Review Article
Molecular mechanisms of NF-κB signaling pathway in the development and progression of esophageal carcinoma

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Abstract: Esophageal carcinoma (EC) is one of the leading causes of cancer-associated death worldwide. However, its precise mechanism of development and progression remains incompletely illustrated. Nuclear factor-kappa B (NF-κB) has played an established role in regulating innate immunity and inflammation. In addition, NF-κB can also regulate expression of numerous genes related to cell proliferation, anti-apoptosis, angiogenesis, invasion and metastasis. Thus, it plays a critical role in the progression of a variety of cancers, including EC. EC patients with high NF-κB expression level are usually associated with worse therapeutic effect and dismal prognosis. Consequently, NF-κB is recommended in plenty of studies as a therapeutic target. Therefore, better understanding the molecular mechanisms of NF-κB signaling pathway contributes to uncovering novel targeted therapy strategies for EC. In the current study, the effects of NF-κB on the development and progression of EC were explored, and its oncogenic contribution to each step of carcinogenesis was also highlighted. Furthermore, the prospect of therapy targeting the NF-κB pathway for treating EC was also discussed.

Keywords: Esophageal carcinoma, NF-κB signaling pathway, molecular mechanism, carcinogenesis, therapeutic target

Introduction

Esophageal carcinoma (EC) is a prevalent malignant tumor worldwide, which is associated with poor prognosis. EC is linked with high incidence and mortality, especially in eastern Asia as well as Eastern and Southern Africa. Esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) are the two major types of EC. Of them, EAC mostly occurs in western countries, while ESCC is highly frequent in less-developed areas [1, 2]. Continuous progress has been made in clinical treatment; nonetheless, the overall 5-year survival remains low, which ranges from 15% to 25% [3]. EC patients have disappointing prognosis, which can be attributed to diagnosis at advanced stage and the propensity of metastasis. In comparison, diagnoses at earlier stages usually result in better outcomes for patients with EC [3, 4]. However, no efficient biomarker for predicting such devastating disease or evaluating its curative effect and prognosis is avail-able so far. Hence, it is imperative to understand the mechanisms underlying EC and to search for effective predictive or prognostic biomarkers. This can establish certain foundation for formulating feasible novel targeted therapy strategy.

Nuclear factor-kappa B (NF-κB) is a pleiotropic transcription factor, which plays a critical role in innate immunity and inflammation. In addition, it is also involved in carcinogenesis through multiple pathways [5]. The mammalian NF-κB family is mainly comprised of five subunits, which are RelA (p65), RelB, c-Rel, p50 (NF-κB1) and p52 (NF-κB2). All of them share the same DNA binding domain, namely, the Rel homology domain. Furthermore, they can form homodimers or heterodimers to function as transcriptional activators. Of them, p50/RelA complex is the predominant heterodimer among a majority of cell types [6]. NF-κB dimers remain latent and inactive in cytoplasm under the action of specific inhibitor IκBs prior to cell stimulation
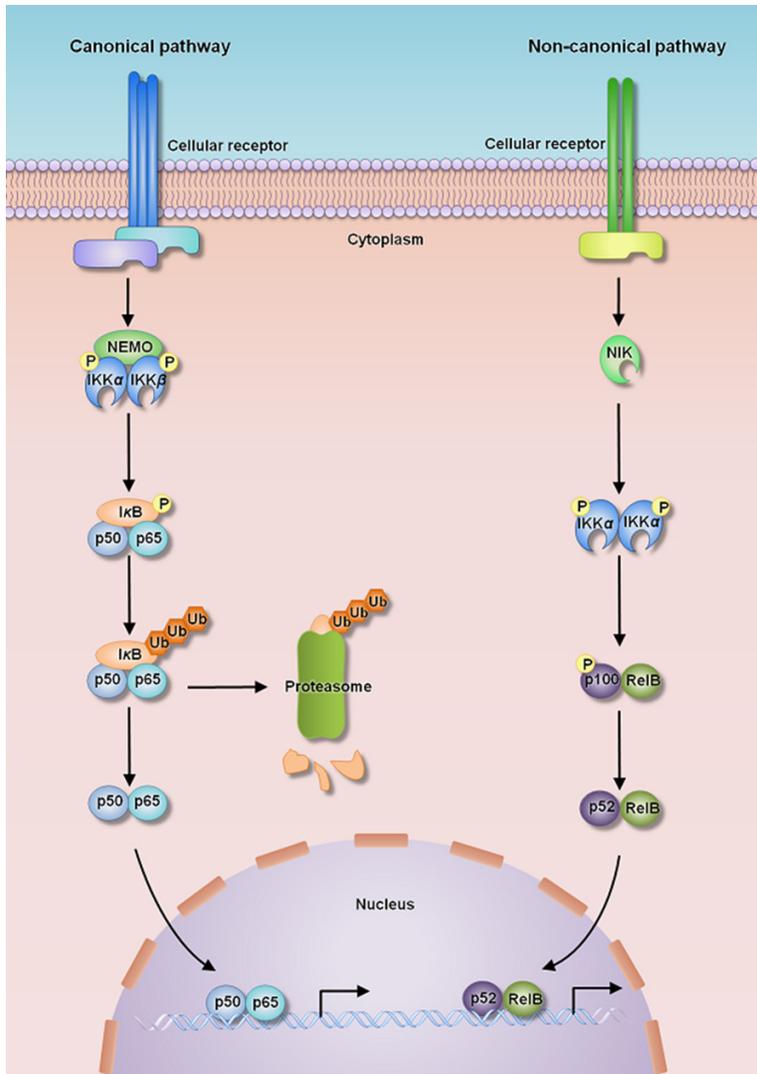
Figure 1. The canonical and non-canonical NF-κB signaling pathways.

ankyrin p100/NF-κB2, the precursor of p52. This will lead to partial proteolysis and nuclear translocation of the p52/RelB complex [6, 7]. Subsequently, the released NF-κB dimmers will enter the nucleus and bind to 9-10 base pair DNA sites (κB sites). In this way, it can influence gene expression events, which may impact cell proliferation, apoptosis, and differentiation. Notably, NF-κB dimers can upregulate IκBα expression to inhibit further transcription, thus generating a negative feedback loop [6, 7] (**Figure 1**).

Plenty of studies have suggested that, NF-κB signaling pathway plays a vital role in the genesis and malignant transformation of various cancers, including EC [8]. The positive expression rate of NF-κB p65 protein in EC tissues is almost 45.3%~79.0%, which is remarkably higher than that in adjacent normal esophageal mucosa [9-11]. Activated NF-κB is associated with aggressive clinical biology and unfavorable prognosis. In addition, it is also the independent predictive factor of disease-free survival (DFS) and overall survival (OS) of EC patients [12, 13]. Li *et al.* [14] reported that NF-κB inhibitors could suppress ESCC progression through reducing proliferation, inducing apoptosis, and enhancing sensitivity to chemotherapeutics. This has indicated that therapy strategy targeting NF-κB is of potential value. Furthermore, Hanahan and Weinberg had summarized these processes, which were sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis [15]. The current review was thereby conducted aiming to analyze the molecular mechanisms of NF-κB signaling pathway in the development and progression of EC based on these biologi-

(such as IκBα, IκBβ, IκBγ, IκBε, p100, p105 and *Drosophila* Cactus). In the canonical NF-κB pathway, IκBs are regulated by phosphorylation of IκB kinase (IKK) in a dependent manner. The IKK complex is made up of two catalytic subunits (IKKα and IKKβ), and the regulatory scaffold IKKγ/NEMO (the NF-κB essential modulator) [6]. After cell stimulation, the activated IKK complex will phosphorylate the NF-κB-binding IκB at two N-terminal serine residues, leading to K48 ubiquitination and degradation by the proteasome. Consequently, NF-κB dimers are released into the nucleus [7]. In the non-canonical pathway, the activated NF-κB-inducing kinase (NIK) will phosphorylate and activate the IKKα homodimer. Thereby, the activated IKKα will in turn phosphorylate the inhibitory
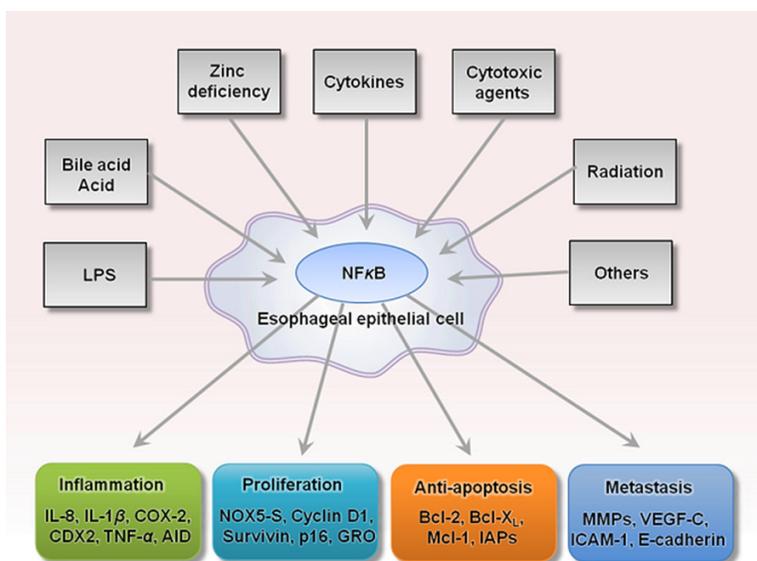
Figure 2. Stimulation-induced activation of NF-κB signaling pathway regulates expression of numerous genes, leading to different biological consequences of esophageal epithelial cells.

cal capacities. Moreover, the feasibility of developing a therapy strategy targeting the NF-κB pathway was also discussed.

NF-κB: from inflammation to cancer

Barrett's esophagus (BE) is a premalignant condition, which is the only known precursor of EAC. It progresses in accordance with the histological sequence of metaplasia-dysplasia-adenocarcinoma [16]. Evidences have shown that, NF-κB expression in biopsy specimens of reflux esophagitis, BE and EAC has been up-regulated by 13%, 60% and 80%, respectively, along with increased proinflammatory cytokines interleukin-8 (IL-8) and interleukin-1 beta (IL-1β) [17]. McAdam et al. suggested in their research that different bile acids and pH levels had diverse effects on NF-κB activation and induction of its downstream target IL-8 [18]. In addition, deoxycholic acid (DCA) exposed at the pH of 6 had exerted the maximum effects on up-regulating NF-κB-mediated gene expression [19]. Burnat et al. reported that DCA could directly stimulate the nuclear translocation of NF-κB, and the inhibition of NF-κB by siRNA-RelA could reduce the expression of cyclooxygenase-2 (COX-2) and caudal-type homeobox 2 (CDX-2) [20]. COX-2, the downstream target of NF-κB, is frequently excessively expressed in tumors, which plays a crucial role in tu-

morigenesis and development of a variety of human cancers, including EC. This can be attributed to its biological functions, such as cell proliferation and migration, angiogenesis and anti-apoptosis [21, 22]. Furthermore, COX-2 is also the key enzyme in synthesizing prostaglandins (PGs). It can increase angiogenesis and invasion, inhibit apoptosis, and stimulate cell proliferation and motility, thus promoting tumor growth [21]. A recent literature has discussed the crosstalk between the NF-κB pathway and the Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) pathway in ESCC. It is found to stimulate cell growth, cell cycle and angiogenesis, thus accelerating growth of ESCC [23]. In this study, down-regulated COX-2 mRNA expression by siRNA can silence NF-κB and STAT3, respectively, suggesting that COX-2 may be a common downstream gene regulated by both STAT3 and NF-κB. Meanwhile, JAK2 inhibitor can also block the activation of NF-κB p65, in addition to the inactivation of STAT3. This has indicated that the JAK/STAT3 pathway regulates cancer growth through interacting with the NF-κB pathway [23]. Plenty of evidences have suggested that, as COX-2 inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin and meloxicam, can target the NF-κB/COX-2/PGs pathway. In this way, they can reduce proliferation of ESCC cell and induce apoptosis both in vivo and in vitro [24-26]. These findings have revealed the potential and prospect of NSAIDs in preventing and treating abnormal esophageal changes.

CDX1 and CDX2 are two homeobox proteins of the caudal-related homeobox gene family, both of which are demonstrated to be important mediators in BE development [27, 28]. NF-κB signaling is the primary regulator of CDX1 expression. In contrast, CDX2 expression is regulated by DCA-induced NF-κB signaling, as is previously described [20, 28]. Contrary to DCA, ursodeoxycholic acid (UDCA), which is the

most hydrophilic bile acid, can inhibit the NF-κB signaling pathway in the progression from BE to EAC. Thus, it can exert its cytoprotective effects. Furthermore, inhibiting the activation of NF-κB/CDX2 pathway may repress the inflammation-metaplasia-carcinoma sequence [29, 30]. It is reported that, the NF-κB signaling pathway can mediate the aberrant expression of activation-induced cytidine deaminase (AID) in BE and EAC, under the induction of bile acid [31]. AID is known to induce somatic mutations in human host DNA sequences, thus promoting carcinogenesis [32]. AID can accumulate genetic alterations of tumor-related genes, such as mutations of genes *TP53* and *CDKN2A*, in BE epithelial cells and EAC cells, thereby exerting its genotoxicity [31]. Thus, bile acid-induced activation of NF-κB/AID pathway plays a vital role in mutating oncogenes. Subsequently, it can accelerate the progression from BE to EAC. Besides, the direct stimulation of bile acid, and altered microbiome in BE also provide the advantageous conditions for activating the NF-κB signaling pathway. Long-term bile acid reflux will impair the mucosal barrier in distal esophagus. What's worse, it will expose the squamous epithelium to microbiome from oral cavity, esophagus and gastric cavity [33]. Thus, the destroyed homeostasis may lead to changed composition of microbial ecosystem in esophagitis and BE in addition to the chronic inflammation. Yang *et al.* suggested in their research that, the altered microbiome was dominated by the increase in Gram-negative anaerobe/microaerophile while decrease in Gram-positive bacteria in esophagitis and BE [34]. Lipopolysaccharide (LPS), a natural ligand of the Toll like receptor 4 (TLR4), is the major outer membrane component of Gram-negative bacteria. The bacterial product LPS stimulation may activate TLR4, thus eliciting the activation the downstream NF-κB [35]. The activated LPS/TLR4/NF-κB pathway can thereby up-regulate expression of genes encoding proinflammatory cytokines, such as IL-1β, IL-8, tumor necrosis factors-alpha (TNF-α), and proinflammatory enzyme (COX-2). Finally, a series of inflammatory responses will be evoked in BE and EAC [33]. In turn, cytokines such as IL-1β, IL-8 and TNF-α, can activate NF-κB by cytokine receptors through the non-canonical pathway. As a result, a positive feedback loop can be constructed [33]. Moreover, Mohamed *et al.* had demonstrated that *Helicobacter pylori* and

Helicobacter pylori extracts could directly activate the NF-κB/COX-2 pathway in esophageal epithelial cell lines in the absence of *H pylori* LPS [36]. Therefore, antibiotic therapy targeting the altered microbiome may potentially attenuate the detrimental effects of Gram-negative bacteria-induced LPS/TLR4/NF-κB pathway. Thus, the role of NF-κB pathway in the progression from inflammation (BE) to cancer (EAC) can be speculated based on these data (**Figure 2**).

The role of NF-κB in promoting proliferation and anti-apoptosis in EC

Apoptosis is important in maintaining human homeostasis. This can be attributable to its role in keeping the balance between cell proliferation and death. Apoptosis inhibition is a key process in tumor initiation and development. The apoptotic pathway is mediated by initiator caspases, BCL2 family and inhibitor of apoptosis protein (IAP) family. Of them, the BCL2 family proteins can suppress (anti-apoptotic subunits Bcl-2 and Bcl-X_L) or increase (pro-apoptotic subunits BAX and BID) mitochondrial permeability and regulate the release of cytochrome *c* [37]. Bcl-2 and Bcl-X_L, which are recognized as the downstream target genes of NF-κB, can increase tumor cell survival [38]. Xia *et al.* reported in their research that, overexpression of high-temperature requirement protein A1 (HtrA1) could block the NF-κB pathway in ESCC cell lines. Thus, it could reduce the expression of Bcl-2 and Bcl-X_L [39]. Down-regulation of platelet-derived growth factor-D (PDGF-D) can induce apoptosis via blockage of NF-κB pathway in another ESCC cell line model. Meanwhile, decreased Bcl-2 and increased BAX levels as well as elevated caspase-3 activity can also be observed [40]. *Mcl-1* is another Bcl-2 family member, which is an anti-apoptotic gene regulated by NF-κB. The elevated Mcl-1 level may enhance ESCC cell viability *in vitro*, after the activated NF-κB binds to the human *Mcl-1* promoter region [41]. IAP proteins can regulate the apoptotic pathway by means of suppressing the activities of caspases and effector caspases [42]. IAPs are the downstream target genes of NF-κB, which can in turn mediate the ubiquitin-dependent signaling events, thus activating the NF-κB pathway [38, 43]. Survivin is the smallest member of mammalian IAP family, which exerts its biological functions through

preventing cell apoptosis and inducing proliferation in diverse cancers [44]. As a downstream target gene of NF-κB, survivin can thereby activate the NF-κB pathway through binding to the IKKβ promoter region and sequentially sustaining the elevated IKKβ expression in ESCC cell line [45]. It is not surprising that interaction with survivin/IKKβ/NF-κB/survivin pathway contributes to forming a positive feedback. This may play a critical role in regulating apoptosis of EC. However, more studies are required to investigate the specific mechanisms of NF-κB in the apoptotic pathway of EC.

Axl, the receptor tyrosine kinase, acts as an oncogene, which is involved in cell proliferation, differentiation, apoptosis and metastasis. Sound evidences have indicated that up-regulated Axl can be observed in numerous cancers, including ESCC, which is correlated with the dismal prognosis for cancer patients [46, 47]. Axl phosphorylation and the consequent activation may activate the lipid kinase phosphatidylinositol 3-OH kinase (PI3K) pathway. As a result, second messengers related to cell proliferation, survival and invasion will be produced, which have played vital roles in cancer pathogenesis [47]. In addition, the up-regulated PI3K may stimulate its major effector, which is the serine/threonine kinase Akt (protein kinase B), thus leading to the activation of NF-κB pathway [48]. Notably, the activation of PI3K/Akt/NF-κB signaling pathway can induce cell proliferation and apoptosis inhibition, which will impact the genesis and development of both ESCC and EAC [47, 48]. Apart from Axl, the PI3K/Akt/NF-κB signaling pathway in EC can also be mediated by other factors, such as inhibitor of differentiation or DNA binding (Id-1), JAK2 and TC21 [49-51]. As a member of the helix-loop-helix proteins, Id-1 contributes to the proliferation and survival of human cancer cells. It was shown in the study by Bin *et al*. that, inhibition of Id-1 by siRNA might suppress the PI3K/Akt/NF-κB signaling pathway in ESCC cells, thus enhancing TNF-α-induced cell apoptosis. This indicates that Id-1 plays a certain role in inducing the activation of PI3K/Akt/NF-κB signaling pathway and protecting ESCC cells from apoptosis, especially apoptosis induced by TNF-α [50]. As is shown in another study, PI3K enzymatic activity is increased in JAK2 immunoprecipitation, suggesting that

JAK2 can activate the PI3K/Akt pathway. Subsequently, it leads to increased phosphorylation and transcriptional activity of NF-κB. Such process is carried out under the stimulation of glycine-extended gastrin (G-Gly). G-Gly is a mitogen for several gastrointestinal tissues, which is secreted by G-cells to mediate cellular signaling events, thus promoting cancer growth [49]. In other words, G-Gly may increase COX-2 transcription and prostaglandin E_2 (PGE_2) production through the JAK2/PI3K/Akt/NF-κB pathway, thus inducing proliferation of EAC cells [49]. High expression of TC21/R-Ras2, a subunit of the R-Ras family, has been detected in numerous cancers, including EC [51]. It is suggested in a recent study that the over-expressed TC21 may upregulate the expression of Cyclin D1 through the PI3K/Akt/NF-κB pathway in ESCC cell lines. Consequently, it will result in cisplatin-induced increased cell survival and apoptosis inhibition [51]. Cyclin D1 is a crucial regulator of cell cycle progression, which can mediate cell transition from G1 to the S phase [52]. Consequently, the activated NF-κB can up-regulate Cyclin D1 expression to regulate cell cycle progression, thereby promoting the proliferation of EC cells.

Reactive oxygen species (ROS), which is known as an obvious factor involved in cancer progression, is associated with increased cell proliferation and decreased apoptosis. Low pH level is to the benefit of generating ROS and subsequently damaging cell chromosomes, thus promoting the development from BE to EAC [53]. EF-hand calcium binding domain 5-S (NOX5-S), the NADPH oxidase, can enhance ROS production and evoke the up-regulation of COX-2/PGE_2 pathway through activating the NF-κB signaling. As a result, it can enhance cell proliferation and apoptosis inhibition in Barrett's adenocarcinoma cell lines [54]. In return, ROS can result in NOX5-S overexpression through activating NF-κB, thus a positive feedback loop has been constructed. Interestingly, the mitogen-activated protein kinase (MAPK) extracellular signal-regulated kinase 2 (ERK2) is involved in the pathway as a downstream target of ROS as well as the activator of NF-κB [55]. Therefore, the NOX5-S/ROS/ERK2/NF-κB/NOX5-S positive feedback loop may contribute to regulating other factors, such as the COX-2/PGE_2 signal. Alternatively, it may cause DNA damage, hence accelerating tumorigenesis as well as EC pro-

gression. For instance, microsomal prostaglandin E synthase 1 (mPGES1) is a subunit of the membrane-associated proteins, which is involved in eicosanoid and glutathione metabolism (MAPEG) family. Meanwhile, it is also a downstream target of NF-κB in BE or EAC induced by bile acid [56]. mPGES1 can elevate the transformation from COX-2-derived prostaglandin H_2 (PGH_2) to PGE_2 on the basis of such positive feedback pathway, and thereby enhance cell proliferation [56]. In addition, acid-induced hypermethylation of *p16* gene promoter is mediated by DNA methyltransferase 1 (DNMT1) through the sequential activation of NOX5-S/ROS/NF-κB pathway. Finally, it will lead to increased cell proliferation and tumorigenesis of EAC [57].

Increasing evidences have implicated that, dietary zinc deficiency (ZD) has accounted for one of the pathogenesis factors of ESCC, which can activate NF-κB through different pathways [58, 59]. S100 proteins are the small calcium-binding proteins of EF hand motif, which can regulate diverse cellular signal transduction pathways, including under cancer circumstances [60]. S100s can bind to their downstream ligand receptors for advanced glycation end products (RAGE), hence constructing a complex. Such complex is a multiligand receptor of immunoglobulin superfamily [61]. The S100s/ RAGE complex may provoke the activation of NF-κB. Notably, three S100s subunits, namely, S100A14, S100A8 and S100A9, have been detected to be engaged in the S100s/RAGE/ NF-κB pathway under ESCC environment [58, 61]. ZD is shown in a study on rat model to regulate the expression of S100A8/A9 dimer as well as its interaction with RAGE. Consequently, it can activate the NF-κB/COX-2 pathway, thus promoting the initiation and progression of ESCC [59]. Another mechanism of NF-κB pathway in ZD esophagus requires the involvement of microRNA (miRNA). miRNA is the short non-coding RNA, which can mediate expression of various genes, thus functioning as oncogene or tumor suppressor gene [62]. ZD-induced over-expression of oncogene miR-31 contributes to down-regulating its direct target serine/threonine kinase 40 (Stk40), a known negative regulator of the NF-κB signaling pathway [58]. Consequently, it can be figured out that, both S100s/RAGE/NF-κB and miR-31/Stk40/NF-κB pathways underlying the interaction of Zn deficiency can increase cellular proliferation and

suppress apoptosis, thus promoting esophageal neoplasia. Different with oncogene miR-31, miR-34a and miR-138 are known as the tumor suppressor genes in EC, which have opposite function. Both of them can suppress the development of various cancers; however, their mechanisms of interacting with NF-κB underlying ESCC are quite different. Intriguingly, NF-κB can specifically bind to κB site in miR-34a promoter of ESCC cell line, which can subsequently up-regulate the transcriptional activity of miR-34a, thus accelerating cell growth arrest or apoptosis. This has revealed that NF-κB plays a potential role in suppressing tumor development [63]. As a tumor suppressor miRNA, downregulation of miR-138 is frequently associated with ESCC progression. MiR-138 silencing can promote K63 polyubiquitination of NF-κB signaling intermediaries, which are TNF receptor associated factor 2 (TRAF2) and receptor-interacting protein (RIP1). In this way, they can activate the IKK complexes and hence result in IκBs degradation, eventually leading to the release of NF-κB to the nucleus [64]. On the other hand, the down-regulated miR-138 can induce lipid raft formation, which functions as a physical platform for various molecules. In addition, it is essential to the activation of proximal NF-κB signaling molecules, such as IL-1β, IL-8 and TNF-α [64]. Lipid rafts are required in K63 polyubiquitination of TRAF2 and RIP1, as well as in the binding of TNF-α with TNF receptor (TNFR) [64]. In addition, up-regulation of the lipid raft protein flotillin-1 (FLOT1) facilitates the TNFR signaling transduction and activation of NF-κB pathway in ESCC cells [65]. TNF-α-induced activation of NF-κB can increase transcription activity and regulate the inflammatory cytokines, such as TNF-α, thus generating a positive feedback loop. TNFR1 can activate the NF-κB pathway. Moreover, the overexpression in EC109 cell lines has been demonstrated to promote apoptosis, which may potentially be suppressed by the excessively activated NF-κB [66]. Different from FLOT1, glutathione peroxidase 7 (GPX7), an antioxidant enzyme that is frequently silenced in BE tumorigenesis, can promote the degradation of TNFR1 and TRAF2 proteins. Subsequently, it will result in the inhibition of NF-κB signaling pathway [67].

Growth-related oncogene (GRO), a member of the CXC chemokine subfamily, can bind to its receptor CXC motif chemokine receptor 2 (CXCR2). In this way, it will form a functional

autocrine chemokine loop, which can promote cell proliferation in EC cell line. Zinc finger transcription factor early growth response-1 (EGR-1) is a downstream target regulated by the GRO/CXCR2 complex. On the one hand, its overexpression may contribute to the proliferation of ESCC cells [68]. On the other hand, the elevated EGR-1 level can down-regulate IκBα while up-regulate p65 expression, thus facilitating the activation of NF-κB. Furthermore, NF-κB inhibition will down-regulate the expression of both GROα and GROβ, suggesting that NF-κB can regulate the transcriptional activation of GRO in ESCC [68]. Hence, the involvement of NF-κB plays a central role in constituting a positive feedback loop for GRO/CXCR2/EGR-1, which can promote cell survival and facilitate the sustained proliferation in ESCC.

Collectively, these precious evidences have illustrated the mechanisms linking NF-κB to diverse proliferative and apoptotic pathways. Furthermore, they have highlighted the pivotal role of NF-κB in promoting cell proliferation and suppressing apoptosis, thus triggering the genesis and development of EC (**Figure 2**).

The role of NF-κB in facilitating invasion and metastasis in EC

NF-κB pathway is involved in multi-step biological processes, including degradation of extracellular matrix (ECM), as well as activation of cancer cell adhesion, migration, and angiogenesis. Thus, it can promote tumor invasion and metastasis [69]. Matrix metalloproteinases (MMPs) are the target genes of NF-κB, which can digest ECM molecules and reduce cell adhesion, thus facilitating cancer invasion and metastasis [38]. Besides, NF-κB is suggested in numerous studies to upregulate the expression of MMPs subunits MMP-2, MMP-7 and MMP-9, thereby affecting EC invasion and metastasis [10, 70, 71]. Vascular endothelial growth factor (VEGF) is widely recognized to positively regulate the shaping of new blood vessels, which is an essential process in cancer growth [72]. Notably, NF-κB is shown in a recent study to enhance cancer angiogenesis through up-regulating the transcriptional level of VEGF-C in ESCC [73]. Furthermore, NF-κB-derived VEGF-C may contribute to tumor-induced lymph angiogenesis in the presence of Notch 1 signaling. This has provided more ave-

nues for the dissemination of ESCC cells to lymph nodes [11]. Similarly, intracellular adhesion molecule-1 (ICAM-1) is the target gene regulated by NF-κB. In addition, the NF-κB-induced ICAM-1 can promote the transendothelial migration of cell in EAC, thus enhancing the metastatic potential [74]. By contrast, E-cadherin contributes to maintaining cell adhesion, the perturbation of which may result in decreased adhesion between tumor cells, thus promoting invasion and metastasis [75]. Additionally, reduced E-cadherin and increased Vimentin levels are the hallmarks of epithelial-mesenchymal transition (EMT). EMT is a critical step in the invasion and metastasis of various cancer types, including EC [10]. As was shown in the research by Wang *et al.*, NF-κB inhibition silenced by siRNA could up-regulate E-cadherin expression and down-regulate Vimentin expression. This suggests that NF-κB can decrease E-cadherin expression and induce EMT, thus enhancing invasion and metastasis in ESCC [10]. Cells detaching from ECM usually result in anoikis, which is essential for the homeostasis in human body. However, anoikis in malignant cells is often inhibited by various pro-survival signals, such as β-catenin, leading to increased survival after detaching from ECM and elevated possibilities of invasion and metastasis [76]. Elevated level of polo-like kinase 1 (PLK1), a highly conserved serine/threonine kinase, can suppress proteasomal degradation of β-catenin, thus protecting EC cells from anoikis. The activated NF-κB RelA can directly bind to *PLK1* promoter region. Thus, it can provoke the transcriptional activity of PLK1 and subsequently inhibit the degradation of β-catenin. Finally, it can lead to anoikis resistance and thereby the increased invasiveness of ESCC cell [76] (**Figure 2**).

The role of NF-κB in inducing chemoradiotherapy resistance in EC

Tumor resistance to radiotherapy and chemotherapy is one of the main causes responsible for the dismal prognosis of EC. 43 treated patients with localized EC at uniform stage were enrolled in a previous clinical trial [13]. Results in that clinical trial suggested that patients with activated NF-κB had aggressive pathological features and poor treatment outcome. Furthermore, they had developed resistance to chemoradiotherapy. In addition, 9 (60%) out of the 15 patients with precondi-

tioned negative NF-κB had transformed to positive NF-κB after treatment [13]. It suggested that NF-κB activation could be triggered by chemotherapy or chemoradiotherapy in clinic [13]. As was shown in a recent study conducted by Li et al., the median survival time of patients with positive or negative NF-κB activation in the post-radiotherapy ESCC specimens were 13 and 35 months (P<0.01), respectively [9]. However, the median survival time in pre-radiotherapy patients showed no statistically significant difference. Furthermore, NF-κB activation can be induced by radiation of ESCC cell line in a dose-dependent manner. In turn, the activated NF-κB can decrease the effectiveness of radiotherapy for patients with ESCC [9]. It is shown in ESCC cell line models that, tumor cells with activated NF-κB induced by TNF-α have displayed poor sensitivity to 5-fluorouracil (5-FU) compared with the control group [77]. Moreover, accumulating evidences have suggested that ESCC cells with NF-κB silencing induced by p65 siRNA show enhanced sensitivity to 5-FU both *in vivo* and *in vitro* [77, 78]. Compared with p65 siRNA, curcumin, which is the NF-κB inhibitor extracted from the root of *curcuma longa L,* is more effective on suppressing ESCC development both *in vitro* and *in vivo* [79]. Curcumin may block the NF-κB pathway through inhibiting the phosphorylation and degradation of IκBα, thus leading to decreased expression of NF-κB downstream genes [80]. Curcumin is associated with the minimal systemic side effects. Therefore, the orally administered curcumin has been used as the chemopreventative agent against tumorigenesis for BE patients in clinical trial [81]. Taken together, targeting NF-κB may be an efficient approach for EC patients who have developed resistance to chemoradiotherapy (**Figure 2**).

Conclusion

As can be figured out based on these valuable data, persistent NF-κB activation is involved in almost all processes during the genesis and progression of EC, including inflammation, proliferation, anti-apoptosis, angiogenesis, invasion, metastasis, and chemoradiotherapy resistance (**Figure 2**). Furthermore, blockage of the NF-κB pathway will shut off all these carcinogenesis processes, thus attenuating cancer growth. Finally, and also the most importantly, further in-depth mechanistic exploration and extensive clinical trials are urgently needed, so as to investigate the feasibility of NF-κB as a tumor biomarker and the effectiveness of novel therapy strategies specifically targeting NF-κB pathway in EC.

Acknowledgements

Disclosure of conflict of interest

None.

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