

Research progress and prospect of circular RNA in multiple myeloma

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Abstract

Circular RNAs (circRNAs) are a novel type of covalently closed RNAs recently found to be involved in several physiological and pathological processes. A series of studies have proved that cyclic RNAs are related with the genesis and development of tumors, for example circ_0007841 and PVT1. Some circRNAs are strictly related to advanced clinical stage and poor prognosis, including circPTK2, circ-RNF217, circ-AFF2, circ-MYBL2, circ_0069767, circ-CDYL, circ_0000142, circRNA_101237 and exo-circMYC. In addition, circRNAs are involved in drug resistance and complications, they are circ-CCT3, Circ-007841, ciRS-7, circPVT1, circ_0001821, Exo-circ-G042080 and circCHEK1_246aa. Therefore, we propose that circRNAs can be considered as potential diagnostic and prognostic markers, which can induce chemoresistance, and might indicate novel therapeutic targets for multiple myeloma. Targeting cyclic RNA therapy will bring spring to the treatment of multiple myeloma.

Keywords: Multiple myeloma, Circular RNA, Diagnosis, Prognosis, Chemoresistance, Complication, Therapeutic target

Introduction

Multiple myeloma (MM) is a clonal plasma cell neoplasm manifested by anemia, hypercalcemia, impairment of renal function and bone destruction [1]. It is now the second most common malignancy in hematology. Over the past half century, the introduction of novel drugs (proteasome inhibitors, Immunomodulators and monoclonal antibodies) and application of hematopoietic stem cell transplantation have prolonged the survival period in most of the patients [2-5]. However, it is still incurable, and part of patients progress rapidly in a short time considering with poor prognosis at baseline. Therefore, we still need to search for new treatment option, which requires us to have a more comprehensive understanding of its pathogenesis and disease progress.

Circular RNAs (circRNAs) are a type of non-coding RNA that consists of an unspecific length of nucleotides, characterized by covalently closed-loop structures with neither 5' to 3' end nor poly-adenylated tail [6,7]. Numerous studies have shown that circRNAs play key roles in the initiation, proliferation, migration and invasion of cancers [8]. Notably, several studies have revealed that abnormal expressions of circRNAs are related to the risk or prognostic factors of the disease in hematological malignancies. However, limited evidence about the role of circRNAs in MM is available currently.

CircRNAs are Potential Diagnostic and Prognostic Biomarkers as well as Treatment Targets in Multiple Myeloma

Firstly, several experiments have explored the effects of different circRNAs on MM. For example, Wang et.al found that circ_0007841 was highly expressed in bone marrow (BM) plasma cells of MM compared with normal controls [9]. Besides, Increased PVT1 concentration which codes for both circRNAs and linear ncRNAs were also found in MM BM cells compared with normal subjects.

It's more obvious in MM patients with MYC mutations [10]. These indicate that circ_0007841 and PVT1 probably participate in the occurrence of MM.

In our previous study we screened the circRNA expression profile in MM. We found that 122 circRNAs were upregulated and 260 circRNAs were downregulated in MM compared with healthy controls by microarray. Further reverse transcription quantitative polymerase chain reaction (RT-qPCR) validation in larger sample size identified 3 circRNAs (circPTK2, circ-RNF217 and circ-AFF2) that were potential biomarkers for identifying the risk and prognosis of MM [11]. Other researchers also proved it. A study assessed circ-MYBL2 in MM patients, and it was remarkably decreased in MM bone marrow and serum compared with healthy controls. It was also proved to be strictly related to advanced clinical stage and poor prognosis. Serum levels were extremely precise in diagnosing MM [12]. Another research found that the expression of circ_0069767 in MM was significantly higher than that of the normal controls. And patients with high expression of circ_0069767 had longer PFS and OS [13]. Their other research analyzed another circRNA, circ-CDYL, which was significantly increased in MM. This provided great diagnostic and prognostic value. A functional study demonstrated that circ-CDYL prolonged the survival of MM cells and increased DNA synthesis while suppressing programmed cell death [14]. Another biomarker of MM activity and progression is circ_0000142, which is highly expressed in MM patients, and its high levels was correlated with the advanced International Staging System (ISS) and the Durie-Salmon staging system [15]. In another project, Liu et al. found that the presence of circRNA_101237 in MM cell lines and in the BM of MM patients with recurrent or refractory disease was remarkably increased, especially in patients positive for 1q21 amplification, p53 or 13q14 deletion, and t(4,14) and t(14,16). Furthermore, this circRNA was strictly correlated with the outcomes of MM subjects, as its increased expression was association with shorter OS and PFS [16].

Finally, Zhou et al. proposed that circ-ITCH expression was under-expressed in MM patients compared to healthy controls, which might serve as a potential biomarker and treatment target for MM [17]. Circ_0000190, a circRNA located in the cytoplasm, was decreased in both BM and peripheral blood of MM patients. While the target of circ_0000190, miRNA-767-5p, was increased. This suggested that circ_0000190 reduced cell survival and growth and provoked an increase in programmed cell death of MM cells [18,19].

Exosomes are small extracellular vesicles with a size between 30 and 100 nm. They can be carried on circRNAs, mRNAs, and other noncoding RNAs [20,21]. And they are transferred via endocytosis or directly union with the targeted cell membrane, thus allowing intercellular interactions between the cell and remote cells or far tissues [20-22]. An experiment reported that the levels of serum exosomal (exo) circMYC, a circRNA originated from the MYC gene, were significantly increased in MM patients compared with normal volunteers. While the level of circMYC in circulating exosomes in BTZ-resistant subjects was higher than that in non-resistant subjects. Moreover, the amount of exo-circMYC was associated with the Durie-Salmon and the ISS stage, and with deletion 17p, and t(4;14). Statistical analysis demonstrated that a high exo-circMYC concentration was an independent predictor of poor outcomes in MM subjects, with higher rates of relapse, higher percentages of mortality, and reduced PFS compared to patients with low exo-circMYC expression [23].

CircRNAs were Proved to be Related with Drug Resistance and MM Complications

In their study, Liu et al. evaluated the possible effect of circular RNA chaperonin which enclosed TCP1 subunit 3 (circ-CCT3) in BTZ resistance. The silencing of circ-CCT3 enhanced the sensitivity of cells to BTZ [24]. Besides, in another research, circ-007841 was also reported to enhance bortezomib and doxorubicin resistance in MM cells [25,26]. Moreover, a report described genome expression configurations of circRNAs in IMiD-sensitive and IMiD-resistant MM cells. The authors found that genome circRNA expression revealed IMiD sensitivity and that ciRS-7 was significantly decreased circRNA in patients with acquired resistance [27]. Finally, steroids are a cornerstone of MM therapy. Wan et al. demonstrated that circPVT1 was increased in glucocorticoid-resistant cells, while its reduction increased sensitivity to glucocorticoid administration [28].

Researchers also found that some circular RNAs play a role in MM complications. A clinical program in MM subjects also assessed the expression of circ_0001821 in the BM and MM cell lines. Results showed that its concentrations were increased compared with healthy controls, and its levels were correlated with bone disease, hemoglobin, and Beta-2-microglobulin [29]. Zhang et al. evaluated the relationship between serum exo-circRNAs and MM-related peripheral neuropathy (PN). They found that 265 increased circRNAs and 787 regulated circRNAs were at least a two-fold alteration in their expression in MM subjects compared with normal controls. Bioinformatics examination suggested that increased circRNAs possibly accelerated MM related PN. Furthermore, analysis revealed that chr2:2744228-2,744,407+ might provoke MM-derived PN. All this suggest that exo-circRNA might represent a possible new therapeutic target for MM-related PN [30]. Another complex exo-circ-G042080 was tested highly expressed in the blood of MM patients and its expression was positively associated with MM-correlated myocardial damage. It might represent a novel diagnostic biomarker of MM-related heart damage and a possible therapeutic target [31]. Gu et al. revealed the result in their research that MM cells could secrete circCHEK1_246aa in the BM niche to increase the invasive potential of MM cells and promote osteoclast differentiation [32]. In a word, circular RNAs widely participated in every stage of MM.

Prospect

Through the above studies, we can see that cyclic RNA plays a certain role in the occurrence, development, complications, and drug-resistance of multiple myeloma. Therefore, we should perform more research to clarify their roles, so as to provide more ideas for the diagnosis, staging, prognosis, and treatment of multiple myeloma.

At present, the diagnostic criteria for multiple myeloma is very clear. However, we usually need to do many tests and examination items to finally diagnose the disease. It takes a lot of time and money. If we can identify the changes of specific cyclic RNA in multiple myeloma in the future, it may simplify and shorten the diagnostic process. In addition, by analyzing the cyclic RNA spectrum of patients, we can more accurately evaluate the stage and prognosis. This helps us to develop individualized treatment plans for patients to achieve precision medical treatment.

As to the treatment of multiple myeloma, we have mentioned that the disease is still incurable. And with the increased usage of

chemotherapy treatments, the incidence of drug resistance gradually rose, and the PFS gradually shortened. The patient progressed to be a recurrent refractory stage of multiple myeloma finally. Although autologous stem cell transplantation or allogeneic transplantation may prolong the PFS and OS of patients to some extent, while most patients eventually will relapse or even die. If our future research on cyclic RNA is deep and precise enough to indicate a targeted cyclic RNA therapy, we may achieve a complete cure of the disease. At least it can overcome drug resistance or provide new treatment options for multiple myeloma.

As mentioned above, cyclic RNA also plays a certain role in the occurrence and development of MM complications, so targeted cyclic RNA therapy may prevent the clinical progress of the disease. Since cyclic RNA is widely involved in the life activities of tissues and cells, we boldly guess that in the future, targeted cyclic RNA therapy may reverse the occurrence and development of diseases from the base.

In conclusion, cyclic RNA is involved in the occurrence, development, disease stage, prognosis, complications, and treatment sensitivity of multiple myeloma. Therefore, we predict that targeted cyclic RNA therapy can change the above process and will finally cure the disease. We hope to identify a promising targeted cyclic RNA therapy in the near future.

Abbreviation

circRNA: Circular RNA; MM: Multiple Myeloma; BM: Bone Marrow; exo: exosomal; PN: Peripheral Neuropathy.

Funding

None.

Conflict of Interest

None.

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