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Review

Role of transmembrane glycoprotein mucin 1 (MUC1) in various types of colorectal cancer and therapies: Current research status and updates

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ABSTRACT

Colorectal carcinoma (CRC) is the third most common malignant tumor in the world. In recent years, the morbidity and mortality of CRC have increased in the world due to increasingly ageing population, modern dietary habits, environmental change, genetic disorders and chronic intestinal inflammation. Despite recent advances in earlier detection and improvements in chemotherapy, the 5-year survival rate of patients with metastatic CRC remains low. Therefore, novel effective treatment strategies for primary or metastatic CRC have emerged to enhance cure rate as well as elongation of patient's survival. Immunotherapy has been proposed for a potentially effective therapeutic approach to the treatment of CRC. Tumor vaccination in preclinical and clinical studies has supported the antitumor activity induced by immunization with CRC cell vaccines. Epithelial cell molecule Mucin 1 (MUC1), a transmembrane glycoprotein aberrantly overexpressed in various cancers including CRC, has been used as a candidate target antigen in the peptide, dendritic cell, and whole tumor vaccines. Several clinical trials in progress reveal the immunogenicity and suitability of MUC1 that acted as immunotherapeutic vaccines for CRC/colorectal cancer stem cells (CCSC). The present review summarizes the potential roles of MUC1 on CRC/CCSC vaccines according to the latest data. Moreover, this review also discusses the novel strategies for targeting CCSC via inducing an immune response against MUC1 to achieve the best prevention and treatment effects in animal models and clinical trails.

1. Introduction

Colorectal carcinoma (CRC) is a major health problem worldwide and the third leading cause of cancer-related mortality in China. A major cause of mortality is the metastasis of CRC [1]. To date, the major therapeutic CRC methods are surgical procedures, radiotherapy, neoadjuvant, and palliative chemotherapies etc. Despite great advances in the fight against CRC during the last decade, treatment options for advanced CRC is yet to be a limited and unsuccessful, and 5-year survival rate of patients with metastatic CRC remains very low [2]. Therefore, novel approaches to CRC therapy are needed urgently to address this clinical need.

It is known that CRC has been considered a complex disease that arises as result of the accumulation of genetic alterations in key regulatory genes and pathways, including the RAS-MAPK pathway [3], Wnt pathway [4] and P13 K pathway [5]. Recent improvement of our understanding of CRC biology and advances in genomic technologies has led to the identification of a variety of epigenetic alterations strongly involved in cancer initiation and progression. Among the epigenetic marks implicated in CRC the most widely studied are the global DNA hypomethylation [6], the promoter hypermethylation and the miRNAs dysregulations. Interestingly, apart from the generally accepted theory that pathogenesis of CRC consists of genetic mutation of a certain target cell and diversifications in tumor tissue, the colorectal cancer stem cell (CCSC) theory makes a different explanation, which hypothesize that there is a specific and scanty cellular population possessing the capability of self-renewal and differentiation, tightly responsible for initiating and sustaining CRC growth, resisting conventional chemotherapeutics, and tumor metastasis after apparently complete remissions [7–11].

Studies have demonstrated that the immune system has its ability to recognize and eliminate microscopic disease, and it may be paramount in preventing tumor recurrence. Accordingly, the vaccine immunotherapy may be a useful one addition to conditional chemotherapy regimens [12–14]. Growing evidence has shown that CRC vaccines, which target CRC through initiating immune responses against CRC cells, are a promising novel immunotherapy strategy addition to the treatment of CRC. However, CRC-specific vaccines have

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exhibited minimal clinical efficacy in patients with established drug-resistant and metastasis disease [12,13]. Emerging study suggests that the CCSC vaccines [12–14] may broaden the antigenic breadth and function as a tumor-associated antigen, take full advantage of inoculators' own immune system, and induce the immune responses against CCSCs directly to solve tumor cell drug resistance, relapse and immune escape, subsequently not causing side effects [13] and potentially breaking the dilemma of cancer treatment in essence. However, what molecules elicit powerful immune responses in this CCSC-based vaccine requires further studies.

Most studies of immunotherapy have demonstrated that mucin 1 (MUC1), as detected immunologically, is increased in expression in CRC, which serves as an immunogenic molecule involved in TCR and BCR epitopes, and mediates CRC's metastasis and chemical resistance as well as correlates with a worse prognosis [15].

Several approaches have been suggested that MUC1-C is a potential target for the treatment of CRC. CRC patients who overexpress MUC1 may be candidates for treatment with the MUC1-C inhibitor alone or in combination therapy with other agents [16]. A high expression of MUC1 may be used as an independent biomarker in various stages of CRC tumors, which would aid in the early detection of CRC [17]. Interestingly, mounting evidence suggests that MUC1 is also enriched in CCSCs [18], and specific targeting MUC1 may be a new strategy to aid in eliminating CCSCs. In this review, we will update the features and functions of MUC1 in CRC/CCSCs according to the latest scientific findings. Moreover, we will focus on the new therapeutic strategies that specific eliminate CCSCs via inducing an immune responses against MUC1 in the prophylaxis and treatment of CRC regimens.

2. Potential roles of MUC1 in CCSCs

2.1. Self-renewal and proliferation

Normal colorectal tissues include stem cell populations that derive from the functional differentiation of progenitor cells [19]. Similarly, CRC also contain CCSCs that possess the ability of self-renewal and generating tumors [20]. It is well known that NF-κB signaling play an important role in self-renewal, proliferation and differentiation of CCSCs [21–23]. MUC1-C was shown to bind directly to p65, thereby activate NF-κB signaling pathway [24]. Moreover, MUC1-C and p65 complex can bind to NF-κB target genes, forming an auto-inductive regulatory loop [25]. Activated NF-κB signal can induce high interleukin-8 (IL-8)/CXCR1 expression, resulting in mammosphere formation in vitro [26,27]. MUC1 can also activate ERK C/EBPβ signaling and ALDH1A1 expression [28]. Meanwhile, Wnt/β-catenin signaling pathway relates to the self-renewal, proliferation as well as survival of CSCs by affecting BMI-1 [29,30], Nanog and Oct4 expression [31]. B-cell-specific moloney murine leukemia virus integration site 1 (BMI1) was an important ingredient of polycomb repressive complex 1 (PRC1) complex, which was responsible for self-renewal of CSCs [32,33]. It has been demonstrated that MUC1-C may induce occupancy of BMI1 on the CDKN2 A promoter by binding directly to BMI1 [34,35]. Moreover, MUC1-C was further reported to inhibit BMI1 expression through affecting miR-200c [36]. Therefore, overexpression of MUC1-C may down-regulate H2 A ubiquitylation, and in turn inhibit HOXC13 and HOXC5 expression [35]. Importantly, MUC1 was shown to regulate BMI1 through a MYC signal mechanism to maintain stem-like characteristics [36,37]. Attractively, the phosphorylated intracellular tail of MUC1 was reported to be the best site for β-catenin binding, and the combination of two molecules may lead to β-catenin stabilization and overexpression of target gene including MYC and CCND1 [38,39]. Noteworthy, the combination of MUC1 and β-catenin was beneficial for nuclear translocation of β-catenin, which was a key event to regulate gene expression of proliferation and differentiation [40]. For a detailed signal network, please refer to Fig. 1.

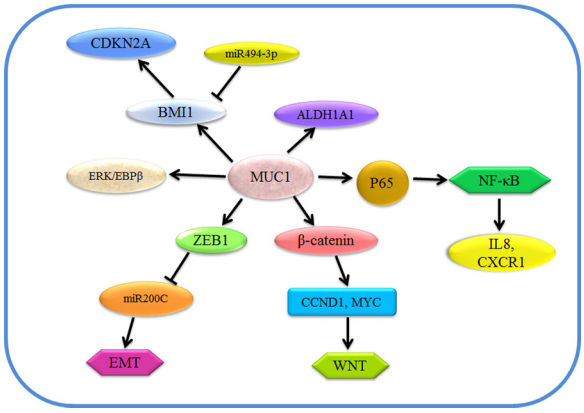

Fig. 1. Potential network of MUC1 on CRC self-renewal and proliferation. MUC1-C was shown to bind p65, activating NF-κB signaling pathway, which plays an important role in self-renewal, proliferation and differentiation of CCSCs. Moreover, the complexion of MUC1-C and p65 can bind to NF-κB signal, inducing high interleukin-8 (IL-8)/CXCR1 expression, resulting in mammmosphere formation in vitro. MUC1 can also activate ERK C/EBPβ signaling and ALDH1A1 expression. Meanwhile, MUC1-1 may induce occupancy of BMI1 on the CDKN2 A promoter by binding directly to BMI1. MUC1-C was further reported to inhibit BMI1 expression through affecting miR-200c. Attractively, the combination of MUC1 and beta-catenin may overexpression of target gene including MYC and CCND1, which was a key event to regulate gene expression of proliferation and differentiation. BMI1: B-cell-specific moloney murine leukemia virus integration site 1; ALDH1A1: aldehyde dehydrogenase 1 family, member A1; CDKN2 A: cyclin-dependent kinase Inhibitor 2 A; ZEB1: Zinc finger E-box-binding homeobox 1; CCND1: Cyclin-D1; EMT: epithelial-mesenchymal transition.

2.2. Drug-resistance and anti-apoptosis

Drug resistance is very important for tumor growth, which may be one of dominant reasons for tumor therapy fail. It has been demonstrated that CSCs can mediate drug-resistance through various mechanisms by which promote tumorigenesis as well as metastasis, leading to cancer relapse. Cancer cells have multiple mechanisms for survival, which includes increase of drug metabolism, improvement of drug efflux, block of drug uptake, variation of drug targets, and so on [41–43]. Accordingly, CCSCs can over express the ABC transportation proteins such as especially ABCG2, MRP1 and ABCB1 [44–47], which help to bump the chemotherapy drugs thereby contribute to cancer survival. Interestingly, Chen Q et al. recently reported that MUC1-induced JNK1 activation could repress cell apoptosis by cisplatin in human colon cancer HCT116 cells [48]. Nath S et al. also reported that MUC1 may contribute to CSC aggressiveness through upregulating ABC transporter [49]. More Interestingly, MUC1 was reported to damage hypoxia-induced cell death by eliminating ROS accumulation and inhibiting prolyl hydrolase-3 (PHD-3) activity [50,51]. Importantly, a wave of recent research revealed that the activation of PI3K/AKT signaling and JAK/STAT signaling may be necessary for MUC1 to induce thyroid cancer cell apoptosis [52–54]. The stemness and MUC1-C expression were also demonstrated to be positive correlated to resistance to paclitaxel [55,56]. Moreover, Liu YH et al. showed that the drug resistance and sphere-forming ability were related to SOX2 and OCT4 upregulation [57]. The upregulation of MUC1 was not only involved in sphere-forming ability, self-renewal, proliferation and differentiation, but also was related to anti-apoptotic activity via promoting AKT, CXCR4 and OCT4/SOX2 expression [58,59]. Furthermore, PI3K/AKT signaling was considered to be associated with MUC1 function, and the binding of MUC1-C and PI3K could be impaired by MUC1 specific inhibitors or MUC1 siRNA [60–62]. Recently, Xu X et al. reported that MiR-551b was upregulation in Anthracycline-resistant HL-60/AR cells, and miR-551b knockdown may promote catalase activity by inhibiting MUC1 [63]. Consistently, Kato K et al. showed that AKT/c-FLIP/COX-2