Proceedings of Anticancer Research, 2023, Volume 7, Issue 1
http://ojs.bbwpublisher.com/index.php/PAR
ISSN Online: 2208-3553
ISSN Print: 2208-3545

Advances in Biomarkers for Multiple Myeloma

Chao Yang, Ji Qi*, Tianhong Jia, Jingping Ran, Wenxuan Cui

Laboratory Department, Affiliated Hospital of Hebei University, Baoding 071000, Hebei Province, China

Corresponding author: Ji Qi, amanghappiness@163.com

Abstract: Multiple myeloma (MM) is the second most common malignancy in hematology. MM is characterized by the malignant proliferation of plasma cells in the bone marrow, accompanied by the secretion of monoclonal immunoglobulin, mainly occurring in the elderly. The clinical manifestations of MM include renal dysfunction, bone destruction, infection, anemia, hemorrhage, hypercalcemia, and hyperviscosity syndrome. The recent discovery of biomarkers related to the diagnosis or prognosis of MM provides an important basis for the diagnosis and treatment of MM. This paper reviews the research progress of biomarkers expressed in tissues and peripheral blood at home and abroad.

Keywords: Multiple myeloma; Markers; miRNA

Online publication: January 12, 2023

1. Introduction

Multiple myeloma (MM) is a plasma cell malignancy, accounting for about 10% of all hematological malignancies, with a higher incidence in male than in female [1], and mainly occurring in the elderly population. It poses serious threats to the health of the population. However, the cause of MM remains unknown.

MM is characterized by the accumulation of malignant plasma cells in bone marrow and the production of high levels of immunoglobulin (Ig). MM can be divided into IgG, IgA, IgM, IgD, IgE, light chain, non-secretory, double, or polyclonal according to the type of M protein produced and its detection in blood and urine. The most common types are IgG kappa and IgA kappa [2]. Some of the common clinical manifestations of MM include increased blood calcium (C), kidney damage (R), anemia (A), bone damage (B), and other CRAB symptoms. The presence of these symptoms signifies an active or symptomatic myeloma (AMM). The onset of MM can be divided into three stages, with a slow progress from monoclonal gammopathy of undetermined significance (MGUS) to smoldering multiple myeloma (SMM), and then to AMM. In China, there are 27,800 newly diagnosed MM patients every year. MGUS and SMM progress toward AMM at a rate of 1% and 2% per year, respectively [3]. Although there are many traditional biomarkers used in the experimental diagnosis of MM, their sensitivity and specificity are low. Hence, it has always been a challenge to make an early diagnosis and carry out early intervention for MM. The survival and prognosis of MM are still not ideal although its treatment methods are constantly being innovated. With the development of research, there are new biomarkers that have shown potential in predicting the disease progression of early MM, which is beneficial for its early diagnosis and subsequent targeted therapy. In this paper, we review several potential biomarkers related to the early experimental diagnosis of MM that have been discovered in recent years to provide a theoretical basis for improving the clinical diagnosis rate of MM.

2. Biomarkers expressed in serum

2.1. Circulatory tumor cells (CTCs)

Circulatory tumor cells (CTCs) are tumor cells that shed from the primary tumor or metastasis and subsequently enter the circulation [4]. CTCs are present in every stage of MM. CTC load can be used to evaluate the efficacy of treatment and the prognosis of patients. It has been shown that patients with high CTC load after treatment tend to have poorer prognosis [5]. Studies have shown good consistency between CTCs in MM and tumor cells at the primary site; hence, the number and genetic characteristics of CTCs can be used as stratified indicators of MM risk, and the characteristics of primary tumor cells can be reflected by studying CTCs when evaluating the efficacy and biological characteristics of tumor cells during treatment [4].

2.2. Circulating tumor deoxyribonucleic acid (ctDNA)

ctDNA is a characteristic tumor biomarker. It is a DNA fragment from the tumor genome that carries certain characteristics (including mutation, deletion, insertion, rearrangement, abnormal copy number, methylation, *etc*.) in the circulatory system and is mainly derived from necrotic or apoptotic tumor cells, circulating tumor cells, and exosomes secreted by tumor cells [6]. Due to the high degree of consistency between certain corresponding tumor tissues and plasma samples, especially in metastatic breast cancer, colorectal cancer, and non-small cell lung cancer, ctDNA can be used for noninvasive gene mutation analysis.

2.3. Micro-ribonucleic acid (miRNA)

2.3.1. Micro-ribonucleic acid (miRNA)

miRNA is a short (about 22 nucleotides long) non-coding RNA fragment with the ability to regulate gene expression at the post-transcriptional level [7]. It is involved in the occurrence and development of tumors. Abnormal expression of miRNA has been observed in various conditions, including hematologic malignancies. Common changes in gene expression have been observed in tumor cells' miRNA, which may be caused by deletion, translocation, or amplification. These mechanisms lead to changes in target gene expression. Depending on the genes they affect, miRNAs can act as carcinogenic or tumor suppressor genes. Therefore, miRNAs can be used as promising biomarkers for cancer detection and prognosis [8]. The most well-recognized miRNAs are *miR-15a* and *miR-16*. They are located at chromosome *13q14* and have similar sequences. They perform tumor suppressive functions and are involved in the regulation of cell proliferation, differentiation, and apoptosis. The decreased expression of *miR-15a* and *miR-16* in MM promotes proliferation by increasing the expression of calcineurin binding protein 1 (CABIN1) [9].

The results of a study showed that *miR-15a-5p*, which belongs to cluster *15a/16* located on chromosome *13q14*, is upregulated in MM. Three miRNAs *miR-134-5p*, *miR-107*, and *miR15a-5p* have also been found to be upregulated in MM and MGUS. These three miRNAs may be used as potential diagnostic markers. Combining *miR-107* and *miR-15a-5p* with hemoglobin can help distinguish MM from MUGS, thereby enabling early treatment and thus improving prognosis [10]. The role of miRNA as a biomarker for detecting the transition from asymptomatic to symptomatic MM is critical in clinical settings. However, the current available data are still too tentative to be statistically significant. Hence, this should be the focus of follow-up research.

2.3.2. Exosomal micro-ribonucleic acid

Currently, bone marrow biopsy and tissue biopsy are the main diagnostic methods for MM in clinical settings. However, these procedures may cause pain to patients. Since miRNAs can be stably contained in exosomes, their composition is less complex than that of serum, and samples can be obtained in a non-invasive way, serum exosomal miRNAs can be used as an ideal, non-invasive, and reliable tumor marker

[11]. Studies have shown that serum exosomes contain high abundance of specific miRNAs with good stability and have the potential to be used as new non-invasive molecular markers for disease diagnosis and prognosis [12]. Exosomes are vesicles that oscillate between 50 nm and 100 nm in size and can be released by various cells. They contribute to the pathogenesis and progression of MM. Exosomes contain proteins, cytokines, lipids, microRNAs, long non-coding RNAs, and circRNAs that regulate interactions between MM plasma cells. Through exosomes, mesenchymal stem cells confer chemotherapy resistance to MM cells, while myeloma cells promote angiogenesis, influence immune responses, and cause bone damage. They can affect the prognosis of MM patients [13]. A growing body of evidence has shown that exosomes, isolated from the peripheral blood of patients with MM, may be used as biomarkers to predict the progression of MM. In a study by Zhang *et al*. [14], an overlap of 10 miRNAs with the greatest variation was observed. The upregulation of *miR-513a-5p, miR-20b-3p*, and *let-7d-3p* and the downregulation of *miR-16-5p, miR-15a-5p, miR-20a-5p, miR-17-5p, miR-125b-5p, miR-19a-3p*, and *miR-21-5p* were involved in bortezomib resistance in MM patients. These 10 miRNAs are considered to be a potential predictive group for drug resistance in MM patients. Such predictive panels are important for selecting the most appropriate treatment for patients. Therefore, more extensive and in-depth studies are needed to prove the use of exosomal miRNAs as novel markers in the diagnosis, survival, and prognosis assessment of MM patients.

2.4. Multicolor flow cytometry (MFC) immunophenotype

The Chinese Guidelines for Diagnosis and Treatment of Multiple Myeloma (revised in 2020) have recommended the use of antibodies labeled with more than four colors when MFC is performed for MM examination; the antibodies should include CD38, CD138, CD56, CD19, CD45, CD20, kappa light chain, and lambda light chain. Conditions can be added to other antibodies, such as CD27, CD28, CD81, CD117, CD200, *etc*.

2.4.1. CD38

CD38 is a type II transmembrane glycoprotein consisting of a 45kD single chain with three distinct domains, namely intracellular (20 amino acids), transmembrane (23 amino acids), and extracellular (257 amino acids) structures. It is expressed in early differentiated CD34+ stem cells and mature immune cells, including T cells, B cells, granulocytes, and natural killer (NK) cells, but not in quiescent immune cells. However, the expression of CD38 is not limited to immune cells (including mature cells and precursor cells); instead, it is also expressed in solid tissues, such as brain, eye, prostate, intestine, pancreas, muscle, bone, and kidney [15]. CD38 is a transmembrane glycoprotein that mainly plays the role of cell membrane receptor and extracellular enzyme in the human body. It is highly expressed on the surface of myeloma cells but continuously expressed on the surface of lymphocytes, myeloid cells, red blood cells, and other cells at low levels [16]. CD38 is highly specific and highly expressed in plasma cells of patients with MM compared to normal lymphocytes and bone marrow cells [17]. Based on this characteristic, CD38 is considered to be a promising target in the treatment of MM.

2.4.2. CD56

CD56 is a nerve cell adhesion molecule that can mediate mutual adhesion between myeloma cells and stroma. The expression of CD56 molecule can be detected in most myeloma cells of MM patients. The immunophenotype CD56 is a cell adhesion molecule involved in the homing of MM cells. MM cells with low CD56 expression have a higher capacity for proliferation and metastasis [18]. Therefore, low CD56 expression may be involved in the extramedullary lesions and extramedullary recurrence of MM patients. Patients with MM have a high incidence of extramedullary lesions, some of which are occult and

underestimated due to the limitation of examination. However, there is a lack of effective detection indices for extramedullary lesions in clinical work. A negative expression of immunophenotype CD56 has been found to be associated with the occurrence of extramedullary lesions and extramedullary recurrence. Therefore, CD56 may be a potential index that can predict the occurrence of extramedullary lesions and the extramedullary recurrence of MM. The detection of the expression of immunophenotype CD56 may aid early clinical detection of extramedullary lesions or the identification of patients who may suffer from extramedullary lesions [19].

2.4.3. CD45

CD45 is a single chain transmembrane glycoprotein, a common expression antigen of human leukocytes, and a receptor tyrosine protein phosphatase, which is expressed on the surface of various hematopoietic cells. CD45 is a prerequisite for B cell activation and a key molecule in cell membrane signal transduction. CD45 is widely found on the surface of leukocytes. In normal hematopoietic cells, only red blood cells and platelets do not express CD45. In B-cell acute lymphoblastic leukemia and acute megakaryoblastic leukemia, abnormal naive cells may or may not express CD45 on the surface. A study has found a correlation between the expression of CD45 in tumor plasma cells of patients with extramedullary recurrence of MM and the prognosis of these patients, irrespective of other prognostic factors. Therapeutic strategies need to be established for patients with extramedullary recurrence and CD45-MM cells to ameliorate adverse outcomes [20].

3. Biomarkers expressed in tissues

3.1. Programmed death factor 1 (PD-1)

As a negative costimulatory molecule, PD-1 is mainly expressed in activated and/or depleted T cells, B cells, NK cells, and antigen-presenting cells. Programmed death-ligand 1 (PD-L1) is expressed in various solid tumors and immune cell subsets [21], while PD-L2 is mainly expressed in activated dendritic cells, macrophages, and mast cells [22]. The binding of PD-1 to PD-L1/2 in MM bone marrow microenvironment can lead to immune escape, migration, and proliferation of tumor cells. MM patients often have immune dysfunction, which may be related to the interaction between T lymphocytes expressing PD-1 and PD-L1/2 and the tumor cells. Blocking this pathway may counteract the proliferation potential and drug resistance of myeloma cells [23].

3.2. Adiponectin (APN)

APN is a cytokine that is mainly secreted by adipocytes. After binding to its receptor, it regulates cell survival, apoptosis, and metastasis through a series of signaling pathways. It plays an antitumor role in a variety of tumors [24]. There is an increasing number of evidence supporting the role of obesity in MM etiology, which may be related to decreased serum adiponectin levels in obesity. Studies have confirmed that MM patients have significantly lower serum adiponectin levels compared with normal controls. The decrease in adiponectin levels may be related to the progression of MGUS to MM [25].

4. Discussion

The pathological process of MM is complex, and it remains a challenge to diagnose MM in the early stage. A comprehensive study of the dynamic changes in gene and protein expressions in the bone marrow microenvironment; CTCs, miRNAs, MFC immunophenotypes, and ctDNAs in peripheral blood; and other potential biomarkers is of great significance to the early detection and treatment of patients with MM. In addition, the detection of miRNAs in peripheral blood and CTCs, MFC immunophenotypes, and ctDNAs in blood biopsies can help clinicians assess the disease status and diagnose MM early without invasive bone

marrow tests. These emerging biomarkers have shown potential in the diagnosis and prognosis of MM. However, the standardization of these biomarkers still requires continuous testing and validation before they can be applied in clinical trials of MM in the future.

Disclosure statement

The authors declare no conflict of interest.

References

[1] Jurczyszyn A, Waszczuk-Gajda A, Castillo JJ, et al., 2020, Primary Refractory Multiple Myeloma: A Real-World Experience with 85 Cases. Leuk Lymphoma, 61(12): 2868–2875.

[2] Sheinkh SP, Irfan SM, Sheikh SS, 2020, Types of Paraproteinemia in Patients with Multiple Myeloma: A Cross-Sectional Study. J PAK Med Assoc, 70(2): 264–267.

[3] Wei Y, Huang Z, 2020, Advances in the Evolution and Early Diagnosis of Multiple Myeloma. J Oncology, 26(2): 81–85.

[4] Miao J, Huang C, Liu Y, et al., 2021, Research Progress of Circulating Tumor Cells in Primary Bone Tumors. Oncology Research and Clinical, 33(10): 789–793.

[5] Foulk B, Schaffer M, Gross S, et al., 2018, Enumeration and Characterization of Circulating Multiple Myeloma Cells in Patients with Plasma Cell Disorders. Br J Haematol, 180(1): 71–81.

[6] Xin C, Wu H, Liu C, et al., 2018, Application and Research Progress of Liquid Biopsy in Multiple Myeloma. International Journal of Laboratory Medicine, 39(10): 1168–1172.

[7] Saudy-Szczyrek A, Mlak R, Mielnik M, et al., 2022, Circulating Serum miRNA-8074 as a Novel Prognostic Biomarker for Multiple Myeloma. Cell, 11(4): 752–792.

[8] Croce CM, 2009, Causes and Consequences of microRNA Dysregulation in Cancer. Nat Rev Genet, 10: 704–714.

[9] Zhang L, Zhou L, Shi M, et al., 2018, Downregulation of miRNA-15a and miRNA-16 Promote Tumor Proliferation in Multiple Myeloma by Increasing CABIN1 Expression. Oncol Lett, 15: 1287–1296.

[10] Li J, Zhang M, Wang C, 2020, Circulating miRNAs as Diagnostic Biomarkers for Multiple Myeloma and Monoclonal Gammopathy of Undetermined Significance. J Clin Lab Anal, 34(6): e23233.

[11] Zhang Y, Chen H, Lu X, et al., 2020, Expression and Clinical Significance of Serum Exosome miR-223-3p in Patients with Multiple Myeloma. Chinese Journal of Laboratory Medicine, 2020(12): 446–451.

[12] Li J, Gu Y, Liu Z, 2019, The Utility of Serum Exosomal microRNAs in Hepatocellular Carcinoma. Biomed Pharmacother, 111: 1221–1227.

[13] Allegra A, Di Gioacchino M, Tonacci A, et al., 2021, Multiple Myeloma Cell-Derived Exosomes: Implications on Tumorigenesis, Diagnosis, Prognosis and Therapeutic Strategies. Cells, 10(11): 2865.

[14] Zhang L, Pan L, Xiang B, et al., 2016, Potential Role of Exosome-Associated microRNA Panels and In Vivo Environment to Predict Drug Resistance for Patients with Multiple Myeloma. Oncotarget, 7: 30876–30891.

[15] Malavasi F, Deaglio S, Funaro A, et al., 2008, Evolution and Function of the ADP Ribosyl Cyclase/CD38 Gene Family in Physiology and Pathology. Physiol Rev, 88(3): 841–886.

[16] Li K, Guan X, 2002, Effect Analysis of Three Detection Methods for CD38 Monoclonal Antibody in the Treatment of Multiple Myeloma Before Blood Transfusion Compatibility Detection. Chinese

Journal of Health Inspection, 32(11): 1366–1369.

[17] Fichs KA, Nagy NA, Lindenbergh PL, et al., 2018, CD38-Targeting Antibodies in Multiple Myeloma: Mechanisms of Action and Clinical Experience. Expert Rev Clin Immunol, 14(3): 197.

[18] Geng C, Yang G, Wang H, et al., 2015, Analysis of the Relationship Between CD56 and Newly Diagnosed Multiple Myeloma. Chin J Internal Medicine, 54(12): 1066–1070.

[19] Huang X, Niu T, Wei C, et al., Multiple Myeloma Tumor Cell CD56 Table the Relationship Between Medullary Disease and Extramedullary Recurrence. Chinese Journal of Experimental Hematology, 201, 29(2): 553–556.

[20] Oka S, Ono K, Nohgawa M, 2020, Clinical Effects of CD45 on the Prognosis of Extramedullary Myeloma Relapse. J Clin Pharm Ther, 45(1): 144–151.

[21] Costa F, Marchica V, Storti P, et al., 2021, PD-L1/PD-1 Axis in Multiple Myeloma Microenvironment and a Possible Link with CD38-Mediated Immune-Suppression. Cancers (Basel), 13(2): 164.

[22] Korkmaz S, Erdem S, Akay E, et al., 2019, Do PD-1 and PD-L2 Expressions Have Prognostic Impact in Hematologic Malignancies?. Turk J Med Sci, 49(1): 265–271.

[23] Ma Y, Yang K, Yang X, et al., 2021, T-Cell Subsets and Myeloma Cells in Newly Diagnosed Multiple Myeloma Patients Expression and Significance of PD-1, PD-L1 and PD-L2. Cancer Prevention Research, 49(1): 40–45.

[24] Wang S, Wang C, Wang W, et al., 2020, Adiponectin Receptor Agonist AdipoRon Inhibits the Proliferation of Myeloma Cells via the AMPK/Autophagy Pathway. Chinese Journal of Experimental Hematology, 28(1): 171–176.

[25] Hofmann JN, Mailankody S, Korde N, et al., 2017, Circulating Adiponectin Levels Differ Between Patients with Multiple Myeloma and Its Precursor Disease. Obesity (Silver Spring), 25(8): 1317–1320.