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REVIEW ARTICLE

Oxidative stress in ulcerative colitis: an old concept but a new concern

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Abstract
Ulcerative colitis is an idiopathic, chronic and relapsing inflammatory bowel disease, which elicits the risk of colorectal cancer, the third most common malignancy in humans. It has been known for a long time that oxidative stress is a major pathogenic factor in the inflamed tissue that can pave the way towards DNA damage and carcinogenesis. However, the DNA damage produced due to oxidative stress in the inflamed tissue is not limited to the local site but extends globally, thereby augmenting the risk of global carcinogenesis. Targeting oxidative stress may provide an exciting avenue to combat inflammation-associated local as well as global DNA damage and the subsequent carcinogenesis. The present review portrays the role of oxidative stress in the pathogenesis of ulcerative colitis and the associated local as well as global DNA damage, which may lead to carcinogenesis.

Keywords: oxidative stress, ulcerative colitis, DNA damage, carcinogenesis

Abbreviations: UC, ulcerative colitis; MPO, myeloperoxidase; SOD, superoxide dismutase; GPx, glutathione peroxidase; GSH, reduced glutathione; ROS, reactive oxygen species, NF-κB, nuclear factor kappa B; IL, interleukin; TNF-α, tumor necrosis factor-alpha; TNBS, trinitrobenzene sulfonic acid; LOX, lipoxygenase; COX-2, cycloxygenase-2; i-NOS, inducible-nitric oxide synthase; Nrf2, nuclear factor-erythroid 2 (NF-E2)-related factor 2; DSS, dextran sulfate sodium; STAT3, signal transducer and activator of transcription 3; ; RNS, reactive nitrogen species; HNE, 4-hydroxynonenal; HPNE, 4-hydroperoxynonenal; 8-oxodG, 8-oxo-7,8-dihydro-2′-deoxyguanosine; 8-NO_2-dG, 8-nitro-2′-deoxyguanosine; CRP, C-reactive protein; DSS, dextran sulfate sodium.

Introduction

Ulcerative colitis (UC), an inflammatory bowel disease, mainly afflicts the population in the western countries. It has now become common in rest of the world due to the adoption of western lifestyle [1]. UC is a chronic gastrointestinal disorder, which affects men and women equally and seems to be linked with inheritable genetic traits. Family aggregation has been predicted for the occurrence of the disease and first-degree relatives of the affected individuals have a relative risk of five-fold or greater [2]. It generally affects a part of colon or the entire colon in an uninterrupted manner and the inflammation is typically confined to the mucosa [3]. It usually has an onset in early adulthood and a life-long impact with long-term disabling symptoms [4]. Patients suffering from UC have a higher risk of developing colorectal cancer, which is the third most common malignancy generally observed in humans [5]. The exact aetiology of UC is not clearly known, however, the condition appears to be associated with the dysfunctional immunoregulation of the gut. Amongst the immunoregulatory factors, oxidative stress is one of the major contributing factors that have already been elucidated to be involved in the perpetuation of the disease [6]. It has been known since years that inflammation results into the generation of oxidative stress, which in turn, paves its path towards DNA damage and ultimately carcinogenesis at the local site [7]. However, a novel concept has emerged that the damage at the local site extends beyond the site of inflammation and may affect other organs globally, in which oxidative stress has a major role to play [8,9]. Oxidative stress-induced DNA damage at the local as well as global sites may further increase the risk of local as well as global carcinogenesis process. This warrants a critical concern to target oxidative stress using appropriate antioxidants in order to treat various inflammatory disorders, such as UC and the associated carcinogenesis.

Complications associated with ulcerative colitis

Patients with UC experience cyclical bouts of clinical symptoms, such as diarrhoea, rectal bleeding and anaemia due to intestinal inflammation, oedema and ulceration [10]. It is characterized with diffused mucosal inflammation that extends proximally from the rectum to a varying degree. Along with severe inflammation and the production of various inflammatory mediators, extensive

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superficial mucosal ulceration develops [11]. Nearly all the UC symptoms occur in the intestine, however, the disease can also cause problems in the extra-intestinal parts of the body. Long-term intestinal inflammation in UC is associated with the development of several extra-intestinal manifestations, such as, arthritis, eye problems, liver complications, osteoporosis, skin rashes and anaemia. It has been reported that certain susceptibility genes in the major histocompatibility complex region on chromosome 6 seem to be linked to the extra-intestinal manifestations in UC [12]. The global effect of UC may be due to dysregulation within the immune system that triggers inflammation in other parts of the body [6]. The risk for developing cancer starts to increase between eight and ten years after the appearance of first UC symptoms [13,14]. UC not only increases the risk of colorectal cancer, but also several extra-intestinal cancers, such as non-Hodgkin's T-cell lymphomas, enteropathy-associated T-cell lymphomas, leukaemia as well as hepatobiliary and rectal carcinomas [15,16].

Role of oxidative stress in ulcerative colitis

Oxidative stress is a potential driving force in the induction and progression of UC. With the progression of UC, the activities of infiltrating leukocytes, neutrophils and macrophages are greatly increased in the colon, resulting in the enhanced generation of pro-oxidant molecules [17]. Cytokines-induced elevated myeloperoxidase (MPO) level also leads to ROS generation [18]. The epithelium of the colon contains multiple antioxidant systems, such as antioxidant enzymes, *viz.*, superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx) and glutathione reductase and low molecular-weight antioxidant molecules, *viz.*, reduced glutathione (GSH) [19]. The enzymatic defence systems in the colonic mucosa are involved in maintaining the reduced state of proteins and protecting the cells against reactive oxygen species (ROS), drugs and heavy metal ions [20]. The thiol-rich protein, metallothionein, plays a vital role in the detoxification of toxic metals and in protection against oxidative damage. It has been observed that the expression of metallothionein significantly increases in the large intestinal epithelial cells of the patients with UC and the expression of metallothionein increases with an increase in the severity of inflammation [21]. The increased metallothionein concentration in UC patients suggests induction of metallothionein synthesis in response to the potential harmful effects of ROS produced during the inflammatory response. The generated ROS may activate metallothionein expression directly through the stimulation of antioxidant response element and specific metal response elements in the promoter region and indirectly by events associated with second-messenger protein kinase pathways [22,23]. Further, various cytokines and pro-oxidants activate nuclear factor kappa B (NF-κB), a pro-inflammatory redox-sensitive transcription factor that has emerged as an important player in the development and progression of UC. NF-κB has been shown to be regulated by the intracellular redox state and oxidative stress results into the activation of NF-κB. In UC, NF-κB activation has been reported to occur in macrophages as well as in epithelial cells [24,25]. Activation of NF-κB has been known to occur in the colonic mucosa of patients with collagenous and ulcerative colitis [26]. It has been reported that intestinal lamina propria macrophages in Crohn's disease and UC display high levels of NF-κB DNA-binding activity which then leads to an increased production of interleukin (IL)-1, IL-6 and tumour necrosis factor-alpha (TNF-α) [27]. It has been suggested that NF-κB may play a central role in the regulation of chronic inflammation by controlling the transcription of inflammation genes [28]. Further, activation of NF-κB involving the p65 subunit has been known to play a role in trinitrobenzene sulfonic acid (TNBS)/ethanol-induced colitis in mice [29]. NF-κB activation has also been reported to increase the gene expression of lipoxygenase (LOX), cycloxygenase-2 (COX-2) and inducible-nitric oxide synthase (i-NOS), which in turn further leads to the generation of oxidative stress [30–32].

Nuclear factor-erythroid 2 (NF-E2)-related factor 2 (Nrf2), a redox-sensitive transcription factor, which belongs to the cap 'n' collar basic leucine zipper region subfamily, is another key regulator of the cellular response to inflammatory cytokines and oxidative stress to multiple tissue and cell types. Nrf2 deficiency results in increased inflammation- and oxidative stress-induced tissue damage. It has been known that in a dextran sulfate sodium (DSS)-mediated mouse colitis model, Nrf2 knockout mice showed increased production of IL-1 β, IL-6, IL-12p40 and TNF-α, compared to their wild-type counterparts [33].

The genesis, path and progression

UC mainly occurs due to inappropriate inflammatory response to a luminal pathogen, abnormal immune response to intestinal bacterial flora, role of cytokines and oxidative DNA damage at the local sites of inflammation in the colon [8,34]. It may also result from an inappropriate inflammatory response to intestinal microbes and the resulting host–microbe interactions in a genetically susceptible individual [3]. In UC, inflammation leads to defect in the mucosal barrier function that results into an increased permeability of the paracellular space and defect in the regulation of tight junctions [35]. Further, the inflammatory response often results in continued epithelial injury, which causes erosions and ulcerations leading to an increased exposure to intestinal microbiota and amplification of the inflammatory response. It has been reported that epithelial dysfunction occurs due to defects in epithelial-cell development or proliferation, barrier function, cell-matrix adhesion, endoplasmic reticulum stress and epithelial restoration after injury [36,37]. UC leads to a pronounced infiltration into the lamina propria of innate immune cells (neutrophils, macrophages, dendritic cells and natural killer T cells) and adaptive immune cells (B cells and T cells). Imbalance between the regulatory T cells and effector T cells (Th1, Th2 and

Th17) plays a major role in the pathogenesis of the disease [38]. Activation of the innate and the adaptive immune system in the intestinal mucosa elevate the levels of TNF-α, IL-1β, IL-17, IL-23 and interferon-γ [3]. Various cytokines, such as TNF-α, IL-1β and interferon-γ, result in the generation of ROS which are the key players in the progression of UC [39]. Increased formation of ROS and reactive nitrogen species (RNS) including superoxide, hydrogen peroxide, hydroxyl radical, hypochlorous acid, nitric oxide and peroxynitrite in the colonic mucosa in animal models of inflammatory bowel disease have been known to be correlated with disease severity and progression [40,41]. ROS are generally produced by the activities of phagocytic leucocytes, which are known to accumulate within the colonic interstitium during the times of active inflammation [42]. It has been reported that ROS lead to the activation of transcription factors, such as NF-κB, activator protein-1 and protein kinase C family members [43–46]. NF-κB is known to regulate the expression of IL-6, which, in turn, leads to the induction of the transcription factor signal transducer and activator of transcription 3 (STAT3) via IL-6/STAT3 trans-signalling pathway [47–49]. Further, STAT3 activation leads to the differentiation of Th17 cells, which are most abundantly found in the intestinal lamina propria [50], which result in increased levels of IL-17, and which are known to play a role in a plethora of inflammatory diseases, including colitis [51].

Contribution to global DNA damage

ROS can damage both nuclear and mitochondrial DNA, RNA, lipids and proteins by nitration, oxidation and halogenation reactions, leading to an increased mutation load [52,53]. Reaction of DNA with these major lipid peroxidation products, such as 4-hydroxynonenal (HNE) and 4-hydroperoxynonenal (HPNE), results in the formation of modified DNA bases, which may contribute to carcinogenesis. Moreover, ROS and RNS may interact with genomic DNA, producing several base modifications with pro-mutagenic potential, such as 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) and 8-nitro-2'-deoxyguanosine (8-NO_2-dG) [54,55]. Further, the lipid peroxidation product, malondialdehyde (MDA), results in the generation of M_1dG adduct, which is a biomarker of oxidative stress [56]. The resulting genetic changes act as the triggering force in chronic inflammation associated human disease pathogenesis. It has been reported that 8-oxodG was expressed more intensely in the mucosa of UC-associated neoplasia and UC without neoplasm in comparison to normal mucosa [57]. Several reports state that UC leads to DNA damage at the local site, i.e., colon. Interestingly Westbrook et al. reported that intestinal mucosal inflammation leads to systemic genotoxicity in UC-induced mice. The authors further highlighted that the global effect of genotoxicity in the peripheral blood is mainly due to oxidative stress [8,58]. It has been speculated that locally activated immune cells may release the reactive species that damage the infiltrating leukocytes. The damaged leukocytes then migrate into the systemic circulation via the lymphatic system [58]. The damaged leukocytes may also migrate into the liver via the hepatic portal vein and then enter into the peripheral circulation. This may be one of the reasons that hepatic abnormalities occur as one of the extra-intestinal manifestations of UC. Approximately 5–10% of patients suffering from inflammatory bowel diseases develop hepatobiliary disorder [59]. The gastrointestinal tract and the hepatobiliary system are closely linked anatomically and all mesenteric venous drainage ascends via the portal vein into the liver. This makes the liver and the biliary system a direct target for damage during the exaggerated colonic inflammatory response seen in inflammatory bowel disease. Further, it has been shown that intestinal inflammation induces DNA damage in extra-intestinal tissues, such as blood, lymphoid organs and hepatocytes in mice with experimental colitis [9]. Recently, we have reported that DSS-induced UC leads to increased hematopoiesis and induces both local as well as systemic genotoxicity in mice [60]. Thus, UC leads to not only local but also global DNA damage, which is partly mediated via the generation of oxidative stress. It has been reported that oxidative stress regulates the gene expression of various cytokines including TNF-α [61]. TNF-α inhibitors have been proven to be effective for the treatment of inflammatory bowel disease and the associated extra-intestinal manifestations [62]. This implies that TNF-α has a role in the development of extra-intestinal manifestations in UC. However, the exact role of ROS-induced TNF-α in modulating the expression of various transcription factors, such as NF-κB, STAT3 and Nrf2 as well as inducing DNA damage in the extra-intestinal tissues needs to be further explored to establish a direct linkage.

Contribution to global carcinogenesis

Oxidative stress is a hallmark of UC and plays a vital role in the pathogenesis of the disease and the associated carcinogenesis. ROS and RNS can react directly with DNA bases to form pro-mutagenic exocyclic adducts with a five-membered ring (etheno adducts) or a six-membered ring (propano adducts) attached to DNA bases [63,64]. ROS and RNS have also been known to inhibit or impair the activity of DNA repair enzymes thereby increasing the mutation load ultimately leading to carcinogenesis. The 8-oxodG DNA adduct, which is formed due to exposure of DNA to ROS, is repaired by the DNA repair enzyme, Ogg1. It has been reported that DNA repair-deficient Ogg1 mice show an increased susceptibility to chronic inflammation and the subsequent carcinoma. Ogg1 deficient mice showed significantly increased mutations in the colon as evident from enhanced staining intensities of 8-oxodG positive inflammatory and epithelial cells. [65]. Further, the adaptive imbalance in base-excision repair enzymes, AAG, the major 3-methyladenine DNA glycosylase and APE1, the major apurinic site endonuclease, has been known to be associated with frameshift

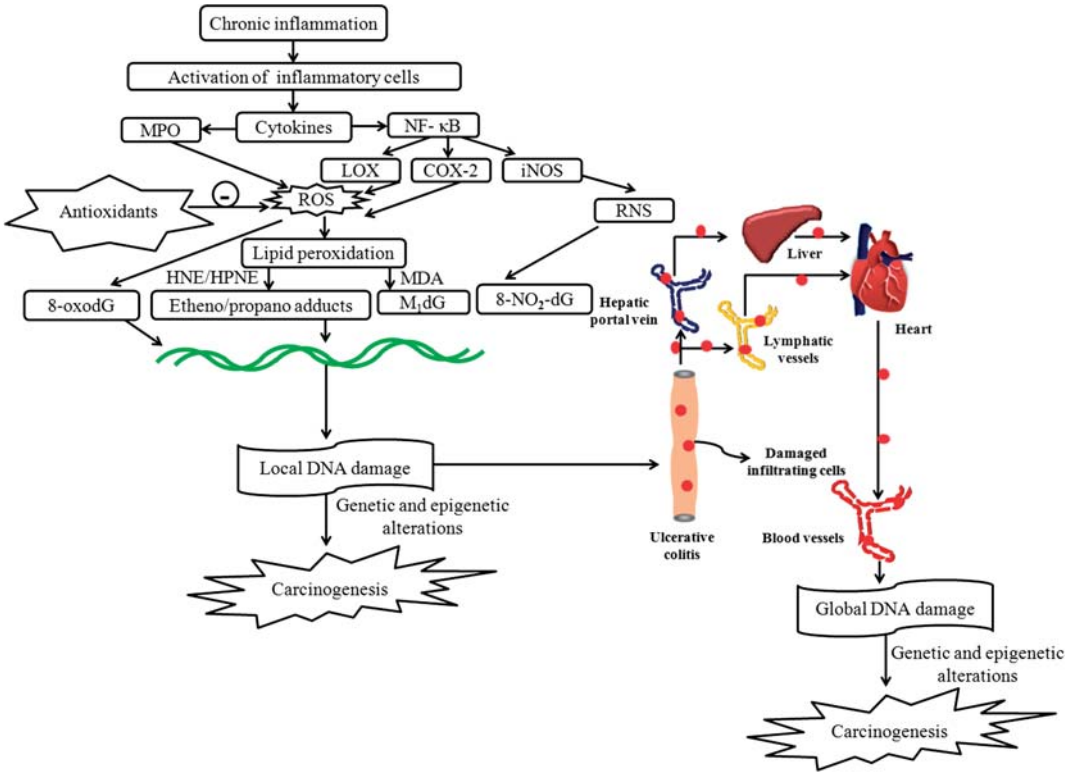

Figure 1. Mechanisms involved in oxidative stress-induced local as well as global DNA damage, which may lead to carcinogenesis and the possible intervention with anti-oxidants.

mutations and microsatellite instability in UC patients [66]. Studies with human biopsy and colectomy samples reveal that ROS and RNS have been implicated in the pathogenesis of UC and the associated carcinogenesis. An increasing number of experimental and clinical evidence suggest that ROS, such as, superoxide, hydrogen peroxide, hydroxyl radical, and halogenated oxidants may play an important role in the pathogenesis of inflammatory bowel disease [42]. It has been reported that amount of serum hydroperoxides, which is related to the free radicals from which they are formed, is elevated in proportion to tumour invasion and has a significant positive correlation with tumour size in the patients with colorectal cancer [67]. Patients with colorectal cancer have been known to depict significantly increased levels of protein carbonyl, advanced oxidation protein products and 8-oxodG as well as significantly decreased levels of vitamins C and E as compared to the control group [68]. Apart from causing genetic changes, ROS can lead to epigenetic alterations in DNA methylation patterns which can affect the regulation of expression of many genes, such as silencing of tumour suppressor genes like p53, *CDKN2/p16/MTS,* retinoblastoma and von Hippel-Lindau (VHL), and activation of proto-oncogenes such as BRAF, KRAS, *Ha-ras* and *raf* [69–75]. Further, ROS can result in aberrant hypermethylation of tumour suppressor gene-promoter regions, such as CpG islands, leading to gene silencing and thus progression towards a malignant phenotype [76–78]. Hence, oxidative stress can be considered as one of the important triggering factors in provoking UC and the associated colorectal cancer.

Role of biomarker studies in ulcerative colitis

There is no single confirmatory test or examination for the diagnosis of UC and hence a combination of symptoms, clinical examination, laboratory indices, endoscopy and histology are being applied to assess the severity as well as to predict the outcome of the disease [79]. The present biomarkers are mostly identified in serum, stool and some of them in the intestine. Serum C-reactive protein (CRP) appeared to be the most reliable factor reflecting the activity and extension of lesion in UC. In a study from Mayo Clinic, it was concluded that serum CRP levels were associated with increase in the biomarkers of inflammation in a cohort of 43 UC patients [80]. Active gut inflammation in patients with UC leads to migration of leucocytes to the gut that produce several proteins, which may be detected in stools [81]. Faecal markers are non-invasive, simple, in-expensive, sensitive and specific parameters to detect gastrointestinal inflammation. It has been reported that lactoferrin is the most suitable neutrophil-derived faecal marker of inflammation for clinical applications [82]. The levels of myeloperoxidase, lactoferrin and eosinophilic chemotactic factors indicate activation of neutrophils along gut mucosa during the exacerbation of the disease and the measurement of these can give indirect evidence of colonic inflammation in a non-invasive manner [80]. It has been reported that faecal calprotectin is strongly associated with colorectal inflammation, indicating the presence of the disease [83]. Further, tropomyosins, microfilament-associated proteins found in all eukaryotes, have been implicated in the pathogenesis of UC.

Anti-tropomyosin autoantibodies have been detected in the sera of patients with UC and hTM5 (one of the isoforms of tropomyosin) has been reported as the predominant immunogen in UC patients [84]. Further, aldolase B, an isoenzyme of the class I fructose 1,6-bisphosphate aldolase enzyme and elafin, a peptidase inhibitor, have been found to be up-regulated in UC patients [85].

Intervention of anti-oxidants in ulcerative colitis

Use of antioxidants may serve as a therapeutic strategy to combat oxidative stress and the associated carcinogenesis. Various antioxidants have been reported to ameliorate the oxidative stre**ss** and show the protective effects in animal models as well as in humans [86–90]. Further, mucosal healing in UC has been considered as a paradigm of success to reduce the severity of the disease [91]. Several antioxidants may partly help in healing the mucosa by combating oxidative stress in colon and thereby may have beneficial effects for the treatment of UC. It has been known that glutathione supplementation in a rat model of TNBS-induced experimental colitis significantly improved colonic damage and decreased lipid peroxidation [92]. It has been demonstrated that curcumin has a prophylactic role in DSS-induced UC murine model and its activity is mediated partly through its antioxidant and anti-inflammatory properties [93]. Resveratrol has been reported to reduce oxidative damage in mice with DSS-induced UC by reducing MDA levels and increasing GPx and SOD levels in the colon [94]. Clinical use of antioxidants to reduce the severity of UC has been reported [95,96]. Thus, various evidences demonstrating the role of antioxidants in the attenuation of UC convincingly reveal the impact of antioxidants on the course and the progression of the disease. Mechanisms involved in oxidative stress-induced local as well as global DNA damage, which may lead to carcinogenesis and the possible intervention with anti-oxidants have been depicted in Figure 1.

Future prospects

Oxidative stress is a risk factor for the development of chronic inflammatory diseases, such as UC. It is the main culprit driving inflammation towards DNA damage, which in turn, leads to carcinogenesis. Repair of DNA lesions formed by inflammation-associated reactive oxygen and nitrogen species is an important aspect for the protection against colon carcinogenesis [97]. Intervention of nutritional anti-oxidants has been well recognized to reduce the inflammatory symptoms against inflammatory joint disease, acute and chronic pancreatitis as well as respiratory disorders [98]. Further, the concept of mucosal healing is gaining acceptance to measure the disease activity against Crohn's disease and UC [91]. Recent findings point out that UC exerts local as well as global effects and perturbs the cellular genomic integrity, in which oxidative stress plays a vital role. This increases the risk of global carcinogenesis. It is perhaps the right time to critically look for the disease process and to explore appropriate agents that will be effective both in preclinical as well as clinical situations.

Declaration of interest

The authors report no conflicts of interest. The authors are responsible for the content and writing of the article.

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