Colorectal Cancer

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Contributor: Hsiuying Wang

Colorectal cancer (CRC) is the third leading cause of cancer death in the world. Treatment with 5-Fluorouracil (5-FU) is known to improve survival in CRC patients. Most anti-cancer therapies trigger apoptosis induction to eliminate malignant cells. However, treatment resistance is a major challenge in the development of effective therapies. The microRNAs (miRNAs) play important roles in CRC treatment resistance and CRC progression and apoptosis. This review discusses the role of miRNAs in contributing to the promotion or inhibition of apoptosis in CRC and the role of miRNAs in modulating treatment resistance in CRC cells.

apoptosis colorectal cancer resistance microRNA

1. Introduction

Colorectal cancer (CRC) is a type of cancer that starts in the colon or rectum. CRC is the third most common cancer diagnosed in the United States. It is also the third leading cause of cancer death in the world, and its incidence is rising in developing countries [1]. Lately, due to progress in screening techniques and improvements in treatment, the death rate from CRC has decreased. Although CRC typically affects older adults, its incidence and mortality are rising among young adults [2].

2. Causes of Colorectal Cancer

Environmental and genetic factors play major roles in the pathogenesis of CRC; nutrition plays a causal and protective role in the development of CRC [3]. CRC can also be influenced by other factors such as dietary habits, smoking, a low level of physical exercise, an aging population, and obesity. Among the genetic factors, Sprouty (SPRY) is an intracellular regulator of receptor tyrosine kinase (RTK) signaling. Members of the SPRY family (SPRY1–4) of proteins have been identified as modulators of RTK signaling. SPRY2 functions as a putative oncogene in CRC [4]. The *SMAD7* gene, which is involved in transforming growth factor-beta (TGFβ) signaling, was found to be evolved in CRC [5]. In addition, low socio-economic status was associated with an increased risk of CRC in the US [3][6].

3. Treatments for Colorectal Cancer

The treatment options for CRC include surgery, chemotherapy, radiotherapy, and targeted therapy. Patients with CRC in its earliest stage usually have surgery as the first treatment. Chemotherapy (adjuvant treatment) may also be used after surgery. A combination of two or more treatments is often suggested, depending on the stage of

cancer development. Although surgery and chemotherapy have long been the first choices for CRC patients, the prognosis has never been satisfying for metastatic CRC patients. Targeted therapy is a new option that has successfully prolonged the overall survival for CRC patients [7]. Chemotherapy includes both single-agent therapy and multiple-agent regimens. The single-agent therapy used is mainly fluoropyrimidine (5-FU)-based, and multiple-agent regimens include one or several drugs, such as oxaliplatin, irinotecan, and capecitabine. Although 5-FU remains the gold standard of first-line treatment for CRC, relapses frequently occur, indicating the existence of cancer cells that are therapy-resistant [8]. The use of a nano drug delivery system has been discussed to improve the therapeutic outcome of 5-FU [9]. The therapy 5-FU enhances the sensitization of CRC cells to drug-induced apoptosis. The therapy 5-FU might activate caspase-6 to trigger colon cancer cell apoptosis. Resveratrol is a natural polyphenolic compound. The therapy 5-FU and resveratrol combination treatments cause anti-cancer activities by inhibiting STAT3 and Akt signaling pathways, thereby increasing CRC cell apoptosis [10].

4. Apoptosis

Apoptosis is the process of programmed cell death that occurs during normal development and aging and is a homeostatic mechanism to maintain cell populations. In normal tissues, there is a balance between the generation of new cells and the loss of cells. Cells frequently die through the apoptosis process. The two main pathways in apoptosis are the extrinsic and intrinsic apoptosis signaling pathways [11][12]. The extrinsic (or death receptor) pathway that initiates apoptosis involves transmembrane-receptor-mediated interactions. These involve death receptors that are members of the tumor necrosis factor (TNF) receptor gene superfamily. In addition, caspases are the primary mediators of apoptosis. The intrinsic pathway of caspase activation is initiated by events such as DNA damage and growth factor withdrawal. These events lead to changes in the integrity of the mitochondrial membrane, which is regulated by BCL-2 family proteins.

Apoptosis is of particular interest to researchers who study cancer. When something goes wrong in a cell, this damaged cell is quickly destroyed by apoptosis, which can prevent the development of cancer. Otherwise, the damaged cell may survive and develop into a cancer cell. Cancer cells can evade apoptosis and continuously divide. The p53 tumor suppressor plays a critical role in protecting normal cells from malignant transformation, and the tumor suppressor gene TP53 is mutated in ~50% of human cancers. The p53 tumor suppressor acts as a major barrier to neoplastic transformation and tumor progression through its unique ability to act as an extremely sensitive collector of stress inputs and to coordinate a complex framework of diverse effector pathways and processes that protect cellular homeostasis and genome stability [13]. Reactivating p53 in cancer cells has been an interesting research area. A specific inhibitor of cap-dependent translation, 4EGI-1, was found to cause an increase in p53 internal ribosomal entry site (IRES) activity to induce cancer cell apoptosis [14]. Mouse models show that genetic reconstitution of the wild type p53 tumor suppression functions rescues tumor growth, indicating that either restoring wt-p53 activity or inhibiting mutant p53 oncogenic activity could be promising cancer therapeutic strategies [15]. The mechanism through which p53 prevents tumor development is known as the induction of apoptotic death in nascent neoplastic cells. However, recently, this concept has been challenged, because gene-targeted mice that lack the critical effectors of p53-induced apoptosis do not develop tumors spontaneously [16].

Chemotherapy forces cancer cells to undergo apoptosis by causing DNA damage or cellular distress. However, cancer resistance commonly occurs in chemotherapy and often leads to therapeutic failure. Cancer drug resistance can occur through different mechanisms, including apoptosis suppression [17]. Abnormalities in apoptotic function contribute to both the pathogenesis of CRC and its resistance to chemotherapeutic drugs and radiotherapy [18]. Overexpression of mutated p53 is often connected to resistance to standard medications. MDM2 is a negative regulator of p53. Small molecules that can switch off the activity of MDM2 have been identified, and these MDM2 inhibitors increase the activity of combination treatment with standard chemotherapy [19]. The perspective that drug ineffectiveness results from tumor–host interactions was proposed, and it is understood that such an interaction might open new opportunities to overcome the development of resistance to cancer chemotherapy [20].

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