

Research Progress in Relationship between Chronic Inflammation and Development of Esophageal Cancer

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Abstract: As a common malignant tumor of the digestive tract, esophageal cancer has a high incidence in China, accounting for about half of the global incidence. The pathogenic factors are complicated, primarily related to eating diet, obesity, gastroesophageal reflux disease, and Barrett's esophagus. In this article, through the literature search of Web of Science, PubMed, and CNKI, we analyzed the transformation of inflammatory cells cytokines. We activated the inflammatory pathway in chronic inflammation of the esophagus. These form the tumor microenvironment suitable for tumorigenesis, proliferation, and metastasis, essential in transforming inflammation, metaplasia, and adenocarcinoma of the esophagus. Therefore, understanding the relationship between chronic inflammation and esophageal cancer development can provide new ideas for preventing and treating esophageal cancer.

Keywords: Gastroesophageal reflux disease; inflammatory factors; inflammatory pathway; esophageal cancer

1. Introduction

According to the Analysis of the Global Cancer Statistics Report released by the International Agency for Research on Cancer (IARC), in 2021, there were 604,100 new cases of esophageal cancer and 544,076 deaths in 2020, with the incidence and mortality rate of males were being 2 or 3 times that of females [1]. The incidence and mortality rate of esophageal cancer in China is twice higher than the world average, and the number of new cases accounts for 53.70% of the global total and the number of deaths for 55.35% of the world [2, 3]. Esophageal carcinoma, a malignant digestive tract tumor, mainly comprises esophageal squamous cell carcinomas (ESCC) and esophageal adenocarcinoma (EAC). Early clinical symptoms are mostly non-specific, which can easily be ignored and delay the disease, and endoscopic screening can significantly reduce morbidity and mortality [4]. Surgery, radiology, chemistry, and other comprehensive treatments are used frequently in clinical practice. Despite years of challenging exploration, targeted drugs, pembrolizumab, and nivolumab, can also use as part of esophageal cancer treatments but cannot satisfy all of them [5]. Therefore, seeking safe and efficient drugs is a major clinical problem to be solved urgently.

2. Etiology

As a typical lifestyle cancer, esophageal cancer is closely related to the patient's adverse lifestyle and dietary eating habits, such as long-term consumption of foods rich in amines or fungi, hot diet, coarse diet, alcohol consumption, smoking, Etc. [6, 7]. Obesity, gastro-esophageal reflux disease (GERD), and Barrett's esophagus (BE) are also related, and the cancer is the result of multiple factors [8-10].

2.1. Obesity

Excessive accumulation of abdominal adipose tissue increases intra-abdominal pressure, causing gastric compression, disrupting the normal functioning of the gastroesophageal connection, and

promoting gastroesophageal reflux disease. At the same time, the remaining adipose tissue re-secretes pro-inflammatory cytokines to activate inflammatory responses and metabolic alterations in the body [9, 11].

2.2. Gastroesophageal reflux disease

Gastroesophageal reflux disease is an esophageal inflammatory injury caused by the lower esophageal sphincter's transient relaxation and the esophageal mucosa's direct stimulation by gastric reflux. Its epidemiology is related mainly to obesity and Western lifestyles [6]. Prevalence ranges from 2.5% of China to 51.2% of Greece, and 30% of Westerners are currently affected by the disease [12, 13]. Although most patients can recover spontaneously, 10%-15% of GERD still convert to BE [12-14]. Persistent chronic inflammatory states will promote the release of pro-inflammatory mediators to enhance cell growth and invasion, thereby supporting tumorigenesis. So far, the key cytokines involved in this process, including IL-8, IL-6, TGF- β , and IL-1 β , have been increasingly confirmed to recruit inflammatory cells to promote cancer [15].

2.3. Barrett's esophagus

Barrett's esophagus (BE) is EAC's only known pathological precursor, characterized by replacing normal squamous epithelium in the distal esophagus with specialized intestinal columnar epithelium [14]. Barrett's esophagus can be developed from GERD has an increased risk of developing esophageal cancer under chronic inflammation, approximately 30 times that of the general population, which is a classic model of inflammation-related cancers [15-17]. Today, approximately 90% of all Esophageal adenocarcinoma in the United States are EACs, and EACs that develop from BE have increased six-fold over the past 30 years [18]. Anti-inflammatory drugs such as aspirin have been found to reduce chronic inflammation and thus reduce the probability of BE developing EAC, suggesting that inflammation is one of the causes of EAC [19].

3. Microenvironment changes caused by inflammation

Several studies have shown that cancer treatment should focus on tumor cells and the tumor microenvironment and its changes. Chronic inflammation promotes the formation of a microenvironment that favors tumor changes. The tumor microenvironment contains different cell populations, signaling factors, and structural molecules with which tumor cells interact to inhibit apoptosis, promoting immune evasion, proliferation, invasion, and metastasis [20].

3.1. Immune cells

Immune cell infiltration can be found at BE, dysplasia, and EAC stages. Generating pro-inflammatory factors and other tumor secretory factors to create an immunosuppressive environment to help tumor cells evade host responses, thereby facilitating tumorigenesis and development [21, 22].

3.1.1. Myeloid derived suppressor cells

Myeloid-derived suppressor cells (MDSCs) can modulate anti-tumor immunity by inhibiting T cell activation, NK cell killing, and inducing regulatory T cells [23]. Stairs et al. found that MDSCs were significantly amplified in a p120-catenin-deficient ESCC mouse model and were able to activate fibroblasts to induce connective tissue hyperplasia [24]. In addition, elevated levels of MDSCs have been observed in patients with esophageal cancer, which were associated with advanced disease, poor prognosis, and treatment resistance [25, 26].

3.1.2. Regulatory T cells

Regulatory T cells (Tregs) regulate the proliferation and activation of B cells, and T cells modulate the cytotoxic effect of NK cells in the normal physiological state. However, Treg initially suppresses inflammation but subsequently secretes immunosuppressive cytokines, interfering tumor-associated antigen delivery, and inhibits cytotoxic cell function, to weakens antineoplastic immunity [27]. Tregs amplification was found in peripheral blood and mucosal tissues of patients with esophageal cancer, related to tumor invasion, metastasis, and reduced survival after chemotherapy [28].

3.1.3. Tumor-associated macrophages

Tumor-associated macrophages (TAM) promote tumor development, induce angiogenesis, and enhance tumor cell invasion [29]. In a GERD rat model, M1 macrophages are recruited to the inflammation site, activating the STAT3 pathway in epithelial and mesenchymal cells, promoting M2 macrophage polarization and accelerating cancer progression [30]. Th2 cytokines of EAC are upregulated, exacerbating MDSC-mediated M2 macrophage infiltration [31].

3.1.4. Carcinoma-associated fibroblasts

Growth factors secreted by Carcinoma-associated fibroblasts (CAFs) can change the extracellular matrix to form tumor niches and promote tumor cell migration [28]. Nobuhide et al. co-cultured human bone marrow-derived mesenchymal stem cells with ESCC cells. They found that it could induce the expression of α -smooth muscle actin and fibroblast activation protein, which are closely related to the depth of tumor invasion, lymph node metastasis, and poor prognosis [32]. Hajime et al. used clinical samples of esophageal carcinoma to reveal that CAFs promoted lymph node metastasis. They subsequently validated the cell-to-cell relationship in vitro and situ metastasis mouse models, confirming in vitro and in vivo accumulation of CAFs enhanced lymph node metastasis in ESCC. It shows that CAF-targeted therapy could reduce lymph node metastasis in patients with esophageal cancer and improve the prognosis of patients [33].

3.2. Cytokines, chemokines and growth factors

Small molecules, including cytokines, chemokines, and growth factors, play an essential role in promoting inflammation and cancer by enhancing cell proliferation recruiting immune cells. Souza et al. observed lymphocytic infiltration at the beginning of GERD and speculated that gastric acid and bile reflux induce the secretion of pro-inflammatory cytokines by HET-1A esophageal epithelial cells, suggesting that GERD is caused by cytokine excitatory-mediated damage rather than corrosive damage [34].

3.2.1. Transforming growth factor- β

Under normal conditions, the transforming growth factor- β (TGF- β 1) has anti-inflammatory and antitumor effects. However, it can promote tumorigenesis in an abnormal microenvironment [21, 35]. TGF- β 1 was significantly increased in EAC tissue compared with tissue from BE, and TGF- β -related genes TSP-1, POSTN, and TMEPAI are dysregulated in the entire metaplasia-dysplasia-cancer sequence, associated with advanced tumors [36].

3.2.2. Vascular endothelial growth factor

As a critical mediator of angiogenesis, vascular endothelial growth factor (VEGF) mainly triggers endothelial cell proliferation and migration and decomposes extracellular matrix. Under environmental conditions such as hypoxia, tumor and interstitial cells secrete active VEGF. The expression of VEGF-A increases in part of esophageal cancers, which is related to survival, tumor depth, and lymph node metastasis [30].

3.2.3. Transcription factor- κ B

Transcription factor- κ B (NF- κ B) is a candidate factor linking inflammation and cancer. It is involved in cell cycle regulation, lymphocyte maturation, inflammation and stress response, Etc., which is crucial in the inflammatory cascade and is closely related to cancer development [37]. From BE to EAC, NF- κ B and its target molecules IL-8 and IL-1 β are all upregulated [38]. The bile acid deoxycholic acid in the esophagus also activates the NF- κ B pathway. It will upregulate downstream targets, including IL-8 and IL-1 β , which will negative feedback increase NF- κ B activation [39]. However, NF- κ B overexpression occurs only in BE and EAC, suggesting it may be a marker of metaplasia-dysplasia-carcinogenesis [40].

3.3. Hypoxia and oxidative stress

Hypoxia can cause severe DNA damage and induce tumorigenic factors, hypoxia-inducible factors (HIF), which enhance the transcriptional activity of NF- κ B in activated B cells, leading to pro-inflammatory cytokines and T migration increasing lymphocytes, the underlying molecular mechanisms of cytokine-mediated damage [41]. Reoxygenation through the ineffective tumor vasculature can also cause significant oxidative stress by producing nitric oxide and hydrogen peroxide reactive oxygen species. Nitric oxide can increase the aggressiveness of developmental abnormalities and cancer cells by

modulating matrix metalloproteinase and tissue inhibitors of metalloproteinase (TIMP) [42]. HIF-1 α was elevated in BE compared with normal squamous epithelium and was associated with acute and chronic inflammation. There is no further increase in expression in atypical hyperplasia or EAC, which may be an early alteration of tumor progression and inflammation [43].

3.4. Microbiota

The esophageal epithelium is not only exposed to bacteria from the mouth but also to bacteria from the stomach and duodenum that accompany esophageal reflux. Yang et al. found that the distal esophageal microbiota often changes during esophagitis and BE. The microbiome changes from aerobic bacteria to gram-negative anaerobic bacteria during these processes, colonizing the esophagus [26]. Gram-negative bacteria produce lipopolysaccharides, activate Toll-like receptor 4 (TLR4) and the NF- κ B pathway, and cause inflammation through iNOS-mediated relaxation of the subesophageal sphincter, resulting in increased esophageal reflux [44]. At the same time, activation of interleukin, NF- κ B, and MMP causes an inflammatory wound response. After the bacteria pass through the epithelial channel, the microbiome homeostasis is lost, further abnormal activation of TLR4, causing a vicious circle of cellular damage, which is one of the factors of esophageal carcinogenesis [45].

4. Inflammatory pathways

4.1. TLR4/NF- κ B pathway

Toll-like receptors are pattern recognition receptors in the body's natural immune system, activated by microbial components such as lipopolysaccharides and endogenous ligands to induce a significant release of inflammatory factors such as TNF- α , IL-6, NF- κ B, and so on. According to relevant reports, Barrett's esophagus is involved in the TLR4/NF- κ B pathway, associated with genetic damage such as genes such as p50/p65 and CDKN2A aneuploidy evolution [27]. Studies have shown that the favorable expression rates of NF- κ B P50, P65 protein, and mRNA in esophageal carcinoma are significantly higher than in normal esophageal mucosal tissue. With the severity of esophageal lesions, the expression rates of NF- κ B P65 and P50 protein increased from normal mucosal epithelium adjacent to carcinoma, atypical hyperplasia tissue, carcinoma in situ to invasive carcinoma. These results suggest that the expression of NF- κ B P65 and P50 protein is related to the process of esophageal cancer [46]. Daisuke et al. produced a duodenal content reflux model in rats, successfully inducing EAC and ESCC rats. Although bile acids could not cause mutations, long-term exposure triggered NF- κ B p65 activation, potentially inducing genetic mutations and promoting cancerous processes, reflecting the importance of chronic inflammatory stimulation in gastrointestinal tumors [47].

4.2. NLRP3 pathway

NLRP3 inflammasome is a significant complex involved in innate immune defense. It is a protein complex consisting of NLRP3 protein receptors, apoptosis-associated speak-like proteins, and procaspase-1. Studies have shown that LPS activates the NLRP3 inflammasome on Barrett's esophagus, causing the secretion and inflammation of pro-inflammatory cytokines, and promoting inflammation-mediated carcinogenesis of Barrett's esophagus [48, 49]. Yin XL et al. examined the effects of LPS, acids, bile salts, and acidic bile salts on average human esophageal cells. The results showed that acidic bile salts stimulate HET-1A cells to accelerate NLRP3 inflammasome activation to activate caspase-1, leading to pro-inflammatory cytokines and release of lactate dehydrogenase (LDH) [50]. Shuang Yu found that NLRP3, ASC, caspase-1, and IL-1 β mRNA were higher in ESCC tissues than in normal adjacent tissues [51]. Regulating the low expression of NLRP3 mRNA has inhibitory effects on the proliferation, migration, and invasion of ESCC cells. The mechanism is mainly related to the low expression of NLRP3 inducing apoptosis and weakening interstitial epithelial transformation.

5. Conclusion

Esophageal cancer, as a disease with high mortality easily neglected in the early stage, should focus on the discussion's occurrence and development. The transformation of corresponding cells, cytokines, and the inflammatory pathways in the chronic inflammatory environment play a vital role in transforming inflammation-metaplasia-carcinogenesis. An in-depth understanding of the various links of inflammation and their interaction can target the key points and then find effective measures to prevent and treat tumors,

which is the focus of future research on tumor treatment. In addition, inflammatory cell and cytokine transformations occur in inflammation-metaplasia-tumor progression. It can target high-risk groups according to the changing characteristics of each link, provide more resource allocation, avoid unnecessary waste of resources, and provide new ideas for the prevention and treatment of esophageal cancer.

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