucleotide phosphate oxidase (NOX) in the membrane, leading to rapid depletion of oxygen and production of superoxide anion [5, 6].

Cells evolve an antioxidant defense system to maintain homeostasis between the oxidant and antioxidant species [26, 27]. Excessive generation of free radicals beyond the capacity of defense leads to failure of this homeostatic process and oxidative injuries, such as lipid peroxidation and DNA damage, so-called oxidative stress. The antioxidant defense system in cells consists of enzymatic and nonenzymatic antioxidant molecules (Table 1). In addition to the endogenous cellular antioxidant species, natural food is also an important resource of antioxidants. For example, quercetin ($3,5,7,3',4'$, pentahydroxyflavone), a flavonoid present in numerous fruits and vegetables, demonstrates appreciable antioxidant activity by eliminating free radicals and quenching singlet oxygen [28]. Resveratrol, a phenolic substance in red wines, is also a natural antioxidant and anti-inflammatory molecule [29].

2.2. Oxidative Stress Insults in Ulcerative Colitis. While a basal level of ROS may play a protective role in the intestine, the oxidative stress derived from imbalance between ROS production and antioxidant system is harmful, being an important pathogenic factor of UC. ROS are highly active chemical forms that target macromolecules, such as proteins, lipids, and nucleic acids, leading to lipid peroxidation, protein dysfunction, and DNA mutations (Figure 1). Therefore, excessive ROS cause cell and tissue damage, exaggerate inflammation, and lead to far-reaching effects, such as carcinogenesis. Herein we will discuss the protein and lipid damage and cellular effects induced by oxidative stress. Nuclei

(a) Oxidative damage of proteins

(b) Oxidative damage of unsaturated fatty acids

(c) Oxidative damage of DNA

(d) Carbonyl damage of proteins
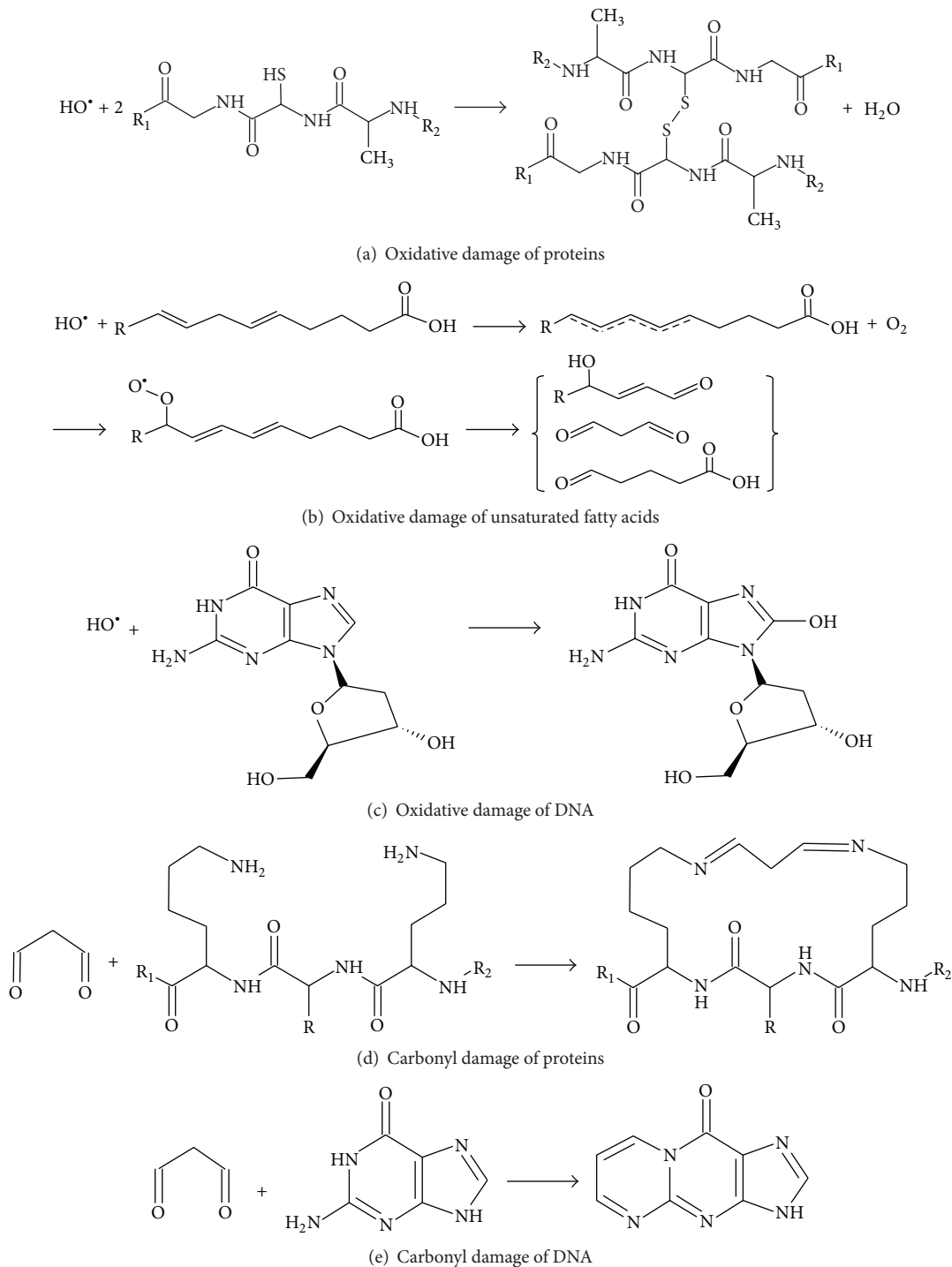

(e) Carbonyl damage of DNA

FIGURE 1: Schematic formulas. Reactive oxygen species and carbonyl compounds are highly reactive, causing protein, lipids, and DNA damage.

acid damage and carcinogenic effects of oxidative stress will be addressed in Section 3.

2.2.1. Protein Damage Induced by Oxidative Stress. Oxidative stress insults proteins. Highly active ROS can readily interact with protein amino acid residues, such as His, Pro, Trp, Cys, and Tyr residues, and cause protein structure changes, polypeptide chain cracking, and loss of the biological activity.

For example, ROS can oxidize sulfhydryl groups (-SH) in the amino acid residues to form disulfide bonds (-S-S-) and cross-link (Figure 1). ROS could also attack the methyl-sulfide group (CH_3-S-) in methionine (Met) and affect hydrolysis and carbonylation of proteins [30, 31].

2.2.2. Lipid Peroxidation Triggered by Oxidative Stress. Lipid peroxidation (LPO) is a serious cellular damage. Reactive

TABLE 1: Oxidant species and antioxidant defense.

Oxidant species	
Reactive oxygen species (ROS)	Superoxide anion ($^\bullet O_2^-$)
	Peroxide (O_2^{-2})
	Hydrogen peroxide (H_2O_2)
	Hydroxyl radical ($^\bullet OH$)
	Hydroxyl ion (OH^-)
Reactive nitrogen species (RNS)	Nitric oxide ($^\bullet NO$)
	Peroxynitrite ($ONOO^-$)
	Nitrogen dioxide ($^\bullet NO_2$)
	Dinitrogen trioxide (N_2O_3)
	Nitrosoperoxycarbonate ($ONOOCO_2^-$)
ROS resources	Mitochondrial electron transition
	Enzyme reactions: peroxisomal oxidases, cytochrome P-450, NAD(P)H oxidases, and xanthine oxidase
	Xenobiotics, drugs, and radiation: cisplatin, doxorubicin, and so forth.
RNS resources	Nitric oxide ($^\bullet NO$) from nitric oxide synthase 2 (NOS2)
	Other RNS from reaction of nitric oxide ($^\bullet NO$) with superoxide anion ($^\bullet O_2^-$) and other reactive species.
Antioxidant defense	
Nonenzymatic antioxidants	Glutathione (GSH)
	Cysteine
	Metallothionein
	Coenzyme Q (CoQ)
	Uric acid
Enzymatic antioxidants	Superoxide dismutase (SOD)
	Catalase (CAT)
	Peroxiredoxin (Prx)
	Glutathione reductase (GR)
	Glutathione peroxidases (GPx)
	Glutathione-S-transferases (GST)
	Thioredoxin and thioredoxin reductase
Natural (food) antioxidants	Vitamin A/C/E
	Flavonoid
	Resveratrol

ROS readily bind to unsaturated fatty acids in lipids that contain multiple double bonds, "steal" electrons, and trigger a free radical chain reaction (Figure 1). This oxidative process usually consists of initiation (production of a fatty acid radical), propagation (creation of a peroxyl-fatty acid radical), and termination (production of electrophilic carbonyls) [32]. This lipid peroxidation process produces two major biological effects, that is, direct membrane damage and permeability and production of lipid peroxides [33]. The common lipid peroxides created by lipid peroxidation include malondialdehyde (MAD), 4-hydroxynonenal (HNE), crotonaldehyde, and acrolein [34]. These lipid peroxides are α,β-unsaturated and highly reactive to cellular proteins and nucleic acids. In UC pathogenesis, lipid peroxides are important secondary injury factors of oxidative stress.

Phospholipids are primary ingredients of cell and organelle membrane and are enriched with unsaturated fatty acids. Therefore, the lipid peroxidation induced by oxidative stress mainly occurs in the membrane, and attacking by ROS would lead to direct structural and functional changes of membranes [33]. Mitochondrial membrane is the site of the respiratory chain that generates ROS in the normal cells. Therefore, mitochondria are the main organelles that are produced and attacked by ROS [35]. In the status of oxidative stress, excessive ROS attack oxidation respiratory chain and lead to obstacle of oxidative phosphorylation, producing more ROS. Excessive ROS also make Ca^{2+} overload in the mitochondria and lead to mitochondrial membrane depolarization and permeability, releasing free radicals into cytoplasm and causing cellular damage in general. Increased

membrane permeability also releases cytochrome C (Cyt-C) and apoptosis inducing factor (AIF) into cytoplasm and activates caspase cascade for apoptosis [36, 37]. Therefore, in oxidative status ROS production by respiratory chain, mitochondrial membrane insults, and ROS release into cytoplasm form a vicious cycle, causing cell death and tissue injury. We will discuss the lesions induced by lipid peroxides in Section 2.3.

2.2.3. Cell Signaling Triggered by Oxidative Stress.

ROS could function as second messengers to activate intracellular signaling pathways, such as NF-κB, a major modulator of UC [38–42]. In the normal intestinal epithelium, NF-κB maintains intestinal epithelial barrier function and coordinates epithelial immune response to microorganisms. On the other hand, as transcription factors, deregulation of NF-κB signaling, such as oxidative activation, stimulates expression of a variety of proinflammatory cytokines in the intestinal epithelial cells, such as TNF-α, IL-1, IL-8, and COX-2, and promotes inflammation and carcinogenesis. In static state, NF-κB in the cells is bound to IκB, inhibitors of κB, and hooked in the cytoplasm. Activation of NF-κB consists of IκB kinase (IKK) activation, IκB phosphorylation and ubiquitinated degradation by 26S proteasomes, and nuclear translocation and DNA binding of free NF-κB, finally promoting target gene expression [43]. Oxidative stress can activate IKK and stimulate nuclear translocation of NF-κB (Figure 2). In the diseased colon tissues of UC patients, NF-κB expression, particularly the p65 (Re1A) and p52/p100 (NF-κB2), is increased, and blockade of NF-κB activity is considered practical treatment of UC [44]. In addition, the activation of p50, c-Rel, and p65 is documented in macrophages in the lamina propria of UC patients [45].

Oxidative stress also activates mitogen-activated protein (MAP) kinase (MAPK) signaling pathways. MAPKs are highly conserved serine/threonine protein kinases functioning in various fundamental cellular processes, such as growth/proliferation, differentiation, motility, and apoptosis/survival, as well as stress response [46]. Conventional MAPKs include the extracellular signal-regulated kinases 1 and 2 (Erk1/2), the c-Jun N-terminal kinases 1–3 (JNK1–3)/stress activated protein kinases (SAPK), the p38 isoforms (p38α, β, γ, and δ), and the Erk5. These MAPKs can be activated by growth factors and mitogens, as well as various stresses. These stimuli activate MAPKK kinases (MAPKKKs) via receptor dependent and independent mechanisms, followed by phosphorylation and activation of a downstream MAP kinase (MAPKK) and then MAPKs. Activated MAPKs phosphorylate and activate specific target protein kinases, such as RSK, MSK, or MNK to mediate biological processes [47]. The increased ROS can activate ERKs, JNKs, or p38 MAPKs [48, 49]. The exact mechanism by which the ROS activate these kinases is unclear, but a plausible mechanism may be relative to oxidative modifications and resultant activation of the signaling effector proteins and inactivation and/or degradation of MAPK phosphatases (see [50] for more details). Nevertheless, the p38 and JNK signaling activated by ROS is involved in the disease progression of UC [51–54]. In UC tissues, p38 MAPK signaling changes are

a molecular signature of UC and proportional to the degree of inflammation [55, 56].

2.3. Carbonyl Stress and a Vicious Cell Damage Cycle.

A class of carbonyl compounds is called α,β-unsaturated carbonyls, also referred to as electrophilic carbonyls. These include acrolein, glyoxal, methylglyoxal, crotonaldehyde, malondialdehyde, and 4-hydroxynonenal (Table 2). As byproducts, these electrophilic carbonyl compounds are constantly produced during the metabolism of lipids, carbohydrates, amino acids, biogenic amines, vitamins, and steroids, as well as some antitumor agents, such as cyclophosphamide [57–63]. Besides endogenous production, daily food consumption may represent the most dangerous exposure of human gastrointestinal (GI) tract to exogenous electrophilic carbonyls which are pervasively present in various beverages and foodstuffs [64–66]. For instance, humans are exposed to crotonaldehyde through the consumption of vegetables (1.4–100 μg/kg), fruits (5.4–78 μg/kg), fish (71.4–1000 μg/kg), meat (10–270 μg/kg), and alcoholic beverages, such as wine (300–700 μg/L) and whisky (30–210 μg/L) [66]. Furthermore, methylglyoxal is a constituent of coffee [67, 68], and acetaldehyde is a carcinogenic metabolite of alcohol consumed [69, 70]. Therefore, human GI tract is repeatedly exposed to carbonyl threats, which are important factors of GI inflammatory and neoplastic lesions (Table 3).

In organisms, there are three main pathways responsible for elimination of intracellular carbonyls, through which carbonyls are oxidized to carbonic acids, conjugated with glutathione, or reduced to less toxic alcohols. Aldehyde dehydrogenases mediate the oxidative pathway of carbonyls, forming carbonic acids [71, 72]; glutathione-S-transferases (GST) catalyze the conjugation of carbonyls with glutathione [73–75]; and aldehyde reductase and aldo-keto reductases (AKRs) are responsible for the reduction of carbonyls to alcohols with NAD(P)H as a coenzyme [75–77]. AKR1B10 is the sole carbonyl-detoxifying enzyme with intestine-specific expression identified thus far [78] and plays a critical role in the inflammatory lesions and malignant progression of the colon [19]. Therefore, in normal conditions human consumption or endogenous production of the cytotoxic carbonyls may be subcytotoxic. However, in oxidative stress, excessive ROS oxidize unsaturated fatty acids and produce a large amount of highly reactive α,β-unsaturated carbonyl compounds, that is, lipid peroxides. For instance, 4-hydroxynonenal (HNE) is at 0.1 to 3.0 μM in normal tissues but increases to ~10 μM in the condition of oxidative stress [79]. Carbonyl accumulation due to overproduction and/or impaired clearance, such as AKR1B10 deficiency [19], would lead to carbonyl stress.

Due to their high reactivity, α,β-unsaturated lipid peroxides are highly cytotoxic and genotoxic. They can interact with free amino groups of proteins (e.g., lysine residue), peptides, and amino acids, with sulfhydryl groups of amino acid residues (e.g., cysteine residue), and with histidine and other residues, forming covalently modified adducts [57, 80–86]. The covalent modifications could lead to protein dysfunction, resistance to proteolysis, or depolymerization. Protein adducts can also act as special second
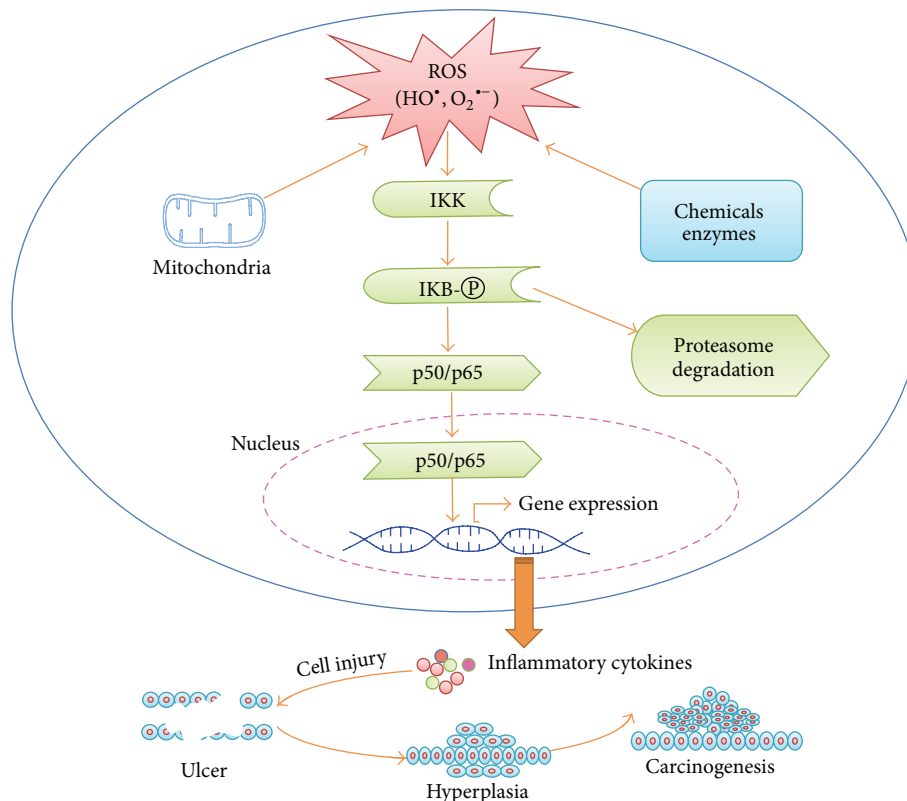
FIGURE 2: NF-κB signaling pathway, inflammation, and carcinogenesis induced ROS. Excessive reactive oxygen species (ROS) derived from mitochondrial membrane, xenobiotics, and enzyme reactions activate IKK. Activated IKK phosphorylates IκB and leads to ubiquitination and proteasome degradation of IκB, releasing NF-κB proteins, such as p50 and p65. The free p50 and p65 translocate into nuclei and drive target gene expression, such as inflammatory cytokines, leading to inflammatory lesions and carcinogenesis.

TABLE 2: Carbonyl compounds and clearance.

Carbonyl compounds	Carbonyl clearance
Acrolein (CH_2=CHCHO) Glyoxal (OHCCHO) Methylglyoxal (CH_3COCHO) Crotonaldehyde (CH_3CH=CHCHO) Malondialdehyde (OCHCH$_2$CHO) 4-Hydroxynonenal (OCHCH=CHCH(-OH)(CH$_2$)$_4$CH$_3$)	(1) Glutathione-S-transferases (GST) catalyze carbonyl-glutathione conjugation (2) Aldehyde reductase and aldo-keto reductases (AKRs) catalyze reduction to alcoholic forms (3) Aldehyde dehydrogenases catalyze oxidation to carbonic acids

messengers or autoantigens, promoting macrophage accumulation, retention, and activation, thus increasing ROS generation. Furthermore, carbonyl-induced protein dysfunction may impair mitochondrial respiratory chain reactions and membrane potential, leading to increased ROS production and release into cytosol. Therefore, in inflammatory conditions (i.e., UC), the carbonyl lesions may create a vicious loop with oxidative stress, aggravating cell and tissue damage [19, 87].

3. Oxidative Stress and Carbonyl Lesions in Colitis-Associated Colorectal Cancer

Colorectal cancer (CRC) is the third most common cancer worldwide with mortality ranked within top four [88, 89].

According to International Agency for Research on Cancer of WHO (http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx), about 1.36 million of new CRC cases were diagnosed globally in 2012, accounting for approximately 69,000 deaths. Clinically, there are two main types of CRC, that is, sporadic colorectal cancer (SCC) and hereditary colorectal cancer (HCC). The latter includes familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC). Colorectal adenoma, colorectal nonadenomatous polyposis, and inflammatory bowel disease are precancerous lesions associated with CRC. The UC patients have an increased risk of developing colorectal cancer, so-called colitis-associated colorectal cancer (CAC) [90], and the cancer risk increases exponentially with the duration of disease [91–93]. A UC patient with 10 years of

TABLE 3: Carcinogenic role of carbonyl compounds.

Diseases/genotoxicity	Species	Carbonyl association	References
Colitis-associated colorectal neoplasms	Mice	Coupled with high carbonyl levels, for example, malondialdehyde	[19, 153]
Stomach hyperplasia, squamous papilloma, and carcinoma	Rats	2,4-Hexadienal exposure	[73]
Precancerous gastritis and gastric cancer	Humans	High serum malondialdehyde levels	[154, 155]
Colorectal cancer	Humans	High serum lipid peroxide levels	[156]
Colon and gastric cancers	Humans	Acetaldehyde from alcohol	[69, 70]
Colorectal adenocarcinoma	Humans	High protein carbonyl levels	[157]
Precancerous colorectal adenopolyps	Humans	High protein carbonyl levels	[158]
Colorectal cancer	Humans	High lipid peroxide levels in tissues	[159–161]
Genotoxicity	Humans	High carbonyl DNA adduct levels in tissues	[58, 162, 163]
Genotoxicity	Cell lines/*in vitro* studies	Production of carbonyl DNA adducts	[164–167]

disease duration has 10-fold higher CRC risk than the general population.

Etiopathogenesis of CAC is complex. In UC, intestinal epithelial and immune cells produce and secrete a variety of mitogenic cytokines that stimulate cell growth and proliferation. Massive ROS and inflammatory cytokines produced in UC tissues activate multiple signal pathways, such as NF-κB, STAT3, p38 MAPK, and Wnt/β-catenin pathways, which mediate cell proliferation, differentiation, and apoptosis/survival [94]. Finally, DNA damage induced by oxidative and carbonyl stresses plays an essential role in the carcinogenic transformation of the disease. Therefore, malignant progression of UC to CAC is a complicated process and oxidative and carbonyl stresses are key factors in this process.

3.1. Sporadic Colorectal Cancer and Colitis-Associated Colorectal Cancer. CRC is a multistaged, complicated disease associated with multiple oncogene and tumor suppressor gene mutations, such as *p53, K-ras,* and adenomatous polyposis coli (*APC*) mutations [95]. In pathogenesis, sporadic CRC often demonstrates an "adenoma-carcinoma" progression, but the CAC experiences a unique sequence of "inflammation-dysplasia-carcinoma" [96]. Patients with UC may experience a long course of dysplasia. Three types of atypical hyperplasia may appear in the carcinogenic process of UC: (1) normal mucosa or mucous membrane with regeneration, also named dysplasia negative type, (2) dysplasia uncertain type, (3) dysplasia positive type. UC patients with high or moderate grade dysplasia are at high risk of developing CAC [97].

CAC also demonstrates a different time line and involvement of gene mutations. In sharp contrast to sporadic CRC, *p53* mutation occurs early and is an important step in the progression of CAC. The *p53* mutations are often detected in mucosa that is even nondysplastic [98, 99], but APC mutations are present at the late stage of CAC [100–103]. *K-ras* mutation plays a rare role in CAC development [104], but

DNA methylation is an early event in UC [105], although less common than in sporadic CRC [106, 107].

3.2. Inflammatory Cytokines and CAC Progression. Inflammatory cytokines produced by intestinal epithelial cells and infiltrated inflammatory cells in UC include IL-1, IL-6, TNF-α, and TGF-β. These cytokines activate mitogenic signaling pathways, stimulate cell proliferation and survival, and thus promote inflammation-associated tumorigenesis. For instance, the plasma level of IL-6 is significantly elevated in patients with IBD, and the increased IL-6 activates STAT3/JAKl signaling, promoting cell proliferation, evolution, and tumorigenic progression [94]; inhibition of JAKl signaling or IL-6 deficiency by targeted disruption diminishes CRC incidence and progression [108, 109].

Tumor necrosis factors (TNF) are proinflammatory cytokines which are produced and secreted mainly by monocyte-macrophages. In this family, TNF-α is an important member that functions in inflammation, immune response, and tumorigenesis. Animal experiments have demonstrated that TNF-α can increase the plasma level of IL-6 [110] and initiate colorectal carcinogenesis mediated by chronic inflammation [111]. To date, TNF-α monoclonal antibody is used for IBD treatment and has demonstrated promising results; this antibody may also be effective in prevention of CAC [112].

TGF-β and family members are secretory signal transduction peptides that regulate cell proliferation and apoptosis. In the normal cells, the major function of TGF-β is to arrest cell division in the early stage of DNA synthesis, induce cell differentiation, or promote apoptosis. Literature reports indicate that mutations in TGF-β signal transduction pathway occur in patients with UC before the formation of colorectal cancer [113]. For example, TGF-βRII mutations have been detected in UC dysplasia and are associated with CAC progression [114].

Finally, inflammatory cytokine IL-1α increases in UC and may be involved in CAC development [115], but compared

to other cytokines, the role of IL-1α in the development and progression of CAC is more complicated. IL-1α may promote cancer progression by stimulating angiogenesis [116]; IL-1α may also promote epithelial repair and prevent CAC by inducing the expression of cyclooxygenase 2 (COX-2), a key enzyme of prostaglandin E_2 (PGE_2) synthesis from arachidonic acid (AA) [117]. PGE_2 is a prominent prostaglandin in the intestine; through binding to E prostanoid (EP) receptor, PGE_2 mediates intestinal epithelial cell proliferation and apoptosis [118, 119]. This is considered favorable to injury repair and remission of UC. In fact, ulcerogenic response of nonsteroidal anti-inflammatory drugs (NSAIDs) in the intestine is ascribed to inhibition of cyclooxygenases and resultant PGE_2 deficiency [120]. In dextran sodium sulfate- (DSS-) induced colitis, COX-2/PGE_2 promotes epithelial cell proliferation; inhibition of COX-2 decreases epithelial proliferation, exacerbates colitis, and prolongs injury phase, thus promoting intestinal injury and dysplasia [121–123]. Therefore, evaluation of IL-1α in CAC development and progression needs to be more cautious.

3.3. Oxidative DNA Damage in CAC Progression.

DNA mutations and resultant protooncogene activation and/or tumor suppressor gene inactivation are a hallmark of cell carcinogenesis, which reprograms cell growth, division, and gene transcription. The high risk of UC patients to develop colorectal cancer is essentially attributed to the increased DNA damage induced by inflammatory oxidative stress and carbonyl lesions. DNA is a ready target of active oxygen free radicals, leading to oxidative DNA damage. Through abstractions and addition reactions, highly reactive hydroxyl radicals react with the heterocyclic DNA bases and sugar moiety, producing carbon-centered sugar radicals and OH- or H-adduct radicals of heterocyclic bases [124]. Further reactions of these radicals yield numerous effects, such as 8,5′-cyclopurine-2′-deoxynucleosides, tandem lesions, clustered sites, and DNA-protein cross-links [124, 125]. Among types of oxidative DNA damage induced by ROS, 8-hydroxy-2′-deoxyguanosine (8-OHdG) or 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG) is a predominant form and a valuable biomarker widely used for endogenous oxidative damage to DNA (Figure 1). For instance, the urinary 8-OHdG is used as a biomarker for risk assessment of cancers and degenerative diseases [126, 127].

GC to TA transversion is a major type of DNA mutations resulting from 8-OHdG adducts [128]; two common target genes of the 8-OHdG damage are *Ras* and *p53*, leading to activation of the protooncogene *Ras* and inactivation of p53 tumor suppressor, driving tumorigenesis [129, 130]. ROS also cause DNA methylation, single- and double-strand breaks, and shortening of telomeres. DNA methylation is an early event in the progression of UC to CAC [105], but less common than in sporadic CRC [106, 107]. Oppositely, DNA breaks and telomere shortening occur more often in the UC-associated tumorigenesis [131, 132]. The telomere shortening induced by ROS could induce chromosome instability, leading to chromosomal loss, heteroploid, amplification, and translocation, driving tumorigenesis [133, 134].
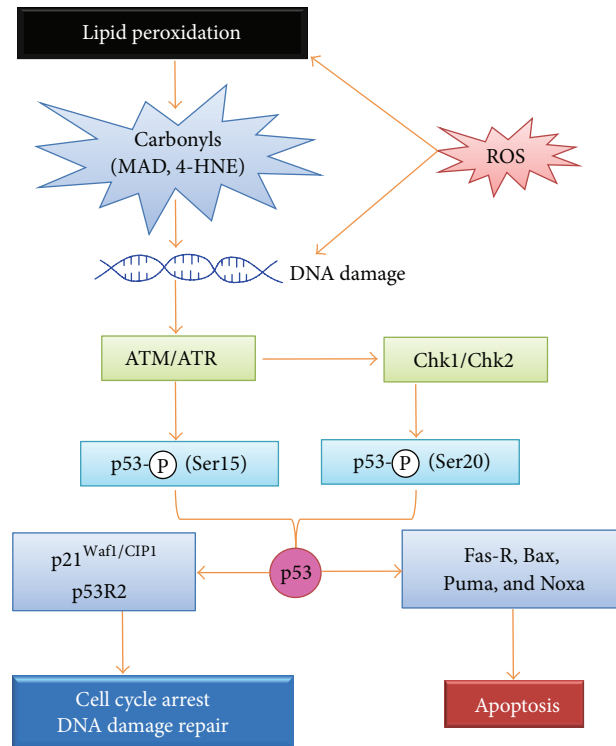

Figure 3: DNA damage induced by oxidative and carbonyl stresses and p53-dependent DNA damage response (DDR). Reactive oxygen species (ROS) and α,β-unsaturated carbonyl compounds produced by lipid peroxidation, such as MDA and HNE, trigger DNA damage, such as double-strand DNA breaks. ATM/ATR senses the breaks and activates p53 by phosphorylating Ser15; ATM/ATR also phosphorylates Ser345 of Chk1/Chk2 and activates Chk1/Chk2, which further activates p53 by phosphorylating Ser20. In cells with mild DNA damage, p53 drives expression of p21$^{Waf1/CIP1}$ and p53R2, leading to cell cycle arrest and DNA damage repair. In cells with severe DNA damage, p53 drives Fas-R, Bax, Puma, Noxa, Apaf-1, and Pidd expression, activating intrinsic and extrinsic apoptotic pathways.

3.4. Carbonyl DNA Damage in CAC Progression.

Carbonyl stress derived from lipid peroxidation is also an important DNA damage factor in UC. Electrophilic carbonyls can readily react with DNA forming covalently modified DNA adducts (Figure 1). The DNA adducts can block DNA semiconservative replication performed by DNA polymerases or arrest transcription driven by RNA polymerases [58, 135–137]. DNA adducts can also cause miscoding and induce DNA breaks [58, 137–139]. For instance, malondialdehyde (MDA) can react with deoxyguanosine in DNA to form an exocyclic adduct, pyrimido[1,2-alpha]purin-10(3H)-one (M1G), which is mutagenic by resulting in frameshift mutations and base pair substitutions [140]. The 4-HNE-dG polymer derived from 4-hydroxynonenal can lead to GC to TA transversion at codon 249 of *p53* gene, driving UC progression to CAC [141, 142].

Of note, DNA breaks induced by carbonyl compounds may activate cellular DNA damage response (DDR), inducing cell cycle arrest for DNA repair or apoptosis (Figure 3). In
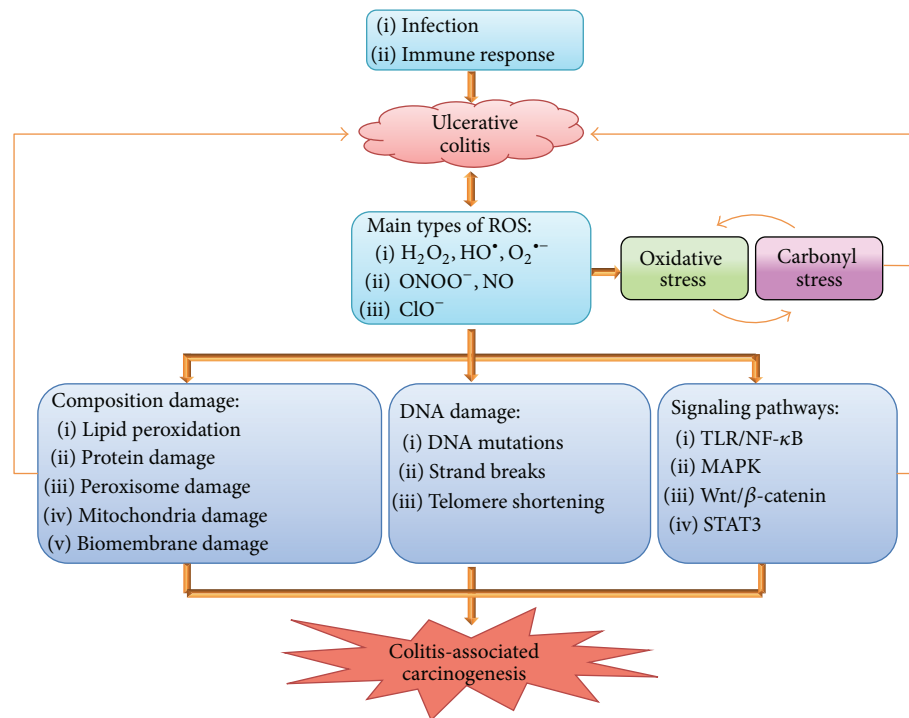
FIGURE 4: Hypothetic model of oxidative stress and carbonyl lesions in ulcerative colitis and associated colorectal cancer. Infection and immune response act as primary initiators to trigger inflammation and inflammatory cell infiltration. In this process, intestinal mucosal crypt abscesses occur and vast reactive oxygen species (ROS) are produced, thus leading to oxidative stress. Excessive ROS exaggerate inflammatory lesions and stimulate epithelial cell proliferation through oxidative insults to proteins, lipids, and DNA and also by activation of cell signaling pathways, eventually leading to ulcerative colitis (UC) and colitis-associated colorectal cancer (CAC). Electrophilic carbonyl compounds play as important secondary factors of oxidative stress to cause cellular and macromolecular lesions, which, together with oxidative stress, may form a vicious cycle. Meanwhile, proinflammatory cytokines produced by epithelial cells and infiltrated inflammatory cells may promote the progression of UC and CAC.

this DDR process, ATM/ATR functions as a sensor of DNA breaks, and p53 acts as a key mediator [143, 144]. Sensing the DNA double-strand breaks, ATM/ATR is activated by phosphorylation, which reaches the peak within 30 minutes [145]. The activated ATM/ATR phosphorylates p53 at Ser15 and/or Chk1/Chk2 at Ser345, and Chk1/Chk2 further phosphorylate p53 at Ser20 [146]. Activated p53 triggers cell cycle arrest for DNA damage repair or apoptosis to eliminate cells with severe DNA damage through selective activation of target gene expression, such as apoptotic genes Fas-R, Bax, Puma, and Noxa or cell cycle monitoring and DNA repair genes p21$^{Waf1/CIP1}$ and p53R2 [147]. Therefore, DDR is considered a barrier of carcinogenesis, and mutations of genes in this pathway are carcinogenic. In fact, p53 mutation is an early event in CAC and occurs even in noncancerous UC tissues [148, 149].

4. Conclusion and Perspective

Early in 1863, a German pathologist Virchow proposed that tumor might be derived from chronic inflammation tissues; in 2009, Hanahan and Weinberg proposed tumor-related inflammation as the seventh hallmark of cancer. To date, the role of chronic inflammation in cancer development

and progression has become an important research focus in tumor microenvironment. In UC, the pathogenesis of CAC is a classical path of nonresolving inflammatory progression to cancer, featured with a unique sequence of "inflammation-dysplasia-carcinoma." Oxidative stress and secondary carbonyl lesions are key factors in the development and progression of UC and CAC; the ROS take an important part in multiple stages of initiation, promotion, and progression of UC and CAC and the secondary carbonyl lesions play an exaggerating role both in oxidative stress itself and in progression of UC and CAC (Figure 4).

To date, antioxidant prevention and treatment have been investigated in experimental animals of colitis and in clinical patients of UC. In animals, antioxidant *G. biloba* extract (EGb 761) showed effectiveness in prevention and treatment of DSS-induced colitis in mice [150], and the *Zingiber officinale* extract demonstrated efficacy in modulating extent and severity of colitis in rats [151]. In humans, consumptions of antioxidant food, such as blueberries, cherries, tomatoes, squashes, and bell peppers have been suggested as supplementary treatment of active UC and prevention of reactivation. More impressively, a clinical trial of rectal d-alpha tocopherol, a powerful vitamin E antioxidant, has shown that "all 14 patients responded clinically to the therapy and remission was induced in 9 of them (64%)"; no adverse

events were reported and no patients were hospitalized for "worsened disease activity" [152]. These preclinical and clinical approaches suggest that antioxidant treatment may be a novel mode of UC management and prevention of malignant progression. Further studies are warranted.

Abbreviations

AIF:	Apoptosis inducing factor
AKR1B10:	Aldo-keto reductase 1B10
APC:	Adenomatous polyposis coli
CAC:	Colitis-associated colorectal cancer
CAT:	Catalase
COX-2:	Cyclooxygenase 2
CRC:	Colorectal cancer
DSS:	Dextran sodium sulfate
GSH-PX:	Glutathione peroxidase
IBD:	Inflammatory bowel disease
MAD:	Malondialdehyde
NOX:	Nicotinamide adenine dinucleotide phosphate oxidase
OS:	Oxidative stress
Raf:	Root abundant factor
ROS:	Reactive oxygen species
SCC:	Sporadic colorectal cancer
SOD:	Superoxide dismutase
TGF-β:	Transforming growth factor β
TNF-α:	Tumor necrosis factor α
UC:	Ulcerative stress.

Conflict of Interests

Authors declare no conflict of interests regarding the publication of this paper.

Authors' Contribution

Zhiqi Wang wrote draft. Sai Li draw figures. Duan-Fang Liao, Yu Cao, Xuefei Tian, and Rong Zeng contributed to literature search and discussion. Deliang Cao revised the paper. All authors read and approved the final version of this paper.

Acknowledgments

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