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Review

Redox Imbalance in the Development of Colorectal Cancer

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Abstract

Redox imbalance is resulted from the destruction of balance between oxidants and antioxidants. The dominant oxidants are reactive oxygen species (ROS), which are involved in multiple cellular processes by physiologically transporting signal as a second messenger or pathologically oxidizing DNA, lipids, and proteins. Generally speaking, low concentration of ROS is indispensable for cell survival and proliferation. However, high concentration of ROS is cytotoxic. Additionally, ROS are now known to induce the oxidative modification of macromolecules especially proteins. The redox modification of proteins is involved in numerous biological processes related to diseases including CRC. Herein, we attempt to afford an overview that highlights the crosstalk between redox imbalance and CRC.

Key words: CRC, oxidative stress, redox modification, cysteine residues.

Introduction

CRC is a major health problem all over the world. Every year, more than 1.2 million patients are diagnosed with CRC, and almost 0.6 million died, making CRC the third most common cancer and the fourth most common cause of cancer-related mortality at present [1, 2].CRC initials a growth called polyp, which begins from the inner surface of the colon or rectum. There are two types of polyps commonly found in the colon or rectum: hyperplastic or inflammatory polyps, and adenomas or adenomatous polyps, which are prone to turn into cancers [3]. In addition, the dysplasia cells in the lining of the colon or rectum may also develop CRC, and is more commonly seen in people with certain IBD like Crohn's disease or ulcerative colitis, in fact, the IBD is the top three high risk factors for CRC [4]. CRC holds other risk factors as well, including age, sex (the risk is higher in women than in men at young ages), smoking, family history of CRC, over drink of alcohol, red meat diet, obesity, diabetes and so on [1]. The CRC therapy strategies are rare at present and mainly dependent on surgery combined with chemotherapy and/or radiotherapy, which is effective against early stage of CRC but poorly effective against advanced stage of CRC especially cancer with metastasis or postoperative recurrence [5]. As a consequence, it is in urgent need of the markers in early diagnosis of CRC and intervention targets in cancer therapy.

Essentially, oxidative stress is an imbalance between ROS production and the counteractive ability of antioxidants [6]. Free radical involving oxygen can be referred as ROS [7]. Generally, there are two kinds of ROS, the free radicals such as superoxide anion ($O_2^{\bullet -}$), hydroxyl radical ($^{\bullet}OH$) and the non-radical molecules such as hydrogen peroxide (H_2O_2), singlet oxygen ($^1O_2$) [8]. Mitochondrial respiration is the primary source of ROS and almost 90% of ROS are produced by mitochondria [9, 10]. The electrons are

transferred to molecular oxygen by mitochondrial respiratory chain, producing H_2O or $O_2^{\bullet -}$, and SOD can catalyze $O_2^{\bullet -}$ to H_2O_2 which is subsequently converted into H_2O by catalase or to the highly $^{\bullet}OH$ through Fenton reaction [11] (Fig. 1). Apart from mitochondrial, the NADPH oxidase (NOX), which is mainly response to stress, is another source of intracellular ROS [12] (Fig. 1). As for the elimination of ROS, there are endogenous and exogenous small molecular antioxidants, or enzymatic and nonenzymatic antioxidants [13] (Table 1). The metabolism of these antioxidants regulates the cellular concentration of ROS to prevent cellular damage. For example, $O_2^{\bullet -}$ is converted into H_2O_2 by SOD, and then, H_2O_2 is disintegrated into water and oxygen by CAT [14].

Table 1. Antioxidants category

Type	Name	Refs
Endogenous	GSH; alpha-lipoic acid; coenzyme Q; ferritin bilirubin; uric acid; metallothionein; melatonin and L-carnitine;	[13, 157]
Exogenous	NAC; butylated hydroxytoluene; propyl gallate; tiron; pyruvate; butylated hydroxyanisole; selenium;	[13, 157]
Enzymatic	SOD; CAT; GPX;APX	[158]

On account of the high activity, ROS can react with most of the intracellular substances especially with cysteine residue of proteins, which is called redox modification [15]. In fact, redox modification of proteins are involved in physiology and pathology processes like metabolisms, neurodegenerative diseases and cancers [16, 17]. Considering this, we mainly discuss the function of ROS in the development of CRC and summarize related advances.

The relation between oxidative stress and CRC

In physiological condition, the ROS production and the ROS scavenging ability of antioxidants keep a rough balance, and ROS can assist cell proliferation, migration and differentiation, regulate intermediate products, control the homeostasis of cell and tissue, and activate the survival pathway upon stress response [18, 19]. However, under the pathological condition, excessive level of ROS accumulation due to altered equilibrium between ROS and antioxidants may lead to different kinds of diseases such as atherosclerosis, diabetes, neurodegeneration, and cancer including CRC [20, 21]. Accumulating evidences found that CRC risk factors like smoking and alcohol consumption were involved in ROS production [22, 23]. What's more, studies also revealed that more ROS will be generated in chronic disease of the gastrointestinal tract [24]. For example, oxidative stress is a characteristic of chronic IBD and may increase colon cancer risk [7]. Moreover, through monitoring serum markers such as MPO and oxLDL, researchers observed that the oxidation process begun development in the polyp stage of CRC as well [25]. Thus, it is possible that these risk factors contribute to colorectal carcinogenesis in a ROS dependent way. However, how do these diseases turn into cancer are still not fully understand.

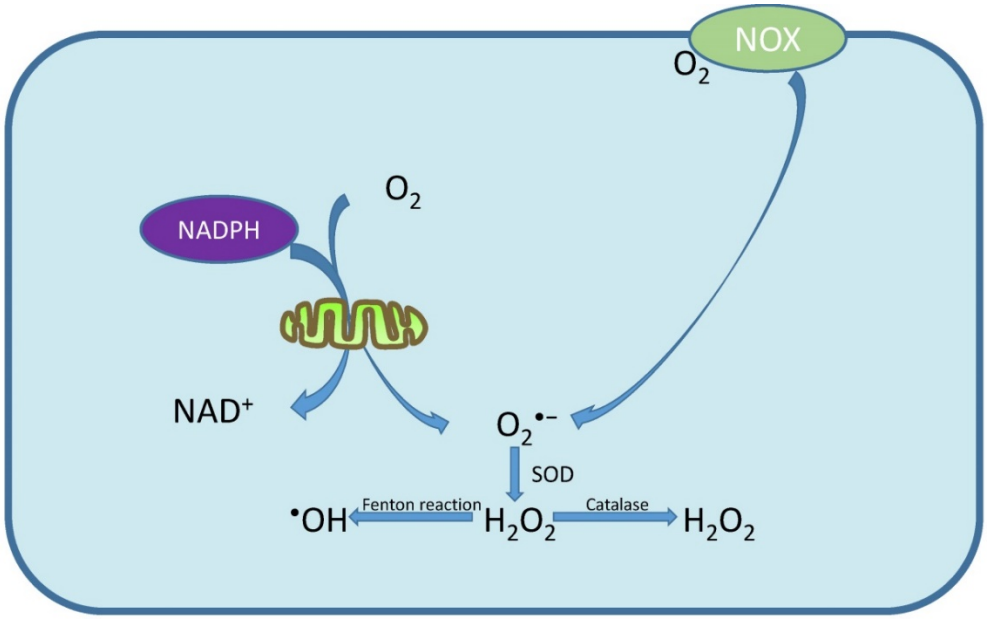

Figure 1. Mechanism of ROS production. O_2 is mainly transformed to $O_2^{\bullet -}$ by mitochondrial respiratory chain and NOX. $O_2^{\bullet -}$ will be catalyzed to H_2O_2 by SOD, and H_2O_2 is subsequently converted into H_2O by catalase or to $^{\bullet}OH$ through Fenton reaction.

Chronic oxidative stress is a risk factor for CRC [26]. ROS exhibit a high biological activity that could react with substances especially DNA, lipids, and proteins. Thus, excessive level of ROS can affect cancer cell growth, metabolism, invasion and metastasis through gene mutation, DNA damaging, protein conformation transition and so on [22, 27]. For example, through reacting with pyrimidines, purines and chromatin proteins, •OH can induce base modification, genomic instability as well as genetic alteration, all of which contribute to carcinogenesis [28].

ROS-related genetic alteration in colorectal carcinogenesis

It is widely known that ROS-induced DNA damages and genetic mutations are critical causes of cancers including CRC [29]. The main intracellular DNA lesions caused by ROS are single and double strand DNA breaks, and the common genetic mutations include p53, KRAS, APC, and BRAF mutations [30]. For example, a direct relation among oxidative stress, DNA damage and elevated frequency of p53 mutation in CRC has been observed [23]. Most extensively studied endogenous DNA damage by ROS is the formation of 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG) [31]. As the biomarker of oxidative stress, 8-oxodG level is higher in colorectal tumors than in normal mucosa [31]. Moreover, increased 8-oxodG is also found in leukocytes and urine of CRC patients [32]. In fact, researchers had concluded that levels of 8-oxodG could be applied in clinical practice as an additional and helpful marker to diagnose cancer [33, 34]. Otherwise, 8-oxodG could also induce mismatched pairing and result in switches of cytosine (C) to adenine (A) and/or guanine (G) to thymine (T) [35]. Thus, 8-oxodG is an important cancerogenic factor as well [36]. Fortunately, there are numerous kinds of DNA repair enzymes which could repair the damages induced by 8-oxodG [37]. For example, 8-oxoguanine DNA glycosylase 1(OGG1) and MYH enzyme could repair DNA by detecting and removing the 8-OHdG or mismatched A [38]. However, the activity of OGG1 and MYH enzyme were regulated by ROS, for example, investigators observed that ROS could inhibit the activity of OGG1 through oxidizing the cys326 of OGG1 [39]. In addition, compared with nuclear DNA, mitochondrial DNA is particularly prone to be oxidatively damaged and is more meaningful in colorectal carcinogenesis [40]. Interestingly, apart from that ROS could generate DNA damage, on the contrary, DNA damage could generate ROS as well[41]. For example, study reported that H2AX could regulate Nox1-mediated ROS generation after DNA damage [42]. Thus, a circulated pathway formed, in which ROS and DNA damage promote each other to strengthen the genetic alteration.

ROS induces lipid peroxidation in CRC

Lipid peroxidation comes from the free radical oxidation of polyunsaturated fatty acids in biological systems [43]. The commonest lipid peroxidation products are MDA and HNE, the levels of which in the CRC tissue are significantly increased with clinical staging [44] (Fig. 2). Although the role of MDA and HNE are still not fully understand, researchers have observed that the HNE could promote the expression of COX-2 which directly induces APC loss and subsequently reduces the degradation of β-catenin, then, the β-catenin translocates to the nucleus and acts as a transcription factor in concert with the T-cell factor-4 (TCF-4) to induce colorectal carcinogenesis [45, 46] (Fig. 3). On the other hand, COX-2 produced prostaglandin can regulate tumor associated angiogenesis, promote cell migration, and inhibit apoptosis, all of those three processes are causes for carcinogenesis [47].

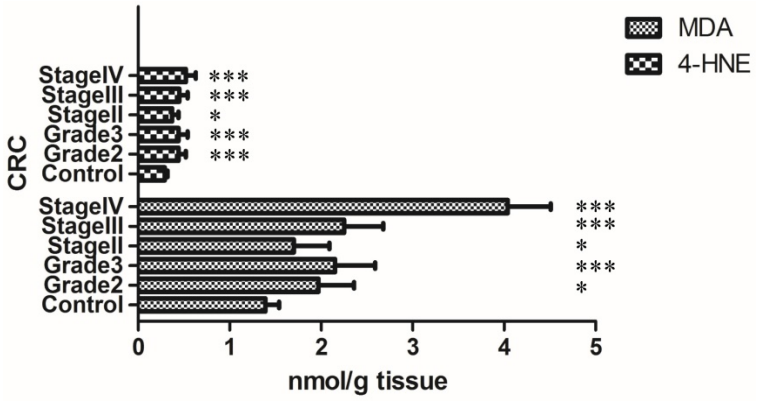

Figure 2. Lipid peroxidation levels with clinical staging of CRC. Lipid peroxidation is significantly increased with clinical staging of CRC. Grade2, 3: histological grade of CRC; Stage II, III, IV: clinical stage of CRC; Control: normal colon mucosa. Collation of data from Elzbieta Skrzydlewska *et al* [44] (Original data do not include Gade1 and stage I CRC).

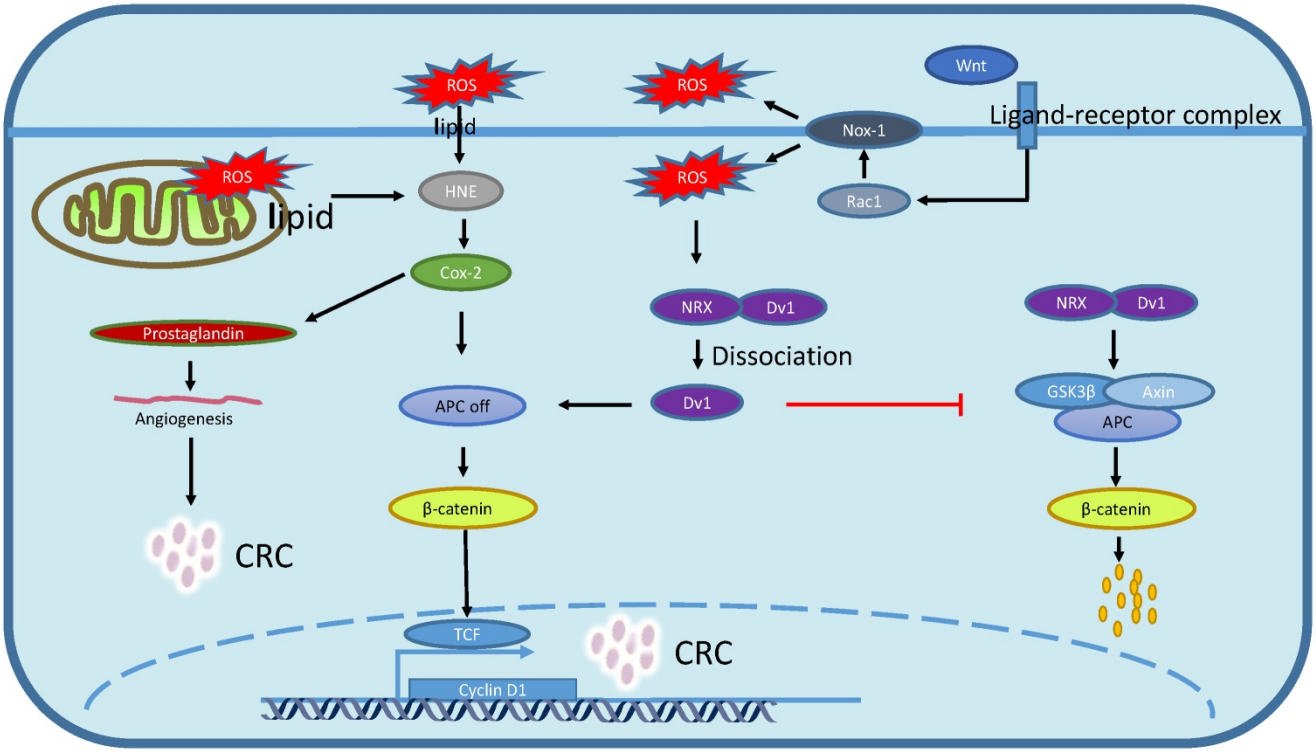

Figure 3. Redox regulation of Wnt/β-catenin signaling pathway and lipid peroxidation. Lipid peroxidation-generated HNE promotes cox-2 expression which induce APC mutation or loss, and the APC loss subsequently inhibit β-catenin degradation that contribute to β-catenin nucleus translocation and targeted genes transcription. Wnt/β-catenin activation aggrandizes Nox1-produced ROS which in turn triggers the dissociation between NRX and Dv1, then dissociated Dv1 suppresses APC expression which results in β-catenin nucleus translocation and targeted genes transcription.

The COX-2 inhibitor such as NSAIDs application is an effective way to prevent CRC. For example, aspirin is used to prevent and treat CRC [48]. NSAIDs, especially acetylsalicylic acid could bring about 50% decrease in CRC incidence and mortality [49]. Moreover, numerous phase III randomized controlled trials that evaluate the role of aspirin in the treatment of CRC are ongoing [50]. In spite of this, NSAIDs application will result in numerous kinds of adverse effects such as ulcers, internal bleeding, kidney failure, heart attack and stroke [51]. Interestingly, latest study demonstrated that some adverse effects of NSAIDs were results from ROS produced by NSAIDs [52]. In addition, MDA could induce DNA damage by directly reacting with DNA, and the product is a DNA adduct called M1G which may contribute to cancer [53].

ROS induces protein oxidation in CRC

Redox modification of thiols on cysteine residues

The protein oxidation in the condition of oxidative stress includes a series of reactions, which are divided into two kinds, the irreversible reaction and the reversible reaction [54]. The irreversible reaction results in protein aggregation and degradation [15]. And the reversible reaction includes methionine side chains oxidation and cysteine side chains oxidation [55]. Most intracellular proteins contain cysteine residues which are usually located in the activity center of proteins. Thus, oxidative cysteine modification is involved in numerous biological events [56]. ROS can reversibly oxidize the active thiol group of cysteine residues into sulfenic acid (R-SOH), inter/intramolecular disulfide bridge (R-S-S-R/R-S-S-R′) or protein-S- glutathione (GSH) disulfide, all of which could be reduced to thiol again [57].The most abundant intracellular ROS are hydrogen peroxides (H_2O_2), thus, the intracellular cysteine residues are usually oxidized by H_2O_2. In the redox reaction, H_2O_2 transfers hydroxide radical (OH^-) to cysteine thiolate (RS^-). According to the concentration of H_2O_2, the reaction products could be cysteine sulfenic acid (R-SOH), cysteine sulfinic acid ($R\text{-}SO_2H$) or cysteine sulfonic acid ($R\text{-}SO_3H$) [58]. However, the cysteine sulfenic acid(R-SOH) group and cysteine sulfinic acid($R\text{-}SO_2H$) are not stable, and they could be deoxidized back to cysteine thiolate (RS^-) by reducing agents such as thioredoxin, glutaredoxin, peroredoxin and dithiothreitol [59, 60]. Because of the properties, redox modification on cysteine residues could influence function of proteins reversibly and consume ROS by generating cysteine sulfenic acide (R-SOH) and cysteine sulfinic acid ($R\text{-}SO_2H$) [61]. Otherwise, cysteine residues

modification could cause allosteric interaction in proteins and alter or eliminate protein function permanently as well [62]. Redox modification on protein cysteine thiol has been shown to regulate protein activity involved in transcription, translation and function performing [63]. For example, the redox regulation of Keap1 by oxidation of thiols cause activation of Nrf2 [64]. In addition, a large number of proteins have been identified as redox sensitive proteins in recent years, most of which are involved in the initiation, progress and prognosis of CRC [65]. Thus, it becomes necessary to assess the status of cysteine residues redox in CRC. In this part, we highlight the relation between redox modification in protein cysteine residues and CRC development.

Multiple roles of redox modification in CRC

Accumulating evidences have shown that moderate level of ROS functions as signaling messengers promoting proliferation and invasion of cancer cells, whereas, redox proteins could scavenge basal ROS and function as "tumor suppressors", or prevent excessive ROS to act as "tumor promoter" [66]. Redox modifications of proteins involved in CRC oncogenesis are through signaling pathways and transcriptional factors modulation [65]. Thus, targeting redox-sensitive signaling pathways, proteins and transcriptional factors as an anticancer strategy offers great promise to prevent and treat CRC.

Redox sensitive/regulate pathways

Cell signaling transduction usually includes 3 steps: upstream transmembrane signal transduction, midstream cytoplasm signaling pathways and intranuclear signal transduction. Extracellular stimulation could often induce alteration of intracellular redox status, which will affect conformation and function of signal molecules to regulate the signal transduction pathways [67]. It is well accepted that intracellular redox imbalance is involved in abnormal activation of some pathways that are closely related with CRC initiation and development, such as the Wnt/β-catenin signaling pathway, PI3K/AKT signaling pathway and the JAK/STAT signaling pathway [68-70].

For example, in the absence of Wnt signaling, NRX binds to Dv1, which will stabilize the Axin, Apc and GSK3β destruction complex, then sequentially phosphorylates β-catenin which subsequently mediates the degradation of β-catenin (Fig. 3). When Wnt signal is activated, ligand-receptor complex triggers Rac1 activation to induce the production of Nox-1-derived ROS which subsequently oxidizes NRX to dissociate Dv1 from NRX and results in suppressing the degradation of β-catenin, which will contribute to CRC carcinogenesis by activating targeted genes like c-Myc [71] (Fig. 3).

PI3K/AKT signaling pathway is closely associated with colon cancer as well, and inhibition of this pathway provides a therapy strategy that may result in curable colon cancer [72]. Studies revealed that ROS could trigger the activation of PI3K and subsequently induce the colorectal carcinogenesis [72-78]. For example, functional studies of oxidative stress observed that the expression of STMN1 and PI3K-AKT-mTOR signaling pathway were involved in ROS-induced and ITGB3-mediated migration and invasion of CRC cells [73]. Furthermore, excessive level of ROS could activate PI3K signaling pathway by oxidizing PTEN cys124, and that will result in CRC [74, 75]. And *in vitro* study found out that selenite-induced CRC apoptosis was through inhibition of ROS dependent PI3K/AKT pathway [76]. In addition, since EGFR can deregulate the PI3K signaling pathway, the redox modification of EGFR may involve in PI3K pathway activation as well [77]. For example, EGFR can be activated through redox modification of EGFR cys797 [78].

Multiple growth factors and cytokines work as activator in JAK/STAT signaling pathway [79]. Recent studies revealed a prominent role for JAK/STAT pathway in promoting CRC cell growth and survival [68]. In addition, ROS can activate the CRC-related JAK/STAT pathway as well. For example, Sang-Kyu Park demonstrated that short time of H_2O_2 stimulation induced the activation of STAT pathway by phosphorylation of the Tyr705 of STAT3, which induced the overexpression of cyclinD1 and inhibition of CRC cell apoptosis [80-82] (Fig. 4). EGFR is one of the STAT activators [83], and the redox modification on EGFR cys797 could indirectly activate STAT as well [78] (Fig. 4). Moreover, oxidized low density lipoprotein (oxLDL) could strengthen the combining capacity of STAT1 and STAT3 [84]. And dimerization of STAT3 can be generated by oxidative modification of STAT3 cys253, which promotes its translocation to nucleus [85] (Fig. 4). However, in addition to redox modification-induced STAT pathway activation, oxidative stress can reverse the STAT activation as well, for example, the activation of STAT3 could be impaired by S-glutathionylation in cys328 and cys542 [86] (Fig. 4).

The MAPK cascades are membrane to nucleus signaling modules that respond to oxidative stress which lead to phosphorylation and activation of down-stream genes required for CRC [87, 88]. For example, the EGFR cys797 can be oxidized and activated by ROS, which initiates the MAPK cascade that is responsible for CRC [89]. Kyoungmun Lee *et al*

analyzed the relation between ROS and MAPK, and found out that the inhibition of PTPs by H_2O_2 resulted in phosphorylation and activation of ERK, p38 and JNK [90]. Except these, ROS can directly oxidize the constituent parts of MAPK as well, for example, in a CRC model, researchers observed that NOX-generated ROS could induce the activation of Ras by S-glutathionylation on cys118 [91]. However, it is controversial that ROS can work as a trigger to turn off the MAPK cascades either, for example, H_2O_2 is able to reduce the activatiy and phosphorylation level of p38, ERK1/2 and JNK by inhibiting the MEK1/2 activities [92]. And *in vivo* study showed that H_2O_2 could suppress p38 activity by oxidizing p38 cysteine residues [93].

Redox-related transcription factors

Transcriptional factors are a group of proteins which could bind to specific DNA sequences to regulate/trigger genes expression, such as NF-κB, p53, HIF-1α and Nrf2. The increasing production of intracellular or extracellular ROS could regulate the activity of transcriptional factors and play a pivotal role in colorectal carcinogenesis [63, 94, 95]. For example, *in vitro* study showed that ethanol could enhance arsenic-induced CRC via NF-κB in an ROS dependent way [96]. In addition, emodin inhibits the proliferation of CRC cells by inducing ROS-mediated p53 activation [97].

NF-κB is an important transcription factor in the regulation of inflammation, cell cycling, apoptosis, metabolism and carcinogenesis, while growing evidence also support a major role in CRC [98]. In the canonical pathway, NF-κB binds to IκB and is detained in cytoplasm. While stimulus triggers a cascade of events which lead to IκB phosphorylation by inhibitor κB kinase (IKK) complex, NF-κB is released from IκB and translocated to the nucleus to regulate gene expression [99]. The activity of IKK complex and NF-κB is prone to be regulated through redox modification on cysteine. Study revealed that IKK complex subunit, NEMO, was an essential activator of NF-κB, and ROS could activate the NF-κB through modification of NEMO, that is, inducing the formation of disulfide bond between cys347 and cys54 by H_2O_2 [74] (Fig. 4). ROS can also inhibit the activation of NF-κB by inducing S-glutathionylation on the cys189 of IKKβ (Fig. 4). Moreover, Takeyuki Nishi *et al* found that p65 subunit and cys62 of p50 were highly oxidized in cytoplasm and strongly reduced in the nucleus, meanwhile, the reduced form of cys62 was essential for the DNA binding activity of NF-κB [73]. Recent studies demonstrated that the role of ROS on NF-κB activation was cell type dependent [74] [100]. For example, in limphycyte cell, ROS induce the phosphorylation of IKK and subsequently activate NF-κB [75], while in pulmonary epithelial cells, H_2O_2 oxidizes cysteine residues to inhibit the activation of IKKβ which could reduce the activation of NF-κB [76].

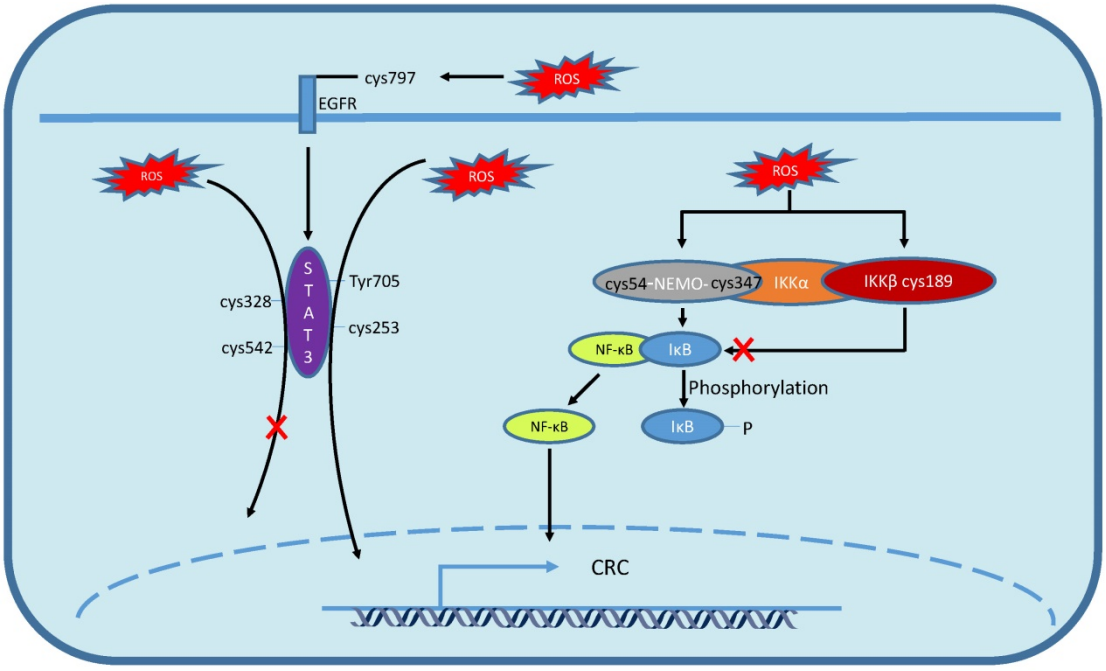

Fig. 4. Redox modification on cysteine residues of NF-κB and JAK/STAT signaling pathway. Intracellular ROS induce the phosphorylation of STAT3 Try705 and triggers dimerisation of STAT3, then, dimerisation of STAT3 translocates to nucleus. Extracellular ROS induces STAT3 activation by oxidation of EGFR cys797 while intracellular ROS induces STAT dimerization by oxidation of STAT3 cys253. Whereas ROS-induced S-glutathionylation on cys328 and cys542 impairs STAT3 phosphorylation, damages STAT3 dimerisation and inactivates targeted gene transcription. The NEMO cys347 and cys54 disulfide bond formation leads to IκB phosphorylation and release NF-κB, then NF-κB translocates to nucleus. Whereas ROS induced s-gluthionylation on cys189 of IKKβ inactivates NF-κB.

P53 is an important tumor suppressor that induces the apoptosis of malignant tumor cells [101]. Redox-related deletion or mutation of p53 could contribute to colorectal carcinogenesis [102]. For example, study showed that the zinc finger protein 148 (Zfp148) was a potent suppressor of p53 under oxidative stress, which contributed to CRC development [103]. Jenna Scotcher showed that p53 was a multiple cysteine-containing protein [104], thus, it is possible that the redox modification of p53 cysteine residues acts as a switcher that trigger on/off p53 activation. For example, previous study reported that cys182 and cys277 were implicated in p53 redox-regulation, while, cys176, cys182, cys238 and cys242 were found to be oxidized residues in p53 under the treatment of H_2O_2 [82]. Oxidization suppressed p53 transcriptional activity which subsequently inactivated targeted genes like Bax and bcl-2 expression and resulted in apoptosis inhibition that may induce CRC [105-107]. On the other hand, GSH-induced p53 inactivation may be dependent on S-glutathionylation of p53 on cys141 and lead to colon carcinogenesis [108].

The rapid proliferation of CRC cells can generate a hypoxic microenvironment that activates the transcription factor HIF1-α by redox modification. For example, Klaus Jürgen Schmitz *et al* reported that under hypoxic condition, the oxidative modification of HIF1-α was downregulated which stabilized the HIF1-α and drove its translocation into the nucleus, where expression of its target genes was upregulated and substantially strengthened the CRC development [109]. While, in basal oxygen condition, ROS can activate and stabilize HIF-1α, for example, John J. Haddad *et al* reported that cytokine-mediated regulation of HIF-1α stabilization, translocation and activation required a non-hypoxic, ROS-sensitive mechanism [110]. The ROS-sensitive mechanism is basically based on redox modification of cysteine residues. For example, recent studies found that HIF-1α was a potential target for S-nitrosation, and the S-nitrosation of cys800 induced the recruitment of p300 co-activator protein to the HIF-1α C-terminal domain which increased its transcriptional activity [111]. And S-nitrosation of cys162 in pVHL could decrease HIF-1α ubiquitination that benefit the angiogenesis and induce colorectal tumorigenesis [109, 112, 113].

In addition to serving as a ROS-sensitive transcription factor, Nrf2 is the most important intracellular regulator of antioxidants [114]. For example, Nrf2 can directly eliminate ROS via regulating GSH metabolism [115]. Recent study reported that Nrf2 can protect against oxidative stress-derived cancer in stomach, skin, bladder and colon [116, 117]. Under physiological condition, Nrf2 binds to keap1 in cytoplasm where it keeps inactivated and is easy to be degraded [118]. While, in the condition of oxidative stress, redox modification of keap1 cys151, cys273 and cys288 could detach the Nrf2-keap1 complex and lead to the dissociation of Nrf2 from keap1 [64, 119, 120]. Furthermore, oxidants and electrophiles-induced phosphorylation of PKC and ERK can subsequently promote phosphorylation of Nrf2 at serine40 which is necessary for the dissociation of Nrf2 from keap1 [121]. Released Nrf2 will be translocated to nucleus where it binds to genes containing antioxidant responsive element (ARE) or electrophile responsive element (EpRE) that initiate antioxidant responses [64, 119, 120]. And the Nrf2-induced adaptive response to ROS inhibits HIF1-α-VEGF signaling, resulting in diminishing angiogenesis and CRC growth [122]. Furthermore, recent *in vivo* and *in vitro* study showed that evolutionarily conserved cysteine residues of Nrf2 like cys119, cys235 and cys506 were necessarily needed in modulation of oxidative stress as well as keap1-induced ubiquitination [123]. Paradoxically, although a large number of evidences indicate that the activation of Nrf2 protect against a variety of cancers, the prolonged activation of Nrf2 has been shown to favor the progression of several types of cancers [124]. For example, researchers observed a continuously elevated Nrf2 expression in lung, breast, ovarian and endometrial cancer [57, 125-128]. And the elevated Nrf2 may be related to cancer proliferation by maintaining redox homeostasis, for example, in A549 cells, researchers found out that Nrf2 could accelerated cancer cell proliferation by promoting GSH synthesis [129]. However, whether a similar effect exists or not in CRC is still uncovered.

Modulation of ROS as anticancer strategy

ROS could mediate the colorectal carcinogenesis through gene mutations, redox related signaling pathways and redox related transcription factors, thus dietary and endogenous antioxidants can prevent cancer by reacting with or eliminating oxidizing free radicals [130]. A large randomized trial investigated the putative preventive role of antioxidants on cancer, for example, the consumption of antioxidants like selenium, vitamin E and β-carotene significantly decreased cancer mortality [131]. A similar prevention effect was also observed in CRC. For example, Melissa Y. Wei *et al* determined that the high level of vitamin D was associated with a decreased risk of colorectal adenoma, including advanced adenoma and recurrent adenoma [132]. Moreover, antioxidants like GSH could inhibit malignant phenotype of CRC [133] and reduce proliferation of CRC by decreasing the

expression of cyclooxygenase-2(COX-2) and the production of prostaglandin [134].

On the other hand, increasing ROS as an anticancer therapy has also been well studied these years [135]. Since overaccmulation of ROS can lead to the preferential killing of cancer cell [136], the utilization of oxidants renders a new way in CRC therapy. The study of Yushuang Ding *et al* supported that promoting ROS overload might be an important strategy for the development of new anticancer drugs [137]. In fact, numerous anti-cancer drugs used by CRC patients are involved in the ROS production (Table 2). For example, 5-Fu is commonly used in the treatment of CRC, especially in CRC at stage III and high risk stage II, alone or together with other drugs [138]. 5-Fu has been used in CRC treatment for more than 40 years and has several mechanisms of anti-cancer effects [139, 140]. In addition to inhibiting the DNA synthesis, altering RNA processing and inducing DNA damage, 5-Fu-activated anti-cancer response can be based on ROS elevation as well [141]. For example, *in vitro* study observed that 5-Fu treatment in CRC cells generated O_2^- that positively regulated p53 proteins and thereby induced cancer cell apoptosis [142, 143]. Tamoxifen is a breast cancer drug, whereas, researchers showed that tamoxifen may play a beneficial role in other malignancies treatment [144]. For example, a murine model study revealed that tamoxifen could inhibit colorectal liver metastases [145]. Moreover, *in vivo* study found that tamoxifen could reverse multidrug resistance of CRC [146]. In addition, a latest study demonstrated that tamoxifen could induce the CRC senescence via antagonizing with CK2α and then promoting ROS generation [147]. Celecoxib is a selective inhibitor of COX-2 and can significantly reduce the risk of colorectal adenomas [148]. The anti-cancer effect of celecoxib is previously considered to base solely on specific inhibition of COX-2 that inhibits angiogenesis by down-regulating VEGF [149]. However, recent study revealed that the anti-cancer effect of celecoxib might be based on ER stress-derived ROS as well [150]. In addition to those specific CRC drugs, there are numerous types of drugs used in cancer therapy including but not limited to CRC, which are also implicated in elevated ROS production. For example, methotrexate can trigger ROS-associated cell apoptosis in different types of cancer [151]. Moreover, irinotecan is a topoisomerases inhibitor that causes oxidative stress among different types of cancer [152]. Meanwhile, the ionizing radiation therapy can also induce accumulation of ROS. For example, after exposure to ionizing radiation, researchers observed an instantaneous and robust release of •OH that oxidized the ETC complex and resulted in mitochondrial dysfunction and CRC cells elimination

Table 2. Anticancer drugs in the regulation of ROS levels

Name	Mechanism of action	Effects on ROS	Cancers	Refs
5-Fu	Inhibits thymidylate synthetase and/or incorporates into RNA and DNA	Induces intracellular increase in $O_2^{\bullet-}$ levels	CRC	[137]
Tamoxifen	Promotes cancer cell senescence	Promotes ROS generation	CRC	[159]
Celecoxib	Inhibits COX2 activity, Induces ER stress by causing leakage of calcium from the ER into the cytosol	Induction of ROS owing to ER stress	CRC	[150]
Methotrexate	Triggers ROS related cell apoptosis	Promotes ROS generation	Different types of cancer	[160]
Irinotecan	Topoisomerases inhibitor	Promotes ROS generation	Different types of cancer	[161]
Mitoxantrone	Trigging cell membrane scrambling	Promotes ROS generation	Different types of cancer	[162]
Paclitxel(Taxol)	Inhibitor of cell division	Promotes ROS generation	Different types of cancer	[163]
Adriamycin	Reduces cell viability through initiating cell apoptosis and strong G2/M phase cell cycle arrest	Promotes ROS generation	Different types of cancer	[164]
Imatinib	Protein tyrosine kinase inhibitor that induce apoptosis	Promotes ROS generation	Different types of cancer	[165]
Camptothecin	Quinolone alkaloid that induces cytotoxicity	Promotes ROS generation	Different types of cancer	[166]
Carboplatin	Cell cycle arrest	Induction of ROS owing to ER stress	Different types of cancer	[167]
Capecitabine	Prodrug that is enzymatically converted to 5-Fu in the body	Promotes ROS generation	CRC	[168]
Cisplatin	Inducing nuclear DNA adducts	Induces a mitochondrial dependent ROS generation	Different types of cancer	[169]
Manumycin	Increasing the ROS production and blocking PI3K/AKT pathway	Promotes ROS generation	CRC	[170]
Cribrostatin 6	Quinone containing product induces apoptotic cell death	Promotes ROS generation	Different types of cancer	[171]

[153]. In addition, drugs that degenerate antioxidants are also found to be involved in CRC therapy. For example, 6-anicotinamide (6-AN) is an inhibitor of G6PD that reduces GSH in the treatment of colon cancer [154].

Conclusion remarks

CRC is a rather complex, multifactorial and multistage disease. As demonstrated previously, the intracellular redox imbalance is a decisive factor in the CRC development and progression. Malignant carcinomas usually characterize as a hypermetabolic state that leads to a persistent oxidative stress state in cellular microenvironment, thus the utilization of antioxidants that antagonize with ROS seems to be a feasible strategy in cancer therapy. But, systematic reviews found out that the use of antioxidants were invalid in cancer therapy, or even reversibly facilitated the progress of cancer [155, 156]. However, the problem is still considered controversial. And the frustrating consequence may partly due to that a certain decreased level of ROS is benefit for proliferation of cancer cells, especially those with very high ROS accumulation but still under the toxic threshold. On the other hand, using oxidants which preferentially kill cancer cells is another way in CRC therapy that has been well studied these years. However, the slight alternation in redox state can be amplified by modification of macromolecules, thus the redox related anticancer substances should be precisely controlled and targeted in body. On the basis of CRC processes, normal colon or rectum cells, polyps, adenocarcinomas and ultimately metastatic CRC, precisely utilizing oxidants and antioxidants with the help of redox sensitive marker is indispensable. Thus, more redox sensitive markers are needed.

Abbreviations

A: Adenine; ARE: Antioxidant response element; C: Cytosine; COX-2: Cyclooxygenase-2; CRC: Colorectal cancer; CAT: Catalase; EpRE: Electrophile responsive element; ER: Endoplasmic reticulum; GSH: Glutathione; GPXs: Glutathione peroxidants; G: Guanine; G6PD: Glucose -6-phosphate dehydrogenase; H2AX: Histone family member x; H_2O_2: Hydrogen peroxide; HNE: 4-hydroxynonenal; HIF-1α: Hypoxia inducible factor 1α; IBD: Inflammatory bowel diseases; IKK: Inhibitor κB kinase; INrf2: Inhibitor of Nrf2; IFN-α: Interferon-alpha; ROS: Reactive oxygen species; JAK: Janus Kinase; Keap1: Kelch-like ECH-associated protein 1; MPO: Myeloperoxidase; MDA: Malondialdehyde; MAPK: Mitogen-activted protein kinase; mTOR: Mammalian target of rapamycin; NOX: NADPH oxidase; NSAIDs: Nonsteroidal anti-inflammatory drug; NAC: N-acety1 cysteine; NIK: NF-κB inducing kinase; Nrf2: Tanscription factor NFE2-related factor 2; $O_2^{\bullet-}$: Superoxide anion; •OH: Hydroxyl radical; $^1O_2$: Singlet oxygen; oxLDL: Oxidized low-density lipoprotein; OGG1: 8-oxoguanine DNA glycosylase 1; OH-: Hydroxide radical; PRXs: Peroxiredoxins; PTKs: Protein tyrosine kinases; PTPs: Protein tyrosine phosphatases; PI3K: Phosphatidyl inositol 3-OH kinase; PKB: Protein kinase B; PTEN: Tension homolog; RS-: Cysteine thiolate; R-SOH: Sulfenic acid; R-SO_2H: Cysteine sulfinic acid; R-SO_3H: Cysteine sulfonic acid; R-S-S-R/R-S-S-R': Inter/intramolecular disulfide bridge; RTKs: Receptor tyrosine kinases; SOD: Superoxide dismutase; TRX: Thioredoxin; TCF-4: T-cell factor-4; T: Thymine; VEGF: Vascular endothelial growth factor; Zfp148: Zinc finger protein 148; 5-Fu: 5-fluorouracil; 6-AN: 6-anicotinamide; 8-oxodG: 8-oxo-7, 8-dihydro-2'-deoxyguanosine.

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Author contributions

All authors contributed to prepare, review, and write the manuscript.

Competing Interests

The authors have declared that no competing interest exists.

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