Biomedicine & Pharmacotherapy 76 (2015) 107–120

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Review

Advances and perspectives of colorectal cancer stem cell vaccine

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ARTICLE INFO

Article history:
Received 6 August 2015
Accepted 20 October 2015

Keywords:
Colorectal cancer
Cancer stem cell
CCSCs vaccines
Therapeutic target

ABSTRACT

Colorectal cancer is essentially an environmental and genetic disease featured by uncontrolled cell growth and the capability to invade other parts of the body by forming metastases, which inconvertibly cause great damage to tissues and organs. It has become one of the leading causes of cancer-related mortality in the developed countries such as United States, and approximately 1.2 million new cases are yearly diagnosed worldwide, with the death rate of more than 600,000 annually and incidence rates are increasing in most developing countries. Apart from the generally accepted theory that pathogenesis of colorectal cancer consists of genetic mutation of a certain target cell and diversifications in tumor microenvironment, the colorectal cancer stem cells (CCSCs) theory makes a different explanation, stating that among millions of colon cancer cells there is a specific and scanty cellular population which possess the capability of self-renewal, differentiation and strong oncogenicity, and is tightly responsible for drug resistance and tumor metastasis. Based on these characteristics, CCSCs are becoming a novel target cells both in the clinical and the basic studies, especially the study of CCSCs vaccines due to induced efficient immune response against CCSCs. This review provides an overview of CCSCs and preparation technics and targeting factors related to CCSCs vaccines in detail.

Contents

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http://dx.doi.org/10.1016/j.biopha.2015.10.027
0753-3322/

1. Introduction

Newly emerging data highlight colorectal cancer as an important risk factor for endangering the people's health [1]. Particularly, on account of the inappropriate consumptions of red meat, alcohol, cigarette as well as antibiotics, the prevalence and the mortality of colorectal cancers has firmly occupied the third most common cancer in both men and women in the United States [2]. As is collected and reported by National Center for Health Statistics, in 2014, approximately 96,830 new cases and among which 50,310 deaths of colon cancer were estimated [3]. The prevention and treatment of colorectal cancers remain a tough problem in the scientific community worldwide. There is no denying the fact that surgical therapy remains the fundamental treatment for non-metastatic colorectal cancers, therefore it become increasingly crucial for researchers to develop original therapeutics for colorectal cancers. Recently, basic and clinical empirical studies demonstrated that colorectal cancer stem cells (CCSCs) played an important role in the prevention and treatment of colorectal cancer [4]. CCSCs represent a population of cells within tumors with highly tumorigenic and chemo resistant properties, tightly relating to tumor cell proliferate and metastasize [5]. It has been verified that merely few dose of CCSCs are capable of reconstituting the growth of colon cancer cells thereby regenerating the original tumor, resisting apoptosis by autocrine IL4 which contributes to chemotherapy resistance as well as drug resistance [6]. Furthermore, these cells have a strong ability to self-renew, differentiate, maintain dormant for years after irradiation or chemotherapy and then CCSCs migrate to distant tissues and organs to initiate tumors [7]. More importantly, just the same as side-population cells, CCSCs own the superiority to bump out the chemotherapy drugs compared to other tumor cells which shows that CCSCs are responsible for tumor drug-tolerance [8]. All in all, CCSCs not only have the characteristics of drug resistance of cancer cells, but also have characteristics of proliferation and differentiation of stem cells thereby present to be a promising therapeutic target for colorectal cancers. Numerous experimental studies have found CCSCs involve in pathological as well as physiological processes of colorectal cancers, therefore concentrated in developing colorectal cancer cell vaccines which target CCSCs along with its microenvironment and relative signaling pathways [9,10]. CCSCs vaccines possess various advantages including enhanced specificity, sensitivity, reliability, and the remarkable therapeutic effect. Additionally, CCSCs present to be the potential target to resolve drug resistance for colorectal cancers therapy. There is reason to believe that innovative CCSCs vaccines may provide a brand new perspective in developing conspicuously efficient therapy approaches of colorectal cancers. In this review, we set out summarizing latest researches on CCSCs along with relative signaling pathways, molecules, genes and microenvironment, thoroughly investigating CCSCs vaccines on targeting CCSCs, signaling pathways, regulative genes and microenvironment and promising researches both basically and clinically.

2. Theoretical basis of CCSCs vaccines: the latest innovative colorectal cancer stem cell theory

According to the classic pathogenesis theory of cancer, colorectal cancers are believed to originate from the accumulation of multiple genetic mutations and hereditary factors for a period of many years [11]. From the perspective of clinical therapeutic effect, the disappointing curative effects on colorectal cancers after chemotherapy and radiation therapy attribute to the drug resistance and metastasis of colorectal cancer cells [12]. Aiming at the two great challenges, researchers have taken many appropriate and practical methods to ameliorate, but the results are still desperate. The prevention and treatment of colorectal cancers remain a tough problem in the scientific community worldwide, which call for more potential and persuasive theory and more effective therapies. More attractively, colorectal cancer stem cell theory gives unique and acceptable explanations for the above two challenges [13]. This theory argues that colorectal cancers contain a minority population of CCSCs responsible for tumor initiation, growth, and recurrence. Naturally, these latent CCSCs might be potentially associated with primary tumor recurrence and metastasis [13]. CCSCs exhibit lower rates of cell division in their niche that allow them to survive after chemotherapy and radiation therapy, and only a subpopulation of CCSCs within a cancer have the exclusive capacity to regenerate a tumor and sustain its growth [14]. Therefore, attentions have been focused on defining new agents and novel therapies for cancer prevention and therapy by eliminating CCSCs.

In contrast to the stochastic model of cancer where all cells in a tumor have the capability to reconstitute a tumor, the CCSCs model offers better explanations to a number of clinical properties of cancer because they have the ability to self-renew, differentiate, and lay dormant for years after irradiation or chemotherapy only to recur, at times, decades later [15]. CCSCs are postulated to be a unique cell population exclusively capable of infinite self-renewing abilities, differentiation capacity, carcinogenicity, drug resistance and metastasis, and with ability to evade conventional cytotoxic cancer therapy [15]. These traits distinguish CCSCs from their more differentiated counterparts, which possess only limited or no potential for self-renewal and tumor initiation [15]. More precisely, several signaling pathways have been reported to participate in the self-renewal behavior of CCSCs, including Wnt/β-catenin, Notch, and hedgehog signaling, which mediate the resistances against radiotherapy and chemotherapy [16]. In addition, the study of CCSCs has transformed over time and necessarily incorporates the tumor microenvironment [17]. The appreciation for the complex interaction among all components of the microenvironment increases with the growth of knowledge in this area [17]. In view of more forward-looking studies, attentions are gradually shifting from merely identifying markers that enrich for CCSCs to untangling the complex web of signaling pathways that determine the stem-like behavior [16,17]. These pathways are often dysregulated counterparts of net-works functionally important in the maintenance of normal tissue stem cells [16,17]. CCSCs are not lonely fighters and they often interact with and modulate signaling of stromal elements to elucidate a paracrine environment favoring tumor growth and invasion [17]. In the next discussion, we will systematically introduce these new perspectives.

2.1. The remarkable characteristics of CCSCs

Given that the colorectal cancer stem cell theory is widely accepted, CCSCs biology is becoming a rapidly developing field within cancer research. It is important to recognize that CCSCs are not strictly abnormal stem cells. By reading lots of literature, we update the remarkable characteristics of CCSCs as the following