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Review

Curcumin's prevention of inflammation-driven early gastric cancer and its molecular mechanism

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ABSTRACT

Worldwide, gastric cancer is the second leading cause of cancer deaths and the fifth most common malignant tumor. Gastric cancer is believed to be caused by a variety of factors, such as genetics, epigenetics, and environmental influences. Among the pathogenic factors, inflammation has been considered as one of the main risk factors for gastric cancer. There are currently limited ways to prevent gastric cancer. Although the combined application of aspirin and non-steroidal anti-inflammatory drugs can reduce the risk, it has great side effects and can easily cause gastric perforation or gastric bleeding. Therefore, an alternative plan is urgently needed. Curcumin is the yellow pigment in the rhizome of the plant turmeric. Current studies have found that curcumin has a protective effect on gastric mucosal damage caused by non-steroidal anti-inflammatory drugs, gastric mucosal damage in rats, and gastric mucosal damage caused by stress bleeding and *Helicobacter pylori* infection. Curcumin shows significant anti-inflammatory and anti-cancer activities by regulating DNA methylation, histone modification, nuclear factor erythrocyte 2 related factor 2 and other related signal pathways. In this article, the latest evidence of curcumin for epigenetic changes in gastric cancer and its potential contribution to gastric cancer were discussed.

Contents

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1. Introduction

Turmeric (*Curcuma longa* L.), as a spice and Chinese herbal medicine, has a long history of use in Asia (Lestari & Indrayanto, 2014). The main components of turmeric are curcumin, volatile oil, polysaccharide and resin. Its superior anti-inflammatory and anti-tumor activities benefit from the presence of curcumin (Gupta, Patchva, Koh, & Aggarwal, 2012). As a pleiotropic molecule, curcumin can interact with the targets of various inflammatory factors. Through clinical use and laboratory research, curcumin may be a potential treatment for many chronic diseases, including gastric cancer, gastritis, rectal cancer and arthritis (Judaki, Rahmani, Feizi, Asadollahi, & Hafezi Ahmadi, 2017). As a result of research, it was found that curcumin can reduce gastritis caused by *H. pylori* infection in mice, which in turn can reduce gastric cancer caused by gastritis (Santos et al., 2015; Kwiecien et al., 2019). Although curcumin has high pharmacological activity, its bioavailability is low. Current experimental studies showed that only a small portion of curcumin will be absorbed in the stomach and intestines after oral administration, most of which will be excreted with feces. It is because curcumin has a hydrophobic structure, leading to low solubility, and the absorbed curcumin is rapidly metabolized in the liver (Golonko et al., 2019; Hoehle, Pfeiffer, Sólyom, & Metzler, 2006). It has been reported that the bioavailability of curcumin is increased through the use of phospholipid complexes. The results showed that the bioavailability of curcumin phospholipid complexes is increased by five times after oral administration compared to curcumin suspensions (Maiti, Mukherjee, Gantait, Saha, & Mukherjee, 2007). The oral availability of curcumin in nanoemulsions (210 μg/mL·min) is nine times higher than that of unmodified crystals (21.4 μg/mL·min) (Yu & Huang, 2012). Although the bioavailability of curcumin has been improved, the mechanism of its metabolism and bioactivity remains to be studied.

Since cancer has become one of the main causes of human death, it is valuable to study the characteristics of cell carcinogenesis in the field of cancer prevention. Among them, chronic inflammation is recognized as the seventh major feature of cancer in the world (Bonomi, Patsias, Posner, & Sikora, 2014). Among the many factors of TME, about 15%–20% of cancer deaths are related to chronic infection and inflammation (Chung & Lim, 2014). In addition, the development of cancer also requires six other characteristics, including sufficient self-proliferation, insensitivity against value-added signals, avoidance of apoptosis, unlimited replication potential, sustained angiogenesis, tissue invasion and metastasis (Fig. 1) (Hanahan & Weinberg, 2000). Gastric cancer is the second leading cause of cancer death worldwide and the fifth most common malignant tumor. And according to statistics, the survival rate of gastric cancer patients in the past five years is relatively low, about 10%–20% (Khan & Shukla, 2006). The current study found that the common gastric cancer pathogenic methods are roughly divided into genetic, epigenetic and environmental factors. And genetic and epigenetic changes have a certain contribution to the development of cancer, such as DNA methylation, histone modification and non-coding RNA regulation (Patel, Roy, & Ravi, 2017). Among them, DNA methylation occupies an important position in the occurrence of gastric cancer (Tahara & Arisawa, 2015).

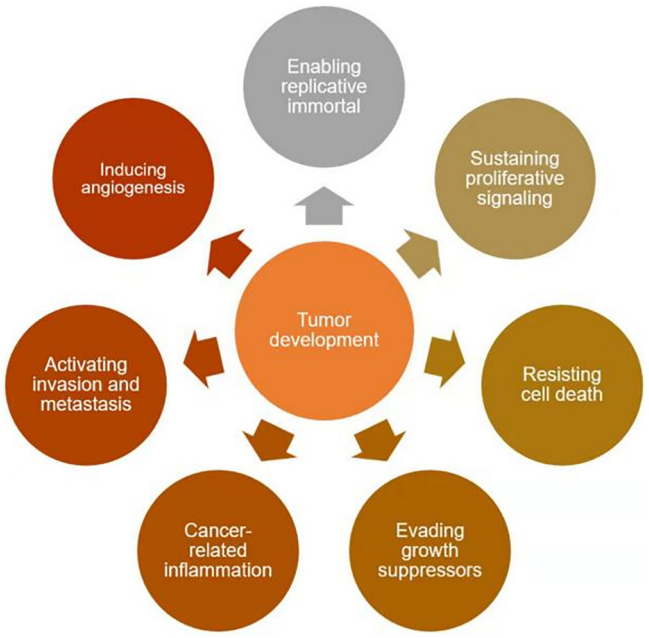

Fig. 1. Seven characteristics of cancer pathogenesis. These include cancer-related inflammation, evasion of growth suppressors, resistance to cell death, activation of invasion and metastasis, induction of angiogenesis, replication immortality, and maintenance of proliferative signals. Either pathway can promote tumor development.

According to IARC statistics, about 2 million of the 12.7 million new gastric cancer cases were caused by *H. pylori* infection, accounting for 16.1% of the total. Other carcinogenic factors include viral carcinogenesis (Plummer et al., 2016; Qu, Dang, & Hou, 2013). Therefore, it is very significant to use effective detection methods to detect *H. pylori*. At present, people use serological methods to detect gastric cancer caused by *H. pylori* infection. The risk of gastric cancer is three times higher than traditional detection methods, and the risk is more than 20 times with more sophisticated detection methods (González et al., 2012). Because it has genetic susceptibility of the host and is related to the occurrence of gastric cancer (it is genetically polymorphic with inflammation caused by *H. pylori* infection). The most critical thing is that the main carcinogenic factor of *H. pylori* has been chronic inflammation (Patel, Roy, & Ravi, 2017). Therefore, the study of factors related to chronic inflammation such as interleukin (IL)-1β, IL-1 receptor antagonists, tumor necrosis factor (TNF)-α and anti-inflammatory IL-10 is particularly significant important (Pereira-Marques, Ferreira, Pinto-Ribeiro, & Figueiredo, 2019). It is a potentially effective research route to verify that curcumin blocks inflammation caused by *H. pylori* infection, thereby achieving gastric cancer prevention.

2. Epigenetics of gastric cancer carcinogenesis

Gastric cancer is the result of the accumulation of multiple genetic and epigenetic changes (Figueiredo et al., 2017). Knowledge of epigenetic changes may be potentially helpful in the diagnosis and treatment of cancer. It has been reported that changes in epigenetics have been used in gastric cancer (Fu, 2015).

2.1. Main signal pathway of gastric cancer

In epigenetics, nuclear factor-κB (NF-κB) and signal transducer and activator of transcription 3 (STAT3) signaling pathways play a crucial role in the conversion of inflammation into cancer, both of which are involved in cell signal transduction. It has been proved that the NF-κB signaling pathway is one of the essential factors for inflammation-induced gastric cancer and colon cancer (Acharyya et al., 2012; Kwon, Moon, Park, Choi, & Park, 2013), and the driven gene products include cytokines or chemokines IL-1, IL-8, TNF, IL-6. Monocyte chemoattractant protein (MCP)-1, matrix metalloproteinase (MMP)-2, MMP-9 and other factors related to inflammation (Zhang et al., 2019). It can promote the

progress of gastric cancer by activating the STAT3 signaling pathway, and many genes transcribed by NF-κB can promote the generation of gastric cancer (Sokolova & Naumann, 2017; Maeda & Omata, 2008). NF-κB and STAT3 signaling pathways secrete a large number of pro-inflammatory factors and interact within the nucleus to provide an environment for tumor growth, making gastric cancer treatment more difficult.

Early literature showed that the NF-κB system has the characteristics of regulatory activation in gastric cancer and may be deregulated (Tye & Jenkins, 2013), but the correlation between its activity and certain pathological features is not yet clear. Through research, it is found that the NF-κB system is the basis for connecting inflammation and gastric cancer. It has been reported that the high nuclear abundance of RelA after surgical resection and immunohistochemical analysis of the tumor is related to the progression of the tumor, and the results indicate that the patient's survival rate is low (Lee et al., 2005). In contrast, the high activity of NF-κB in patients with early gastric cancer is associated with a better prognosis (Cao et al., 2012).

In the stomach, proinflammatory mediators are secreted by autocrine pathways, gastric mucosa or cancer cells, paracrine pathways infiltrate macrophages, neutrophils and lymphocytes, as well as pathogens, certain chemicals and physical damage can also cause secretion of inflammatory mediators (Shin et al., 2011; Zhang, Zhang, & Aboul-Soud, 2017; Shigematsu et al., 2013). High levels of IL-6, IL-10, IL-32, CC-chemokine ligand (CCL) 7 and CCL21, highly expressed CXC chemokine receptor 4, chemokine receptor (CCR) 3, CCR5, CCR7 and orphan nuclear receptor 4A2 are associated with gastric cancer progression and poor prognosis (Chang, Du, Zhao, Ma, & Cao, 2013), and found that IL-6 and TNF are expressed at high levels in gastric cancer tissues. Immunohistochemical analysis showed that the expression of IL-6 and NF-κB was positively correlated, and the levels of IL-6 and NF-κB in gastric cancer tissue were significantly increased compared with normal mucosa adjacent to cancer (Yin, Si, Gao, Gao, & Wang, 2013). Therefore, the NF-κB system provides promising biomarkers for the diagnosis and treatment of cancer patients.

TNF activates NF-κB-dependent CXCL1 and CXCL2 expression through stromal cells and endothelial cells. In addition, these cytokines initiate the production of low molecular weight calcium binding protein S100A8/9 in stromal cells, immune cells, and cancer cells (Acharyya et al., 2012). S100A8/9 can activate NF-κB and mitogen-activated protein kinase (MAPK) p38, leading to the expression of MMP-2 and MMP-12, thereby increasing the migration and invasion of gastric cancer cells (Kwon, Moon, Park, Choi, & Park, 2013). However, TNF cannot directly regulate the calcium or calmodulin signal in cancer cells (Maubach, Sokolova, Wolfien, Rothkötter, & Naumann, 2013). Therefore, TNF is related to other inflammatory mediators in the tumor signal network.

The host's response to *H. pylori* is caused by a highly differentiated molecular dialogue between bacteria, gastric mucosal cells and immune cells. Current research shows that proinflammatory cytokines produced by infiltrating immune cells and epithelial cells directly advance chronic inflammation, which ultimately leads to gastric cancer in infected persons (Altobelli, Bauer, Velez, Cover, & Müller, 2019). STAT3 has a strong functional impact on the gastric mucosa and immune system (Xiao et al., 2018; Chen et al., 2012) and in the context of *H. pylori* acting on the gastric mucosa, it can be a good indicator of inflammation and carcinogenesis through specific intracellular signals. Based on STAT3 as an effective therapeutic target for drugs, the present research work prioritizes the inhibitory effect of gastric cancer caused by *H. pylori* gastritis in the formation stage, thereby preventing atrophic gastritis from becoming more and more serious pathological changes, which eventually leads to canceration.

For *H. pylori* infection, researchers currently believe that STAT3 as a typical tyrosine phosphorylation (pY) transcription factor is activated in gastric epithelial cells, the mechanism may be through the activation of tyrosine kinase Janus kinase (JAK). For example: in patients with gastritis infected by *H. pylori*, the level of pY-STAT3 is increased in *H. pylori* models of mice and gerbils (Alexander et al., 2019; Bronte-Tinkew et al., 2009; Lee et al., 2012). In the *H. pylori* infection model *in vivo*, gastric epithelial pY-STAT3 levels and mucosal inflammation scores were increased. Taking *H. pylori* as an example, it has been confirmed that the transfer of virulence factor-cytotoxin-related gene A to gastric epithelial cells can enhance the induction of STAT3 tyrosine phosphorylation upstream cytokine receptor signaling pathway. The best record is the gp130 signal transduction receptor subunit of the IL-6 cytokine family (Kaebisch, Mejías-Luque, Prinz, & Gerhard, 2014). And STAT3 promotes cancer-promoting inflammatory pathways, including the nuclear factor NF-κB and IL-6-gp130-janus kinase (JAK) pathways, and through anti-tumor immune responses mediated by STAT1 and NF-κB. It plays a dual role in immunization (Yu, Pardoll, & Jove, 2009).

The activation and interaction of NF-κB and STAT3 signaling pathways play a major role in controlling the communication between gastric cancer cells and perfusion cells, and in early gastric cancer can control the cell's anti-apoptotic ability and tumor angiogenesis and invasion ability. In-depth study of the mechanism and influencing factors of NF-κB and STAT3 in gastric cancer will provide new opportunities for the prevention and treatment of gastric cancer.

2.2. Molecular subtypes of gastric cancer

Recently, as advances in genomic technology and high-throughput analysis are conducive to revealing the molecular genetic landscape of gastric cancer, several molecular classification systems have been proposed and different subtypes have been identified (Liu & Meltzer, 2017). In 2014, the Cancer Genome Atlas (TCGA) proposed four subtypes: chromosomal instability (CIN), microsatellite instability (MSI), genetic stability (GS) and Epstein-Barr virus (EBV). The EBV subtype is related to the best prognosis, and the GS subtype is related to the worst prognosis. Compared with the EBV subtype, the overall survival rate of patients with MSI and CIN subtypes is poor, but the overall survival rate is better than the GS subtype (Sohn et al., 2017). Since GS subtypes mostly occur in late gastric cancer, this article focuses on the analysis of the other three subtypes.

When the number of genome changes quickly reaches a certain amount in a short time, that is, when there is a high cumulative mutation rate, tumor cells are classified as genomically unstable cells ((Lengauer, Kinzler, & Vogelstein, 1998). Genomic instability can be divided into MSI and CIN (Kaiser, Meckbach, & Jacob, 2014). Both instabilities indicate the presence of a mutant phenotype in cancer (Planck et al., 2002). The occurrence of high-frequency mutations in the microsatellite region of DNA sequences is characteristic of MSI, which is caused by epigenetic changes encoding DNA, such as *MSH2*, *MSH6*, *PMS2*, and *MLH1* (Latham et al., 2019). If this genomic change occurs on the chromosome is called CIN.

So far, it has been found that genes such as *MET*, *c-MYC*, *TP53*, and *c-ERBB2* are related to the occurrence of gastric cancer, and some of them are related to poor prognosis (Ribeiro et al., 2010). However, the genes related to the CIN type have not been precisely defined, so two common genes need to be analyzed to define CIN-gastric cancer.

One of them is *AURKA* (BTAK), a gene at 20q13, used to encode a serine-threonine kinase that regulates the cell cycle (Gritsko et al., 2003) and has been shown to cause CIN. AURKA plays a role in cen-

trosome integrity and correct cytokinesis (Rajeev, Singh, Asmita, Anand, & Manna, 2019; Pan et al., 2012). Its overexpression leads to centrosome duplication and aneuploidy (Meraldi, Honda, & Nigg, 2002). Since AURKA is amplified in gastric cancer, the cause of its overexpression may be aneuploid. AURKA can also be overexpressed without gene amplification, which may be due to accelerated transcription activation (Bischoff & Plowman, 1999). Because this gene interacts with glycogen synthase kinase (GSK)-3β, it plays a primary role in the regulation of gastric cancer β-catenin (Dar, Belkhiri, & El-Rifai, 2009). Another gene is the *APC* gene, which regulates β-catenin and chromosome segregation (Ribeiro et al., 2010). And *APC* mutation or loss of heterozygosity (LOH) leads to chromosomal structural changes and aneuploidy, which occurs in approximately 22.1% of patients with gastric cancers (Fang et al., 2002).

EBV is a double-stranded DNA virus, belonging to the herpes virus, latently infects B lymphocytes in most adults. The EBV genome was first detected by polymerase chain reaction in 1990 (Burke, Yen, Shekitka, & Sobin, 1990). Since then, approximately 10% of gastric cancers worldwide have been confirmed to be caused by EBV (Naseem et al., 2018). It has recently been reported that EBV-associated gastric cancer (EBVagastric cancer) is the result of proliferation of EBV-infected cells. This fact proves that EBV plays a momentous role in the development of gastric cancer (Shinozaki-Ushiku, Kunita, & Fukayama, 2015). The characteristics of EBV agastric cancer include repeated *PIK3CA*, *ARID1* and *BCOR* mutations, extreme DNA methylation, amplification of JAK2, PD-L1 and PD-L2. *PIK3CA* mutation and JAK2 amplification can lead to overexpression of PD-L1 (Kim, Song, & Lee, 2011). And EBV-positive tumors mostly occur in the male stomach, manifested by high methylation and amplification of JAK2 and PD-L1/2, and 80% have non-silent *PIK3CA* mutations. And all EBV gastric cancers showed hypermethylation of the *CDKN2A* promoter, but lacked the *MLH1* hypermethylation characteristic of the MSI-related CpG island methylation phenotype (CIMP) (Cancer Genome Atlas Research Network, 2014; Geddert, zur Hausen, Gabbert, & Sarbia, 2011). In contrast, MSI subtype tumors are more likely to occur in older women and are characterized by a high mutation rate, including mutations in genes encoding signaling proteins targeting cancer genes (Yu & Jove, 2004).

The defective DNA mismatch repair (MMR) system is considered to be the main cause of high mutations in many gastrointestinal tumors. However, tumors above this threshold are considered excessive mutations, depending on the sequencing method and cancer type (Li et al., 2016). MSI is caused by MMR defects caused by mutational inactivation of DNA mismatch repair genes *MSH2*, *MSH3*, *MSH6*, *MLH1* and *PMS2* or epigenetic silencing, which is characterized by the length of short repeating DNA sequences changed in microsatellites (Yamamoto & Imai, 2015; Boland & Goel, 2010).

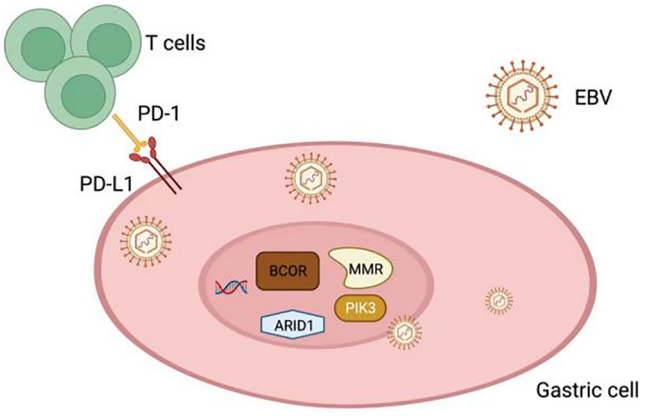

Fig. 2. Microsatellite unstable molecular interaction and EBV gastric cancer. After infection with EBV virus, BCOR, ARID1, PIK3 mutations and PD-1 amplification inhibits the proliferation of T cells, which in turn leads to canceration.

MSI accounts for a high proportion of gastric cancer, about 8%–37%, and the MSI-H phenotype is mainly derived from the apparent methylation of MLH1, rather than germline mutations (Fang et al., 2013). According to the TCGA molecular classification, MSI occurs in 22% of gastric cancers. The TCGA study found 37 significant genes in MSI-H-gastric cancers mutations, including *TP53*, *KRAS*, *PI3K*, *ARID1A*, *PTEN*, *ERBB2* and *ERBB3*. Among them, *ARID1A* is mutated in both EBV and MSI subtypes (Rodriquenz et al., 2020). Although MSI cases usually lack genes that can be targeted for amplification, mutations in *PIK3CA*, *ERBB3*, *ERBB2*, and *EGFR* have been found in other cancers. It was also found that genes in the TGF-β pathway are predicted to be mutations of MSI key drivers frequently in this subgroup, indicating a significant role in gastric cancer biology.

Due to the particularly high cell mutation rate in gastric cancer, it can promote the production of new antigens for immune response, and is a suitable therapy for MSI-H tumors to block immune checkpoints.

As reported in other types of cancer, negative immune checkpoint proteins have been shown to be upregulated in tumors with inflammatory phenotypes of T cells (Liu et al., 2015). Therefore, the efficacy of anti-PD-1 or PD-L1 drugs can be applied not only to MSI and EBV positive tumors, but also to tumors with a high degree of anti-lymphocyte infiltration. Since some promising targeted therapies are being studied in clinical trials, EBV-positive gastric cancers and MSI-gastric cancers seem to have the highest potential value (Sunakawa & Lenz, 2015), in particularly, we will focus on those EBV and MSI sub-assemblies that seem to have the most clinically relevant impact Group (Fig. 2).

The analysis of the gastric cancer subtypes, TCGA genomic data and the new data generated in the current research can prove the clinical significance of the three early gastric cancer subtypes and provide a theoretical basis for the development of reliable new solutions for the prevention and treatment of gastric cancer.

2.3. Epigenetic regulatory mechanism of gastric cancer

DNA-CpG methylation and chromatin remodeling are two vital roles in regulating gene expression. Chromatin remodeling involves modification of conserved lysine residues in the histone tail (Bilgiç et al., 2018; Tahara & Arisawa, 2015). Abnormal methylation of the promoter occurs early in cancer, suggesting that CpG island methylation may become one of the most promising biomarkers for tumor discovery. Since promoter methylation occurs in a specific region of the gene, epigenetic research is more efficient and cost-effective.

Jung-Hoon Park et al (2011) used methylated DNA enrichment technology, combined with a genome analyzer and a new standard algorithm, to analyze the methyl groups in human gastric cancer tissue with a resolution of 50 bp, and the results showed that different CpG densities can be obtained A comprehensive view of the promoter, including CpG islands (CGIs), transcripts, and various repeats. Specifically, CpG methylation in the promoter region may play a key role in inhibiting gene expression by blocking transcription factor binding. Lysine acetylation generally enhances transcription by weakening protein binding to DNA, allowing transcription factors to bind to promoters, and subsequent transcriptional activation (Greene & Chen, 2004). It has been reported that SOCS-1 is down-regulated by promoter methylation in gastric cancer, indicating that it has a significant relationship with gastric cancer lymph node metastasis and advanced tumors (To et al., 2004; Oshimo et al., 2004; Souma et al., 2012). In addition, the

expression of SHP1 negatively regulates the JAK2/STAT3 pathway and inhibits the proliferation, migration and invasion of gastric cancer cells by regulating various target genes (Joo et al., 2016).

In the course of tumor research, chromosomal abnormalities, DNA mutations, and epigenetic disorders of miRNAs or genes involved in their biological development were discovered. Kim et al (2014) and others found that in tumors including gastric cancer, miRNAs may be regulated by DNA hypermethylation. Through candidate gene method, it was found that mir941 and mir1247 were silenced by DNA methylation in multiple gastric cancer cell lines. It was detected that mir941 and mir1247 were dense in primary gastric cancer, but not in normal gastric cancer tissue. In addition, the genes targeted by these miRNAs were also detected and identified. Finally, it was proved that mir941 and mir1247 are regulated by gastric cancer DNA methylation transcription, and they can inhibit gastric cancer by inhibiting oncogenes.

3. Curcumin prevents gastric cancer through non-genetic and epigenetic mechanisms

Curcumin exhibits various anti-cancer activities in gastric cancer, which can inhibit multiple signaling pathways, inhibit the proliferation, invasion, metastasis and angiogenesis of cancer cells (Hassanalilou, Ghavamzadeh, & Khalili, 2019). And it has anti-inflammatory, anti-oxidation and apoptosis-inducing activities (Deguchi, 2015; Kocaadam & Şanlier, 2017; Alibeiki, Jafari, Karimi, & Peeri Dogaheh, 2017). Next, we will focus on the potential mechanism of curcumin treatment of gastric cancer, and study the apoptosis, antioxidant, anti-inflammatory and epigenetic regulation of curcumin.

3.1. Prevent cancer by non-genetic means

According to reports, it was found that curcumin has an effect on gastric cancer cell lines Mgastric cancer-803 (Qiang et al., 2019; Zhang et al., 2015), Sgastric cancer-7901 (Fu et al., 2018; Sun, Zhang, Liu, & Liu, 2019), MKN-45 (Zaidi et al., 2009; Cai et al., 2013), MKN-28 (Li et al., 2017; Li et al., 2017), Bgastric cancer-823 (Mu, Wang, Dong, & Sun, 2019; Sun et al., 2016) and human gastric adenocarcinoma (AGS) (Zheng, Deng, Liu, & Zhao, 2017; Cao et al., 2015). Curcumin has apoptosis and cell cycle arrest effects on the above cells. The mechanisms by which curcumin induces gastric cancer cell apoptosis and cell cycle arrest are different, depending on the type of cell and the dosage of the drug. Usually curcumin-induced apoptosis or inhibition of its proliferation includes activation of RAS/ERK signaling pathway, activation of p53 signaling pathway, inhibition of PI3K signaling pathway (Fu et al., 2018), inhibition of Wnt3a/β-catenin/EMT pathway (Liu, Yuan, Zhang, & Chang, 2019) and down-regulation of c-Myc/H19 pathway (Liu, Xiang, Wu & Wang, 2016). By inducing oxidative stress and regulating epidermal growth factor receptor (Waly et al., 2018; Imran et al., 2018), Caspase-3, Caspase-8 and Caspase-9 (Da, Zhang, Zhang, & Zhu, 2019; Liu, Yuan, Zhang, & Chang, 2019) and other pathways are activated.

The tumor suppressor gene p53 plays an important role in tumor cells. Upregulation of p53 expression can inhibit cancer cell proliferation and induce cancer cell apoptosis (Liu et al., 2019). In addition, recent studies have found that p53 can promote cell proliferation and survival of the molecular mechanism of the phosphatidylinositol-3 kinase (PI3K) signaling network (Song et al., 2020). Western blot results showed that the addition of curcumin resulted in down-regulation of PI3K expression and up-regulation of p53 expression. Therefore, curcumin may induce gastric cancer cell apoptosis and autophagy by inhibiting the PI3K pathway and activating p53 signaling pathway (Fu et al., 2018).

Western blot analysis showed that the accumulation levels of Wnt3a, Wnt5a and nuclear β-catenin in 44as3 cells were higher (Takei, Takigahira, Mihara, Tarumi, & Yanagihara, 2011). Wnt3a is highly expressed in human gastric cancer 44As3 cells, making it highly metastatic. Curcumin can also inhibit the migration and invasion of MKN45 cells, down-regulate the expression of N-cadherin, Snail1, Wnt3a, p-β-catenin, p-LRP6 and Bcl-2, up-regulate the expression of E-cadherin and Bax, and increase Caspase-3, Caspase-8, Caspase-9 activity, induce apoptosis. The underlying mechanism is to inhibit the Wnt3a/β-catenin/EMT pathway, regulate the Bcl-2 signaling pathway and the caspase pathway, and provide new potential strategies for the treatment of gastric cancer (Fig. 3) (Liu, Yuan, Zhang, & Chang, 2019).

Long-chain non-coding RNA (lncRNA) H19 is produced by the paternally imprinted H19 gene, and plays a key role in the progression and metastasis of cancer. Its expression in gastric cancer tissue is higher than that of matched non-cancerous tissue (Li et al., 2014). In addition, previous studies found that H19 was abnormally upregulated in gastric cancer (Gan, Lv, & Liao, 2019), and promoted cell proliferation by directly inactivating p53 (Matouk et al., 2010). The c-Myc oncogene directly induces the expression of H19 by binding to the H19 promoter, thereby promoting the proliferation of cancer cells (Zhang et al., 2014). It has been reported that curcumin can directly or indirectly bind to multiple targets to inhibit the proliferation and survival of cancer cells, indicating that c-Myc is an important gene that is down-regulated by curcumin (Jiang et al., 2019). Gao et al found that curcumin can inhibit the expression of H19 in gastric cancer cells, indicating that H19 plays a vital role in curcumin-induced proliferation inhibition and apoptosis of gastric cancer cells (Liu, Xiang, Wu, & Wang, 2016).

The reactive oxygen species ROS produced by NADPH oxidase 1 promotes the proliferation of gastric cancer cells (Yamamoto et al., 2018). Curcumin has anti-oxidation and anti-free radical pharmacological activities (Tejada et al., 2016). Curcumin can protect gastric cells from oxidative stress through its antioxidant effect (Waly et al., 2018). Another protective effect of curcumin may be through the activation of nuclear factor E2 related factor 2 (Nrf2) and induction of antioxidant enzymes to directly quench free radicals, thereby achieving the effect of treating cancer (Goel & Aggarwal, 2010). Other reports have found that curcumin derivatives also have obvious anti-tumor effects, including the curcumin derivative WZ35 by inducing gastric cancer cells to produce ROS and inhibit the activity of thioredoxin reductase 1 (TrxR1), thereby achieving the effect of treating gastric cancer (He et al., 2019). In addition, curcumin is also an anti-inflammatory drug with strong anti-inflammatory activity. It regulates its inflammatory effects by down-regulating inflammatory transcription factors, cytokines and redox states, and blocking the NF-κB signaling pathway (Jurenka, 2009; Menon & Sudheer, 2007; Shehzad, Rehman, & Lee, 2013). Curcumin can also achieve anti-inflammatory effects through Nrf2-mediated pathways, and can inhibit various inflammatory mediators such as IL-6, cyclooxygenase 2 (COX-2) (Jiang et al., 2020).

3.2. Epigenetic regulation prevents cancer

There are reports that histone acetylation is the result of a dynamic balance of the activities of two enzyme families including histone acetyltransferases (HATs) and histone deacetylases (HDACs). HDACs are a class of epigenetic enzymes that remove acetyl groups from the ε-N-acetyllysine amino acids on histones. In addition, histone modification is one of the most important epigenetic changes because it can alter gene expression and cancer risk. Among them, HATs transfer the acetyl group from the acetyl-CoA molecule to a specific lysine (K) at the N-terminal tail

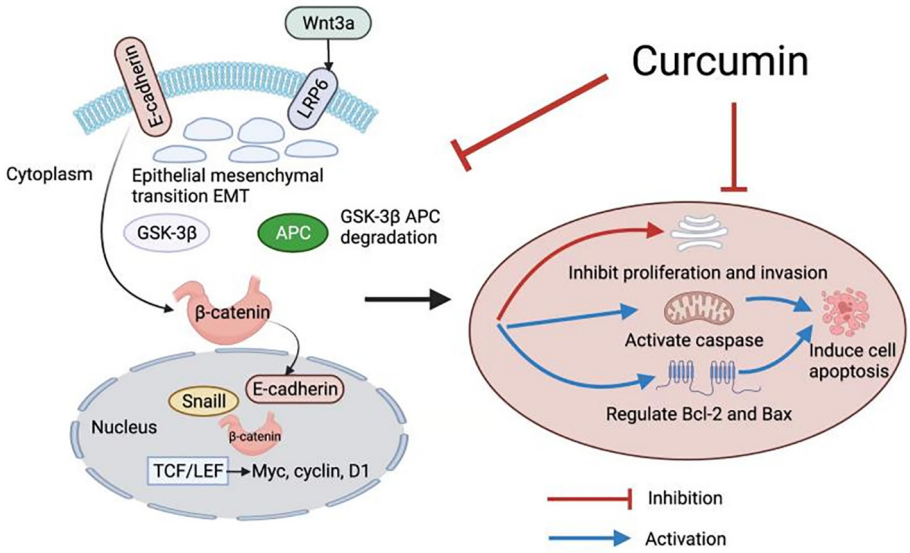

Fig. 3. Curcumin inhibits 44as3 cell proliferation and induces apoptosis via Wnt3a/ β catenin/EMT signaling pathway. Curcumin participates in regulating the EMT process of 44as3 cells by down-regulating N-cadherin, Snaill, and regulating the expression of E-cadherin, suggesting that EMT inhibition is an important mechanism for curcumin to inhibit 44as3 cell proliferation, migration and invasion. Up-regulation of Bax and down-regulation of Bcl-2 caused an increase in the ratio of Bax/Bcl-2, causing apotosis, and inhibiting the Wnt3a/β-catenin pathway to reduce the rate of apotosis. Up-regulation of Caspase-3, Caspase-8, Caspase-9 activity caused 44as3 apoptosis, but inhibition of Wnt3a/β-catenin/EMT signaling pathway can reduce the apoptosis induced by caspase pathway.

of the histone. This reaction changes the total charge of the histone tail from positive to neutral, and makes DNA more easily transcribed. In contrast, HDACs remove acetyl groups from K, preventing transcriptional regulatory elements from binding to promoters, thereby inhibiting gene transcription (Seto & Yoshida, 2014; Di Cerbo & Schneider, 2013). Overall, changes in the expression patterns of HDAC and HATs affect the structure and integrity of many human tumor genomes, including gastric cancer (Gigek et al., 2012; Calcagno, Gigek, Chen, Burbano, & Smith, 2013; Audia & Campbell, 2016). Curcumin inhibits tumor cell proliferation and induces apoptosis by inhibiting HDAC and HAT activities, thereby affecting histone modification (Stefanska, Karlic, Varga, Fabianowska-Majewska, & Haslberger, 2012). This biologically active compound causes a conformational change in EP300, limiting the affinity of H3 and H4 for acetyl-CoA (Reuter, Gupta, Park, Goel, & Aggarwal, 2011).

In SGC-7901 cells, it was found that curcumin can up-regulate the expression of miR-34a and inhibit the proliferation of gastric cancer cells. In addition, curcumin treatment can reduce the levels of Bcl-2, CDK4 and cyclin D1 in gastric cancer tissue (Sun, Zhang, Liu, & Liu, 2019).

Bcl-2 is an oncogene that inhibits apoptosis (He, Wei, Liu, Xu, & Zhao, 2017). CDK4 is a serine/threonine kinase that binds to cyclin D and regulates the transition of cells from G1 phase to S phase. Apoptosis inhibitory protein can inhibit the apoptosis of various malignant tumor cells, induce cancer cell metastasis, and increase the tumor's invasive ability (Sun, Si, Sun, & Si, 2018). Curcumin can downregulate the expression of Bcl-2, CDK4 and cyclin D1 in tumor tissues, inhibit tumor growth and reduce tumor quality.

With the increase of the dose of curcumin in human gastric cancer Mgastric cancer-803 cells, the expression of tonic protein homolog (PTEN) increased, and the level of MicroRNA-21 (miR-21) decreased. These results suggest that curcumin has a negative regulatory effect on the miR-21/PTEN/Akt pathway (Qiang et al., 2019).

miR-21 is a tumor miRNA that is up-regulated in gastric cancer cells (Xiao & Jie, 2019). miR-21 targets a group of target genes involved in tumorigenesis and development (Fan et al., 2020). Phosphatase and PTEN are tumor suppressors that negatively regulate the AKT/pkb signaling pathway by inhibiting PI3K, and are effective targets for tumor cells miR-21. The miR-21/PTEN/PI3K/Akt pathway is involved in tumor growth, migration and invasion. In addition, miR-21 promotes the proliferation and invasion of gastric cancer by targeting PTEN. curcumin shows a strong anticancer effect by inhibiting the miR-21/PTEN/Akt molecular pathway (Qiang et al., 2019).

4. Clinical study of curcumin in preventing gastric cancer

Curcumin, as a common compound of medicine and food, has potential health benefits in cell culture and animal models. Although the therapeutic application of curcumin has been studied as early as 1748, it was first officially used in human diseases in 1937 (Wu et al., 2020). Over the past few decades, many scientists have conducted clinical studies on healthy people and patients, including cancer, oxidation, inflammation and other diseases. Curcumin has so much pharmacological activity that it can regulate many signaling molecules, such as pro-inflammatory cytokines, apoptotic proteins, NF-κB and AST. However, due to the hydrophobicity of curcumin, it causes poor absorption and rapid metabolism, and its low bioavailability seems to have become the biggest obstacle for people to study curcumin.

Recently, it was reported that a pharmacokinetic experiment was conducted in humans, and it was found that curcumin administration increased the mRNA of the antioxidant genes Nrf2, heme oxygenase-1 (HO-1) and NAD (P) H-quinone oxidoreductase 1 (NQO1) Expressed and suppressed the expression of epigenetic genes including *HDAC1*, *HDAC2*, *HDAC3* and *HDAC4* (Vareed et al., 2008). The results of this experiment indicate that curcumin can cause biological reactions in the body, such as antioxidant effects and epigenetic effects, thereby contributing to the overall beneficial effects of curcumin in healthy people (Gibbons, 2005). The report found that among the curcumin carboxylic acid derivatives, curcumin is the most effective HDAC inhibitor, which is better than the HDAC inhibitors valproic acid and sodium butyrate (Cotto, Cabanillas, Tirado, García, & Pacheco, 2010; Vareed et al., 2008).

It is reported that curcumin can reduce the levels of HDAC1, 2, 3, 4, 5, 6, 8 and 11 in different gastric cancer cells (Soflaei et al., 2018).

Recent studies have shown that curcumin can reduce oxidative stress and histological changes associated with *H. pylori*-associated chronic gastritis. In a randomized clinical trial, patients were divided into standard triple therapy group and curcumin triple therapy group. Gastroscopy and histological examination were performed on all patients after the 8th week of treatment. The test results showed that the triple therapy with curcumin significantly reduced the malondialdehyde markers and glutathione peroxide in the patients, and increased the total antioxidant capacity of the gastric mucosa. In addition, the curcumin triple therapy group significantly reduced the oxidative damage to DNA compared to the standard triple therapy group. The results of the study showed that the triple therapy with curcumin significantly reduced the patient's inflammation score. Therefore, the authors concluded that the addition of curcumin can significantly improve the eradication rate (Khonche et al., 2016).

Curcumin can inhibit the proinflammatory NF-κB and motor response of *H. pylori* infected epithelial cells (Vetvicka, Vetvickova, & Fernandez-Botran, 2016). In recent experiments, the addition of curcumin to three treatment options can improve oxidative stress and histopathological changes in chronic gastritis-associated *H. pylori* infection (Sarkar, De, & Mukhopadhyay, 2016; Jet al., 2017). In conclusion, curcumin can be used as a beneficial supplement to improve the protective effect of gastric mucosa on chronic inflammation and prevent carcinogenic changes in patients with chronic gastritis associated with *H. pylori*.

5. Prospects

Gastric cancer is still a difficult public health problem. From genetics to diet, several factors have led to the generation of gastric cancer. Although targeted therapy has produced significant progress, the cure rate of gastric cancer has not increased significantly. As we understand the molecular and epigenetic changes in the development of gastric cancer, we will develop new treatment options, including the use of less toxic diet therapy to prevent gastric cancer or the combination of relatively non-toxic drugs for prevention gastric cancer caused by early inflammation.

Curcumin has therapeutic effects on breast cancer, lung cancer, colon cancer, bone cancer and brain tumors. It provides a new idea for the treatment and prevention of tumors.

Author contributions

Zhang WS: Acquisition, interpretation of data and wrote the manuscript. References management; Cui N: Critical review (reviewing the article before submission); Ye J: References management; Yang BY: References management; Sun YP: References management; Kuang HX: Obtained funding. Overall responsibility, Critical review (reviewing the article before submission).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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