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LITERATURE REVIEW. MODERN CONCEPTS OF THE DEVELOPMENT OF MULTIPLE MYELOMA

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Abstract
Multiple myeloma is - an incurable disease, characterized by significant morbidity and mortality [5, 8, 20]. Among the risk factors for the development of multiple myeloma, as well as other oncohematological diseases, hereditary predisposition, genetic factors, immune system status, as well as exposure to ionizing radiation, toxic substances, unfavorable environmental factors, and prolonged exposure to psycho-emotional stress are of particular importance. [1, 2, 6,9]. Currently, there is no convincing evidence that any of the listed factors play a decisive role in the development of multiple myeloma (MM) [5, 8, 20]. Experimental studies show that the influence of one factor is insufficient for tumor progression. To manifest an oncological phenotype, the simultaneous influence of several factors is required. Modern scientific publications attest to the heterogeneous nature of MM and emphasize the importance of genetic factors in its etiology. [1, 3, 7, 10]. Polymorphisms of the genes of inflammatory factors may be involved in the progression of MM due to the imbalance of pro-and anti-inflammatory cytokines profile. [9, 10, 24, 30]. The family of interleukins (IL), which participate in the immune response and inflammatory processes of MM, consists of a group of lymphatic factors with many biological activities.

Introduction

This point of view confirms that the interleukin family polymorphism is found in patients with MM and is associated with a statistically high risk of MM [20,22,60,61].

To date, it is known that the study of the mechanisms of MM formation has led to the development of a number of theories about the acquisition of malignancy by normal plasma cells [4, 26,32,41,42].

Some researchers believe that the complex mechanisms of multiple myeloma development are due to chromosomal abnormalities and various genome disorders, which lead to genetic instability in the loss of one of the alleles, followed by the loss of heterozygosity [4, 33, 56]. Firsova M.V. (2022) et al. Mamayev E.A. (2018, 2023) presented data indicating that the presence of chromosomal abnormalities such as 17p deletion, t (4;14), t (14;16), trisomy of the 13th chromosome, hyperdiploidy, t (11;14) and t (6;14), classifies them as a high-risk group [33,41,43,55].

Russian scientists (2014) emphasize the important role of tumor cell interaction with the stromal microenvironment in the bone marrow. This interaction is one of the key factors in tumor adhesion and angiogenesis processes, leading to disruption of the balance between osteoblasts and osteoclasts, as well as stimulating tumor growth through the synthesis and exposure of various cytokines (IL-6) [1, 5, 49].

Increasingly, in the diagnosis of modern oncohematology, among the interleukins of the IL-6 family with its IL-6R receptor, it is the main interleukin for T-helper (Th) mediated inflammation, and it is important for maintaining the Th1 / Th2 balance in the inflammatory phase of MM [13,17,19]. These observations indicate that human IL-6 and IL-10 polymorphisms can act as biomarkers for monitoring

the clinical course of MM. [10]. Therefore, the prognostic value of genetic factors is potentially limited by the interleukin genotype, specific interleukin loci, and individual phenotype [14]. Therefore, modern diagnosis of multiple myeloma should include the indication of cytogenetic abnormalities and an international prognostic index, which meets existing classifications and current requirements. [48, 59].
According to the research of K.D. Sharer et al. (2018). Compared to the control cultures, B-cells cultured in the presence of GSK343 showed a 2.5-fold increase in CD138+ plasma cells. The increase was not specific to stimulating LPS, as CD40L, IL4, and IL5 cells also showed a similar increase in the number of CD138+ cells. These results are consistent with an increase in the number of CD138+ plasma cells from Ezh2−/− cells after ex vivo stimulation of CD40L, IL4 and BAFF [12, 25].
According to M.N. Shahzad et al. (2020) IL-6 and IL-1 GG genotypes increased MM risk by approximately 40.8 and 80.2% compared to AA and CC genotypes, and also revealed a significant association between T:C IL-6 and IL-10 polymorphism and MM risk. However, no significant association was found between the C:A polymorphism of IL-6 and IL-10 receptors and the overall risk of developing MM. G:C polymorphisms of IL-1β and IL-6 significantly increased the risk of MM. However, a significant correlation was found between the C:T polymorphism of IL-1α-889 C>T and IL-1β-3737 C>T and the risk of MM [19, 29, 60]. In addition, there are studies by American, French, and Spanish scientists who have noted the biological properties of IL-10, which contribute both to PC proliferation and angiogenesis, but also that they are related to the PD-L1 / PD1 axis, which undoubtedly implies a significant role in the pathogenesis and development of MM [15, 22, 36].
According to Serin Yasemin et al. (2022) the modern understanding of the pathogenic role of lL-10 in MM is underestimated. The ability of IL-10 to induce chemoresistance in cancer is likely related to its immunosuppressive function [50]. These IL-10 blocking methods are primarily based on the developed antagonist targeting IL-10, IL-10 receptors, and pathway factors such as JAK and STAT3. It is assumed that the role of IL-10 may be particularly important in myeloma cells, which exhibit IL-6-independent proliferation loop [51, 55].
Russian scientists (2014) note that the detection of G:A polymorphisms in the IL-6 promoter is more accurate in samples of the Asian MM population. Furthermore, no significant correlation was found between the IL gene polymorphism in the MM samples, classified by ethnicity, and the type of the IL family. These loci of mononucleotide polymorphism can be suitable genetic markers for genetic screening and a promising therapeutic strategy in predicting MM patients.
According to Kozich J.M. et al. (2023), the absence of risk factors at the time of diagnosis does not always determine the favorable course of the disease. Therefore, finding additional prognostic factors is relevant. It was established that a significant increase in IL2, IL6, TNF levels and the number of CD138+ clones (>20%) at the time of diagnosis was associated with an increase in the frequency of disease progression during the study period. A correlation has been confirmed between kidney damage, anemia, elevated CRP levels, multiple skeletal bone injuries, and the presence of genetic changes at the time of diagnosis with a decrease in the progressive survival rate of patients with MM [1, 23, 26].
Thus, the range of factors that contribute to the development of multiple myeloma is quite wide. The mechanisms of its development are characterized by high complexity and remain insufficiently studied to this day [37, 50].
Despite this, it can be assumed that combined exposure to external factors (carcinogens, pesticides, radiation, chemical compounds, infections, viruses, stressful situations, etc.) can lead to irreversible

genetic disorders affecting cell growth regulation. As a result of such disorders, excessive production of cytokines and stimulation of osteoclast activity can occur, which in turn promotes the development of multiple myeloma. Identification of single nucleotide variants in the regulatory regions of cytokine genes may influence the development of the disease.

In recent years, data has been accumulating, and the results show that cytokine signatures can potentially influence the outcome of patients with MM receiving borthesomy. However, the clinical and biological significance of these results requires further study. It was found that only IL-13 levels in serum before treatment significantly affect PFS in patients with MM who received treatment regimens based on borthesomybas. In addition, the serum levels of five cytokines - IL-1Ra, IL-4, IL-7, IL-13, and PDGF-BB - influenced OV in single-factorial analyses. However, multifactorial analysis revealed that only IL-1Ra and IL-4 have independent prognostic value. [167, pp. 1127-1734; 168, p. 112;].

The results of other multicenter studies focused on the cytokine networks that control the growth, progression, and spread of the disease. The complexity of cytokines in the development of MM remains to be studied in detail. In addition to the knowledge that interleukin (IL) -6 is important in the pathogenesis of MM, it was shown that IL-6 is a parakrine factor supplied by the microenvironment consisting of these cells from the myeloid compartment. Since IL-10 was considered an immunosuppressive cytokine that promotes cancer out of immune control, the role of IL-10 in this regard was not fully appreciated, although recent achievements have shown that IL-10 induces both PC proliferation and angiogenesis in MM. Furthermore, combined studies have shown that IL-10 plays a significant role in inducing chemoresistance in many types of cancer; this is due to the actual need for autocrine IL-10 to release MM cells from the IL-6-dependent proliferation loop. MM cells exhibited pronounced chemoattractive activity with elevated levels of CXCL12, CCL5, MIP-1b, and CXCL10, while their association with the expression of immunoregulatory interleukins (ILS), such as IL-4 and IL-10, was also documented.

Currently, there are conflicting results and opinions on cross-interference between IL-10 and PD1/PD-L1, which may be key to the development of targeted intervention therapy, which can be more effective in the treatment of cancer in patients with MM [51, pp. 1449-1455].

According to Turkish researchers, the precise role of IL-10 in the development of cancer has yet to be comprehensively studied, and the promising potential of choosing IL-10 targeting methods in combination with immunotherapy in the treatment paradigm of MM cannot be denied [126].

Therefore, it can be concluded that there is currently no single scheme for diagnosing and predicting the complicated course of MM. As the molecular properties of plasma cells remain unknown, further research is needed to study the genetic abnormalities and mechanisms underlying the pathogenesis of plasma cells, as well as to study new therapeutic strategies to improve the condition of patients with plasma cells, especially those belonging to the high-risk group.

Therefore, MM is a complex, poorly studied disease, manifested by various complications and laboratory signs, which largely determine its course and prognosis. Achievements and the introduction of new technologies in the field of diagnostics (determination of prognostic factors) and treatment of MM contribute to the timely diagnosis of the disease, the appointment of targeted therapy aimed at determining its prognosis and improving the quality of life. Gematological malignant neoplasms and cytokine gene polymorphisms have not been sufficiently studied in the literature. In this regard, research in this area is very relevant and in demand.

Conclusion:

1. literature analysis indicates the presence of a large number of studies on the course of resistance and complicated variants of MM.
2. Identifying genetic disorders plays an important role in predicting the complicated course of MM, but such studies are under active discussion.

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