The Therapeutic Strategies Based on Cytokines in The Treatment of Colorectal Cancer

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Abstract. Originates in the colon or rectum, due to powerful mutation ability and complex pathogenesis factors, the colorectal cancer (CRC) has remained its status of the world's third death causing cancer for several years. Therefore, many medical methods have been produced. Among all the possible strategies, the cytokines targeted strategies showed its advantage in the treatment of cancers in multiple ways. Several typical cytokines whose function are different in colorectal cancer microenvironment, such as TGFβ whose function is vastly different before and after the invasion of tumor and IL-6 which could activate other chemokines to together contribute on the formation of inflammatory tumor microenvironment. There is also a cytokine family (IL-17) that each member has distinctive effect on the tumor cells, together forming a complex network of relationships with indirect promotion, direct promotion and mutual inhibition. Taken the properties of cytokines, the design of targeted therapy like blocking signal pathways, inhibiting the activity of cytokines and modification related genes have emerged and developed, which have more accuracy to cure and less side effect. This review summarized the function of these typical cytokines, their corresponding therapeutic strategies and potential defects, and aim to offer valuable resources for investigating cancer treatments that target pivotal molecules within cytokine-related signaling pathways.

Keywords: Colorectal cancer; cytokine; therapy.

1. Introduction

Colorectal cancer (CRC) arises from genetic mutations and environmental factors like diet and lifestyle, leading to uncontrolled cell growth. Chronic inflammation, gut microbiota dysbiosis, and genetic predispositions contribute to CRC development. Thus it is causing a high death rate and making it a big threaten to the human beings currently. Understanding these mechanisms aids in devising preventive and therapeutic interventions Among all therapeutic strategies dealing with CRC, although surgical resection and chemotherapy are commonly used, the Colorectal cancer's extremely high mutation rate and uncertainty after surgery have brought numerous side effects. Therefore, the treatments concentrated on cytokines is usually considered with high efficiency. Cytokine is a kind of small molecular polypeptide or glycoprotein that is synthesized and secreted by a variety of tissue cells (mainly immune cells), thus combined with a large variety of biological function, including regulating cell growth, maturity, immune response and most importantly, inflammation. The broad definition of cytokines makes their range for research also extensive. Meanwhile, the function of cytokines would be entirely contrary since their target cells and resources varies. For cytokines like TGFβ, they could constantly promote the tumors by inhibiting the proliferation of immune activity cells and inducing the gene expression of primary cancer at the early stage of inflammation, however, a series of mutations of TGFβ caused by later stage make the cytokines' function entirely different [1], which manage to assist the progression of tumor. Unlike TGFβ, some classical cytokines such as IL-6 will start creating signal pathways for tumor cells once they appear. They will combine with other chemokines and together creating a microenvironment that supports the growth of tumor [2]. Same phenomenon happens by IL-17 family, where each member transferring information to benefit the enhancement of tumor microenvironment [3], while some of the members will also act to inhibit tumor growth. With in this review, not only the specific working principle of these typical cytokines above but also the therapeutic strategies related to cytokines' prominent properties in various areas in the tumor microenvironment are represented.

2. The pathogenesis and introduction of colorectal cancer

The onset and advancement of colorectal cancer (CRC) result from a multifaceted interplay of genetic anomalies and environmental influences. Key genetic mutations in genes like APC, KRAS, and TP53 are frequently linked to the inception and advancement of CRC. These mutations have the potential to disturb typical cellular operations, instigating unrestricted cell proliferation and the development of malignant tumors. The progression of CRC typically begins with the transformation of normal colonic epithelial cells into adenomatous polyps, which are benign growths that can develop into cancerous tumors over time. As the polyps grow, they acquire additional genetic alterations that promote their malignant transformation. Eventually, nearby tissues are infiltrated by the cancer cells and subsequently spread to remote organs through metastasis. Screening modalities like colonoscopy, fecal occult blood testing, and stool DNA analysis play a pivotal role in detecting precancerous polyps or incipient tumors during their more manageable stages. Furthermore, breakthroughs in molecular diagnostics and precision medicine have ushered in novel avenues for bespoke therapeutic interventions tailored to the distinctive genetic makeup of each tumor, promising enhanced survival rates and elevated standards of living for CRC patients. Among them, cytokine-based treatment is an efficient molecular targeted therapy.

3. The cytokines and therapeutic strategies based on their properties

3.1. TGFβ

When talking about the transforming growth factor-β (TGFβ) , it is not just a single molecule, but a combination with over hundreds of cytokines and related proteins, which could be found everywhere in the humans' normal metabolism. In addition to its function in early embryonic and tissue formation, TGFβ also plays a role in regulating the growth of tumor microenvironment and related inflammation [4]. After releasing from the large latent complex (LLP), the dimers of TGFβ will bind to a specific receptor that shape totally like TGFβ itself, while there are two kinds of these heteromeric receptors which differ in function, called Type I and Type II. In the canonical signaling pathway, this leads to the phosphorylation of receptors, and related SMAD molecules (R-SMADs) will be activated. After that, some of them combine with another molecule called SMAD4 and together moving to a specific nucleus, promoting the process of transcription. Meanwhile, other SMADs with the inhibition ability can block the signaling pathway of TGFβ at various stages by involving enzymes and proteins that are essential for the signal transduction [4,5].

Although TGFβ initially suppresses tumor growth, TGFβ would start the function for tumor advancement across various cancer types with the enhance of the signaling. In colorectal cancer, elevated TGFβ signaling is linked to disease progression. Specifically, from various mutations of virus to side-effects of prognosis, the raise of TGFβ level includes several factors [6]. Several later methods have focus on therapeutically modulated this special pathway in the tumor microenvironment, considering that TGFβ signaling plays an vital rule in advanced colorectal cancer. These strategies encompass, among others, medications that impede the synthesis of TGFβ as well as inhibitors that target the activity of receptor kinases and the signaling pathways subsequent [7]. For instance, the anti-TGFβ2 antisense oligodeoxynucleotide Trabed ersen has been shown to be effective in preclinical studies on pancreatic cancer and was tested in a phase I study on various solid cancers, including CRC [8]. Nevertheless, there is no way to determine the maximum of tolerated dose since large amount of cytokines are activated against immune system and together form cytokine storm [9]. Given this and analogous findings, researchers had investigated multiple propositions that regarding the signal transduction of TGFβ and the choice of the CRC patients' type, then more effective solutions had been made. In one clinical experiment, the TGFβ was used for evaluating the antitumor activity of BART in several murine tumor models. The researchers reported that bintrafusp alfa (BA), a fusion protein with dual inhibition of TGFβ and PD-L1, showed promising results when combined with radiotherapy (RT). This combination (BART) led to enhanced survival rates in murine tumor

models resistant to multiple therapies, including reshaped the microenvironment where tumors live and lower the rate of poor diagnosis by decreasing the fibrosis of tissue. Consequently, tumor immunity was restored. It is worth mentioning that after the CD8+ T cells from immune system are depleted, the function of BART will reverse to be harmful for human. These findings suggest that with proper dosage of BART combination, it is possible to eliminate the tumors with resistance. At the same time, the side-effect like damaging the epidermal tissue is much less than other medicine, thereby supporting its potentiality in clinical application.

3.2. The pathways between IL-6, JAK2 and STAT3

A single cytokine could be formed from several other cells, and has diverse function on other cells. Take Interleukin for example. Various kinds of cells could have a reaction with it, which has the ability to enhance immune system as well as controlling different cancers. Same as TGFβ, Interleukin is combined with several protein family members. Among them, there is a kind of cytokine that is responsible in the regulation of immune system, called IL-6. By forcing the proliferation of granulopoiesis, nearly all areas of innate immune system such as the movement of hematopoietic cells could be adjusted. IL-6 has the ability to stimulate the tumor cells directly, assisting them to proliferate and invade other cells constantly by regulating immune cells and breaking the defense of the host. The effects IL-6 give to immune cells are tremendous and wide range, which could even affect the cells in the non-immune system. The cells that get controlled usually display characteristics that the hormone levels in their bodies increased significantly [10]. Janus kinase (JAK) is some kind of tyrosine kinase without the receptor, which means it could orchestrate signal transduction upon cytokine-receptor binding. When it comes to the modulation inflammation and immunity by cytokines, is impossible to function well without the signal transducer and activator of transcription (STAT) .STAT is actually a special protein family. In colorectal cancer, these molecules collaborate to form signaling pathways crucial for cancer development and progression, aided by bone marrow-derived myofibroblasts. IL-6 triggers the pathway in order to regulate the cell cycle dynamics and decrease the invasion of immune system, thus fostering the tumorigenesis [11]. Once the STAT3 is over-activated, the production of IL-6 is able to upregulated, creating a loop with positive feedback [12]. Utilizing this unique mechanism, approaches such as CPEB3 have been developed to hinder epithelial-mesenchymal transition by disrupting the communication between cells [13].

3.3. IL-17 Family

In 1993, the Interleukin 17A (IL-17) was first being discovered. Every single section of colorectal cancer such as transport and angiogenesis require this significant cytokine. There are two alternative way for IL-17A to affect, the first is interfere STAT3 pathway and force it to release IL-6 and thus achieving indirect control over CRC. Besides, Il-17A could manage to modify the chemokines inside the microenvironment of CRC directly and leading to enormous change. The "IL-23-IL-17 axis" has emerged as a pivotal factor in autoimmune diseases. From the experimental results, mice that in lack of these two cytokines are then confirmed to have default in immune system. Same results are also found in human by genome-wide association studies (GWASs) and clinical intervention. The IL-17 family consists of six structurally related cytokines: IL-17A (or IL-17), IL-17B, IL-17C, IL-17D, IL-17E (also known as IL-25), and IL-17F. Each member of this family serves distinct functions; for instance, IL-17F is involved in mucosal host defense, IL-17E amplifies TH2 immune responses, and IL-17A predominantly contributes to tumor progression in CRC, inflammation, and autoimmunity [14]. While other members of the group have a promoting effect on tumor growth, IL-17F has been shown to exert a tumor suppression effect in colorectal cancer, potentially by inhibiting tumor angiogenesis [15]. Hence, IL-17 may hold significant promise for colorectal cancer (CRC) treatment. Tosolini et al. have proved that among people who has colorectal cancer, their poor prognosis would cause the overexpression of IL-17A [16]. Based on current clinical data, IL-17 has been observed to have the ability to make stromal cells more sensitive, prompting them to create molecules such as prokineticin and calprotectin which are capable in retrain immune system. This activation mechanism

has been implicated in conferring resistance to anti-VEGF treatment. Furthermore, the underlying molecular mechanisms of IL-17A and the fundamental functions of IL-17F require further investigation before more efficacious clinical therapies and drugs can be developed.

4. Conclusions

Although the special pathogenesis of colorectal cancer makes early detection, prognosis and treatment very difficult, it also provides an effective channel for cytokine-based treatments. The multiple function of cytokines such as activation to form specific compounds, colon cancer cells aggregate to generate structures resembling cancer stem cells, termed spheres. and regulating the homeostasis of the tumor microenvironment through interactions among family members make themselves critical to inflammation and carcinogenesis. Therefore in the special microenvironment of colorectal cancer, taking the advantages of the properties of cytokines, targeted therapies such as blockers of TGFβ ligand−receptor interactions, enhancement of members which has the ability to inhibit the function of other members from IL-17 family and the disruption of the crosstalk between colorectal cancer cells and tumor associated macrophages via IL-6R/STAT3 signaling. Even though uncertainties and flaws constantly emerge, with the continuous development of future technology, the application prospects based on cytokines in colorectal cancer are still very promising.

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