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Research Progress on Correlations between P53 and Colorectal Cancer

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Abstract: ***Colorectal cancer is currently an important health problem worldwide. However, existing treatments fail to meet the need for a radical cure. Additionally, treatment is limited due to toxic side effects and acquired drug resistance. P53 is a tumor suppressor gene encoding P53 protein, which has a significant potential role in the occurrence, development and treatment of colorectal cancer. Many natural products and compounds have been found to interfere with the progression of colorectal cancer by regulating P53, but systematic reviews are lacking. This study systematically reviewed the introduction of P53, the relationship between P53 and the occurrence, development and treatment of colorectal cancer, and the regulation of P53 by natural products and compounds against colorectal cancer. This provides the theoretical foundation for the treatment of colorectal cancer and offer new ideas for the development of novel therapeutic agents for this disease.***

Keywords: Colorecta cancer, P53, Natural Products, Compounds**.**

1. Introduction

Cancer is a significant global health issue, placing immense pressure on public health systems of society. According to the International Agency for Research on Cancer (IARC) there were nearly 20 million new cancer cases, and 9.7 million people died from cancer in 2022. Colorectal cancer is a common digestive system tumor, ranking third among new cancer cases, accounting for approximately 9.6%, and second among cancer-related deaths, accounting for about 9.3% [1]. Thus it can be seen that the colorectal morbidity and mortality are on the rise.

The occurrence and development of colorectal cancer is a complex process that is associated with genetic, lifestyle and environmental factors, and is closely related to some signaling pathways, including the activation of oncogenes such as RAS, the inactivation of certain genes such as TP53, and the important regulatory factors such as NRF2 and AKT which are involved in the development and treatment of colorectal cancer. Among them, the mutation status and expression level of P53 show great potential for the occurrence, development and treatment of colorectal cancer. Therefore, elucidating the role of P53 in the development of colorectal cancer is essential for its prevention and treatment.

2. P53 and Colorectal Cancer

2.1 Introduction to P53

Tumor suppressive gene *TP53* is located on the short arm of chromosome 17 (17p13.1). The P53 protein, composed of 393 amino acids, is structurally and functionally divided into four domains. It can regulate the transcription of numerous genes, which can be roughly divided into four categories: Cell-cycle inhibition, Apoptosis, Genetic stability and Inhibition of blood-vessel formation. These genes play P53-dependent functions in cells. In human body, P53 is negatively regulated by Murine double minute 2 (MDM2) protein [2,3]. Upon exposure to DNA damage, such as double-strand breaks caused by γ-irradiation, ultraviolet irradiation, or chemical-induced DNA damage, as well as oxidative stress, P53 is activated to prevent tumor formation. P53 mutation plays an important role in the occurrence and development of human tumors [4]. The downstream of P53 is focused on the regulation of cell cycle and apoptosis.

2.2 Relationship of P53 to the Occurrence and Development of Colorectal Cancer

The occurrence of colorectal cancer is associated with mutations in multiple tumor-related genes, including the activation of oncogenes and the inactivation of tumor suppressor genes. Among these, TP53, a key tumor suppressor gene, plays a crucial role. The loss of TP53 function leads to unregulated cell growth, resulting in the development of tumors in various organs including the colorectum. In non-highly mutated colorectal cancer, the mutation rate of *TP53* is about 55%-60%. In non-hypermutated colorectal cancer, the mutation rate of *TP53* is approximately 55%-60%, making it the second most common mutation (*APC* mutation > 80%). However, is significantly reduced in hypermutated colorectal cancer [5,6], TP53 acts as a "gatekeeper" in the biological processes of colorectal cancer. It is not only an important target for preventing the occurrence of colorectal cancer but also plays a significant role in its progression. Studies have found that the expression of TRIM67, a TRIM-family protein, is inhibited in colorectal cancer, and its downregulation is associated with poor prognosis of colorectal cancer patients. TRIM67 interacts with the C-terminal region of P53, protecting it from ubiquitination by MDM2, thereby inhibiting the development of colorectal cancer [7]. Similarly, other molecules that activate p53 to suppress colorectal cancer progression include Tumor-suppressive zinc finger protein 24 (ZNF24) [8], the members of the solute carrier (SLC) superfamily-SLC5A7 [9], retinoid-IFN-induced mortality-19 (GRIM-19) [10]. Conversely, Liu et al. screened a circular RNA circMYH9 from the GEO database, which is highly expressed in colorectal cancer, and patients with high circMYH9 expression have shorter recurrence-free survival and lower survival rates than patients with low expression. This circMYH9 can inhibit P53 by recruiting m6A reader hnRNPA2B1 to degrade P53 pre-mRNA, and promote CRC

proliferation by regulating serine/glycine metabolism and redox homeostasis in a P53-dependent manner [11]. Wang et al. found that, as a key regulator of various cancers, Sirtuin 1 (SIRT1) reduces P53 through deacetylation, thus down-regulating the expression of miR-101 and increasing the expression of miR-101 target gene KPNA3, thus accelerating the growth and metastasis of colorectal cancer cells [12]. Other molecules that promote colorectal cancer progression by inhibiting P53 include long non-coding RNAs-LncRNA-HMG [13], Ubiquitin-specific protease 36 (USP36) [14], and Zinc-finger protein p52-ZER6 [15], etc. Therefore, P53 is significantly related to the occurrence and development of colorectal cancer, and its activation or inhibition is directly correlated with the suppression or promotion of colorectal cancer.

2.3 Association between P53 and Drug Resistance in Colorectal Cancer

Currently, the treatment options for colorectal cancer patients, especially those with advanced disease, primarily include surgery, chemoradiotherapy (neoadjuvant and adjuvant therapies mainly involving oxaliplatin, 5-FU, and capecitabine), but drug resistance has become a major issue limiting the effectiveness of drug therapy. With the deepening of research on P53 and colorectal cancer, people gradually noticed that P53 also plays an important role in the drug treatment of colorectal cancer. Relevant studies have compared the chemotherapeutic responses of normal cells and P53-mutant cells. In normal cells, chemotherapy induces increased expression of P53, which subsequently reduces the expression of multidrug resistance 1 (MDR1) through the miR-34a/LRPPRC/MDR1 axis. However, in P53-mutant cells, chemotherapy-induced activation of P53/miR-34a/LRPPRC/ MDR1 signaling pathway is lost [16]. MDR1, a member of the TP binding box (ABC) transporter superfamily, has been shown to participate in the development of resistance to many anticancer drugs, including chemotherapy drugs, kinase inhibitors, etc [17]. Additionally, studies have found that oxaliplatin induces DNA damage in colorectal cancer cells, leading to the activation of P53. This subsequently results in the upregulation of transcription and translation of one of the cytochrome P450 (CYP) genes, CYP2S1, as well as the reduction of endogenous PGE2 biosynthesis and β-catenin expression. Ultimately, the survival and proliferation of colorectal cells are reduced [18]. Lei et al. built a P53 mutant colorectal cancer cell model and transfected pIRES2-ZsGreen1-TRIM29-flag, and found that this process reversed oxaliplatin resistance in colorectal cancer cells. The mechanism is that TRIM29 increases the sensitivity of colorectal cancer cells to oxaliplatin by blocking the transcriptional function of mutant P53 [19]. Therefore, P53 mutation also plays a positive role in chemotherapy resistance of colorectal cancer. Other related studies have found that after oxaliplatin is applied to colorectal cancer cells, the transcription factor c-MYC promotes the transcriptional regulation and expression of tryptophan-aspartate repeat domain 43 (WDR43). WDR43 enhances the ubiquitination of P53 by MDM2 through binding with RPL11, thereby inhibiting P53 expression and subsequently inducing proliferation and chemotherapeutic resistance in colorectal cancer cells [20]. CTCF-binding factor (CTCF) is a transcription factor with 11 zinc fingers (ZF) that is highly expressed in various tumors and plays an important role in regulating the invasiveness of tumor tissues. P53 is its transcription target gene, and CTCC reduces the inhibitory effect of P53 on Hedgehog signaling pathway by inhibiting P53. Activation of the Hedgehog signaling pathway can reduce the sensitivity of colorectal cancer cells to 5-FU, thus promoting chemoresistance to 5-FU in colorectal cancer [21,22]. Therefore, when the expression of P53 is inhibited, chemoresistance in colorectal cancer is activated. To sum up, P53 has great potential in the treatment of colorectal cancer. For many patients with current treatment resistance, activating P53 to enhance the efficacy of existing therapies is a feasible approach and a new strategy to solve the problem of drug resistance of existing therapies.

3. Anti-colorectal Cancer Products by Regulating P53

3.1 Natural Products

Endoplasmic reticulum (ER) stress is the correction of misfolded and unfolded protein aggregates in the endoplasmic reticulum lumen, as well as the disturbance of Ca^{2+} homeostasis caused by various oncogenic stresses. However, continuous activation can lead to Caspase-12-mediated apoptosis and other processes, resulting in cell death. Oridonin, a diterpenoid compound extracted from *Rabdosia rubescens*, has an inhibitory effect on a variety of tumors. Zhou et al. found that it can up-regulate P53, thereby inhibited the transactivation of Transcription Factor 4 (TCF4) and induced ER stress dysregulation, promoting colorectal cancer cell death [23-25]. Curcumin (diferuloylmethane, Cur), a bioactive polyphenol derived from turmeric, exhibits broad anticancer effects. However, its poor absorption limits its application. Masoumeh Ebrahimi et al. developed Gemini-Cur, a nanoparticle-conjugated form of curcumin, which can up-regulate the expression of apoptotic genes such as P53, P21, NOXA, and BAX, and reduce downregulating the anti-apoptotic BCL-2 in both wild-type and mutant P53 colorectal cancer cells [26]. Another natural product that binds Gemini is Chrysophanol, Chrysophanol is a naturally occurring anthraquinone, Alaadin M Naqishbandi et al. constructed a substance -Gemini-Chr NPs, which acts on HCT-116 cells, it can up-regulate the expression of Bax and P53 and reduce the expression of Bcl-2, which has the potential to promote the apoptosis in colorectal cancer cells [27]. Herba Patriniae (also known as Bai Jiang Cao, HP) is widely used in intestinal diseases and cancers, and its component Isovitexin has the effect of promoting apoptosis and inhibiting cell proliferation by activating P53 signaling pathway in a dose-dependent manner [28]. Other natural products that can interfere with the progression and treatment of colorectal cancer by regulating P53 include damnacanthal and morindone (two anthraquinones from Morinda citrifolia L.) [29] and curcumin (a diketone pigment derived from turmeric) [30,31], Tenacissoside G (a bioactive component from the natural plant Marsdenia tenacissima (Roxb.)) [32], etc. In recent years, research on natural active products has gradually increased, and many natural products demonstrating independent antitumor activity as well as synergistic anti-tumor effects when combined with existing drugs. Studies on natural products targeting P53 for colorectal cancer treatment mainly follow two approaches: (1) directly

inhibiting colorectal cancer by regulating P53, and (2) addressing drug resistance by modulating P53. Both approaches have shown significant potential.

3.2 Compounds

Although there are many natural products in nature that can regulate P53 against colorectal cancer, compounds are still the focus of drug development because they have several advantages over natural products, such as: (1) More precise mechanisms of action, the synthetic compound has a more precise molecular structures, which allows for more accurate targeting of specific sites; (2) Higher availability; (3) Easier production. Therefore, the development and utilization of compounds should be given more attention. In recent years, many compounds have been proven to have the ability to regulate P53 to combat colorectal cancer. Metformin is well-known for the treatment of type 2 diabetes. In recent years, studies have found that metformin has the potential effect of inhibiting tumor growth [33], which may be related to its effect on insulin level and glucose metabolism [34,35]. Chen et al. used a colorectal cancer xenograft model with abdominal radiotherapy to evaluate the impact of metformin on the efficacy of radiotherapy, and found that metformin enhances AMPK-dependent mitochondrial autophagy, thereby reducing acute and chronic intestinal toxicity induced by radiation. It also increases the radiosensitivity of P53-mutant colorectal tumors both in vitro and in vivo [36]. Metformin can upregulate the expression of AMPK and P53 in colorectal cancer xenograft cells, thus inhibiting colorectal cancer proliferation. Moreover, it downregulates the expression of carbamyl phosphate synthase 1(CPS1), arginase 1(ARG1), ornithine trans-carbamylase (OTC) and ornithine decarboxylase (ODC) and other urea cycle enzymes, thereby inhibiting the urea cycle and interfering with cytoplasmic ornithine, which is essential for tumor growth [37,38]. Metformin also has the effect of inhibiting aerobic glycolysis, thereby inhibiting colorectal cancer growth and enhancing the efficacy of treatment [39,40]. Therefore, metformin has significant potential for the prevention and treatment of colorectal cancer. Enediyne compounds are a class of highly potent anticancer agents, among which lidamycin (LDM) is a notable example. LDM induces apoptosis in a P53-dependent manner at low doses, but at high doses, it operates in a P53-independent manner through a more direct DNA damage mechanism, leading to rapid apoptosis [41]. Platinum-(IV)-derivative satraplatin is the first orally active lipophilic platinum (Pt)-(IV) derivative. It has demonstrated anticancer activity against multiple tumors, including colorectal cancer. Moreover, G2/M can inhibit the proliferation of colorectal cancer and induces G2/M cell cycle arrest and apoptosis in a P53-independent manner [42,43]. A novel anticancer agent N-[2-(dimethylamino)ethyl]-2, 3-dimethyl-4-oxo-4h-Pyrido [1,2-a] thieno [2,3-d] pyrimidine-9-carboxamid (PTP) can significantly increase the activity of P53. It induces multiple post-translational modifications and activates the transcription of P53 and downstream genes (such as p21 and PUMA) in colorectal cancer cells through mechanisms involving cell cycle arrest, senescence, and cell death [44]. Another compound that may interfere with the progression and treatment of colorectal cancer by regulating P53 is Ihistone deacetylase inhibitor(I-7ab) [45], Ph3Sn (HtpO2) [46], N-(1-oxo-3-phenyl-1-(phenylamino) propan-2-yl) benzamide (SSE1917) [47], etc. Therefore, the mechanisms by which these compounds regulate P53 to combat colorectal cancer are similar to those of natural products.

4. Conclusions and Prospects

As an important tumor suppressor gene, the mutation status and changes in the expression levels of P53 play a significant role in the prevention and treatment of colorectal cancer. Its crucial functions in regulating apoptosis and DNA repair make it a potential therapeutic target for the treatment of colorectal cancer. In recent years, many natural products and compounds have been developed to modulate P53, thereby inhibiting the occurrence and development of colorectal cancer and enhancing the therapeutic effect of chemoradiotherapy for this disease.

At present the studies on P53 is gradually abundant, but there are still many deficiencies, most of which focus on in vitro experiments, with relatively fewer in vivo experiments being conducted. Additionally, the availability of P3 gene knockout mouse models is particularly limited. When developing products that modulate P53, it is essential to combine them with existing therapeutic approaches and conduct combination therapy experiments for validation. In addition, future studies still need to delve deeper into the mechanisms of P53 mutations and its role in different stages and treatment of colorectal cancer, so as to provide ideas and theoretical foundation for subsequent prevention and treatment of colorectal cancer.

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