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Role of the bone marrow microenvironment in tumor transformation of plasma cell dyscrasias

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ABSTRACT
Despite significant progress in the understanding of the pathogenesis of paraproteinemic hemoblastoses, these diseases remain incurable. In their development, they go through the stage of paraproteinemias, benign diseases, characterized by the detection of monoclonal paraprotein in the blood serum and / or urine, presence of clonal plasma cells in the bone marrow or in extramedullary tissues. It remains unclear why some paraproteinemias progress to multiple myeloma or other lymphoid tumors and how malignant progression occurs. An important role in the progression is played by molecular and genetic mechanisms, cytokines. Nevertheless, little is known about how the bone marrow microenvironment influences disease progression. In this review, we made an attempt to summarize the most significant biological, clinical characteristics on the course of paraproteinemias and the role of changes in the bone marrow microenvironment that contribute to malignant transformation.

Key words: *multiple myeloma, monoclonal gammopathy of undetermined significance, bone marrow microenvironment, malignant transformation.*
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Роль микроокружения костного мозга в опухолевой трансформации плазмоклеточных пролиферации

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РЕЗЮМЕ
Несмотря на значительные успехи в понимании патогенеза парапротеинемических гемобластозов, эти заболевания остаются неизлечимыми. В своем развитии они проходят стадию парапротеинемий — доброкачественных заболеваний, характеризующихся появлением моноклонального парапротеина в сыворотке крови и/или моче, наличием клональных плазматических клеток в костном мозге или расположенных экстрамедуллярно. Почему некоторые из парапротеинемий прогрессируют до множественной миеломы или других опухолей лимфоидной природы и как происходит злокачественное прогрессирование, все еще во многом неизвестно. Тем не менее установлена важная роль цитокинов и микроокружения костного мозга при прогрессии заболевания. В этом обзоре мы обобщили наиболее актуальные сведения о роли изменений в микроокружении костного мозга, способствующих злокачественной трансформации.

Ключевые слова: *парапротеинемии, множественная миелома, моноклональная гаммапатия неуточненного значения, микроокружение опухоли, злокачественная трансформация.*
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Источники финансирования: исследование проведено без спонсорской поддержки.

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Plasma cell dyscrasias are a heterogeneous group of diseases that includes monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma (MM), plasma cell leukemia (PL), lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia (WM), amyloidosis and POEMS syndrome (polyneuropathy, organomegaly, presence of monoclonal protein, cutaneous manifestation syndrome). The clinical characteristics of plasma cell dyscrasias are given in Table 1 [1].

Table 1. Clinical characteristics of plasma cell dyscrasias

Plasma cell dyscrasias	Bone marrow: plasma cells or lymphocytes	M-gradient serum / free light chains in 24-h urine	CRAB criteria (yes/no)*
Symptomatic multiple myeloma	> 10 % plasma cells	> 30 g/L / 500 mg	yes
Smoldering myeloma	> 10 % < 60 % plasma cells	> or < 30 g/L / 500 mg	no
Plasma cell leukemia	> 20 % circulation of plasma cells in peripheral blood	> or < 30 g/L / 500 mg	yes
Monoclonal gammopathy of undetermined significance	< 10 % plasma cells	< 30 g/L / 500 mg	no
Primary amyloidosis	< 10 % plasma cells	< 30 g/L / 500 mg	no
Solitary plasmacytoma	< 10 % plasma cells	< 30 g/L / 500 mg	yes
Smoldering Waldenstrom macroglobulinemia	Usually < 30 % lymphoplasmacytic cells	<30 g/L	no
Waldenstrom macroglobulinemia	Usually > 30 % lymphoplasmacytic cells	>30 g/L	no
POEMS syndrome	> 10 % (in cases underlying MM)	>30 g/L (in cases underlying MM)	yes (in cases underlying MM)

Примечание: * only osteolytic bone lesion is taken into account.

Multiple myeloma

Multiple myeloma is a neoplastic disease of the hematopoietic system characterized by clonal plasma cell dyscrasia within the bone marrow, secretion of monoclonal immunoglobulin in the blood serum and / or urine, presence of the foci of lysis, kidney damage, immunodeficiency, and accounts for 10 % of all malignant hemoblastoses [2]. The CRAB criteria are integral to symptomatic myeloma: high calcium levels, kidney failure, anemia, and bone lesion. These changes occur in more than 70 % of newly diagnosed cases and remain the pivotal reason for low indices of patient work capacity [2].

The growth and distribution of tumor plasma cells in the bone marrow, as well as in the case of other cancer types, depend on their dynamic interaction with the microenvironment [2]. The bone marrow microenvironment in multiple myeloma consists of hematopoietic and non-hematopoietic cells (stem cells of the bone mesenchyme, vascular endothelial cells and nerve fibers), as well as soluble components, including cytokines, growth factors,

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and adhesion molecules [3]. Mutated plasma cells disrupt the imbalance in a normal bone marrow niche and interfere with the complex interaction between myelopoietic and lymphopoietic cells with immunocompetent cells, as well as matrix cells and their by-products. Consequently, the resulting tumor environment of the bone marrow mutually increases the dyscrasia of malignant plasma cells [3]. When a tumor clone appears in the bone marrow, clonal plasma cells in the microenvironment begin to behave like a solid tumor, in which all factors, including immunological, hormonal, humoral factors, as well as megakaryocytes interact with each other contributing to the maintenance of tumor growth and its spread [4].

The anemic syndrome is a constituent part of symptomatic myeloma. Its development is based on complex mechanisms that support each other. The anemic syndrome in MM appears as a result of the replacement of the normal cellular structure of the bone marrow with atypical plasma cells [5], which leads to ineffective erythropoiesis. In turn, kidney damage contributes to decreased erythropoietin production, resulting in aggravation of the anemic syndrome. Immunodeficiency states which occur during the progression of the disease contribute to the development of a chronic inflammatory process, which also leads to iron metabolism disorders, thereby maintaining the anemic syndrome [6].

One of the threatening complications is bone lesions of the skeleton with associated severe bone pain and developing pathological fractures. The presence of osteolytic lesions is typical for 80 % of MM patients, and is most often associated with the progression of the disease [2]. Under normal conditions, adult bone is a hard but dynamic organ that undergoes continuous remodeling to maintain normal calcium to phosphate ratio and to control the amount of bone content in response to mechanical load and possible fracture repair. Normal osteogenesis (bone tissue formation) is maintained through the interaction and balance between osteoclasts and osteoblasts. The basis for the appearance of osteolytic foci is the imbalance between these cells. Increased osteoclast activity in MM patients promotes bone tissue resorption, while suppressed osteoblast activity leads to impaired bone formation [7]. The process of bone tissue destruction causes hypercalcemia. Increased production of cytokines (interleukin-6, tumor necrosis factor) maintains the imbalance by stimulating osteoclast activity, leading to stimulation of local resorption, and contributing to the development of pathological fractures. All these mechanisms contribute to the proliferation and maintenance of the spread of tumor plasma cells [7].

An important role in the tumor microenvironment belongs to endothelial cells, which contribute to increased production of factors such as vascular endothelial growth factor (VEGF) and VEGF receptor-2, fibroblast growth factor-2 (FGF2), thus maintaining blood supply and promoting the spread of tumor clones in MM [8].

The blood vessels are essential for the growth and development of tumor and supply of vital oxygen and nutrients. It has been shown that an increase in microvessel density in MM patients is associated with a poor prognosis [8]. Platelet-endothelial interactions in the tumor microenvironment contribute to the dyscrasias of clonal plasma cells in the microenvironment [4].

Monoclonal gammopathy of undetermined significance

Almost all lymphoplasmacytic malignant neoplasms with the presence of monoclonal protein are preceded by monoclonal gammopathy of undetermined significance [9].

Monoclonal gammopathy of undetermined significance (MGUS) is an asymptomatic precancerous disease with plasma cell dyscrasia of less than 10 % of clonal plasma cells in the bone marrow, production of serum M-protein less than 30 g/L, and absent CRAB criteria. There are two different MGUS types:

1. Non-IgM MGUS
2. IgM MGUS. [9].

The risk of non-IgM MGUS progression is approximately 1 % per year and it increases with a serum M-protein level equal to or higher than 15 g/L, and in the presence of an abnormal ratio of lambda and kappa free light chains (<0.26 g/L or> 1.65 g/l). Although MGUS is considered to be a non-malignant disease, it does not mean that it has no clinical significance. No specific treatment is required for these patients, but taking into the account the risk of the disease progression, close follow-up is recommended [9].

One of the main research directions in the field of plasma cell dyscrasias is the study of the risk factors and molecular mechanisms of MGUS progression. However, according to

the data of the performed studies, no specific mutations in bone marrow cells detected in MGUS or in early MM stages have been described [10].

An important role in the dyscrasias of plasma cells of the bone marrow in MGUS is attributed to the microenvironment. Changes in the bone marrow microenvironment lead to the fact that controlled clonal plasma cells become malignant. Currently, there are data indicating that dormant myeloma cells reside in osteoblast niches [10]. Bone marrow infiltration with tumor cells results in increased osteoclast activity and inhibited osteoblast activation, which leads to increased bone resorption and causes osteolytic bone lesions. Osteoclasts, by increasing their activity, release growth factors and cytokines, which promote the dyscrasias of plasma cells. An important role in dyscrasias is also played by bone marrow stromal cells [11].

In recent years, quite a lot of studies confirming the presence of disorders of the skeletal bones in MGUS before transformation into MM have appeared. This is proved by many multi-center studies (Melton et al., Kristinsson et. al., Mayo Clinic studies). According to the data based on the study of rather large groups of MGUS patients, it has been concluded that there is a high risk of fractures of the distal bones of the skeleton. Fractures most often occur in the tubular bones. Based on the fact that hematopoiesis is mainly carried out in the bone marrow of squamous and tubular bones, the authors of these studies assumed that changes in the bone marrow microenvironment may be a factor of high risk of fracture [12].

The research data suggest that osteoblasts and other cells in the bone marrow microenvironment may induce early changes in the plasma cells of MGUS patients. However, until now it is unknown what genetic mechanisms can lead to malignancy of normal plasma cells and their dyscrasias [12].

Plasma cell leukemia

Plasma cell leukemia (PL) is a rare and aggressive form of leukemia and it is represented by plasma cell dyscrasias resulting from the progression of symptomatic MM (secondary plasma cell leukemia) or primary acute plasma cell leukemia, the diagnosis of which is based on the presence of 2×109/L or 20 % of circulating malignant plasma cells in the peripheral blood [13]. Acute plasma cell leukemia accounts for about 0.5 % of MM cases with an overall incidence of 0.4 cases per million. The treatment protocols for plasma cell leukemia are the same as for MM, but the overall results are significantly worse [13].

The morphology and immunophenotype of malignant plasma cells in PL and MM do not differ. The expression of plasma cell markers CD138 and CD38 did not differ between the groups. However, CD56 expression is more likely to be positive in MM, and the expression of the B-cell marker CD20 is more often positive in plasma cell leukemia [14]. As for mutations or gene aberrations, they are not specific, but there is a relative difference in the incidence of changes in plasma cell leukemia. For example, TP53 and DIS3 mutations are more common in plasma cell leukemia than in MM, while NRAS, KRAS, and BRAF mutations in PL are less common than in MM [13]. Translocations involving chromosome 14, t (11; 14), t (14; 16), and t (4; 14) are more common in PL; however, it is known that t (11; 14) is of clinical significance in MM and other hematological diseases referring these patients to the high risk group [15]. Unlike MM, the course of the disease is more aggressive. The clinical presentation of PL differs from that of MM. Due to the rapid displacement of cells of normal hematopoiesis and replacement by tumor plasma cells, anemic syndrome is developing in the peripheral blood. Due to rapid resorption of bone tissue, a large amount of calcium is released, leading to malfunction of the main organs and tissues (there are interruptions in the work of the heart, spastic muscle pain, severe fatigue, and other symptoms). Cytopenia and extramedullary damage to the liver, spleen and other organs are most prevalent. Despite some increase in the overall survival rate, the prognosis remains poor [15].

Light chain (AL) amyloidosis

Light chain (AL) amyloidosis is a clonal disorder of plasma cells characterized by improper deposition of immunoglobulin light chains in the vital body organs which causes their dysfunction. Most frequently, it occurs in patients with MM, MGUS, and Waldenstrom macroglobulinemia / lymphoplasmacytic lymphoma or as an independent disease [16]. The clinical picture is nonspecific in most cases. Difficulties may arise in the differential diagnosis of MM and primary amyloidosis (with plasma cell dyscrasia), since clinical manifestations are caused by the deposition of fibrillar

protein consisting of fragments of light chains (Bence-Jones protein) in tissues. In this case, primary amyloidosis is clinically manifested by symptoms of organ damage - renal failure, nephrotic syndrome, cardiomyopathy, neurological disorders, skin lesions, coagulation disorders in combination with monoclonal protein [17]. In amyloidosis, monoclonal protein, including the Bence-Jones protein, are often found in the blood and urine, an increased number of plasma cells is detected in the bone marrow, but when the bone marrow contains more than 10 % of plasma cells combined with osteo-destructive syndrome, the diagnosis of MM becomes more likely. The final diagnosis is verified on the basis of the results of the histological examination of tissue biopsies [17].

POEMS syndrome

POEMS syndrome is a paraneoplastic syndrome associated with clonal plasma cell dyscrasias. This acronym was introduced by Bardwick J.M. in 1980 [18]. The main criteria for the syndrome are polyradiculoneuropathy, clonal dyscrasia of plasma cells, sclerotic bone lesions, increased VEGF levels, and the presence of Castleman disease. Its additional symptoms include organomegaly, endocrinopathy, pronounced skin changes, fluid retention syndrome, and thrombocytosis. It is essential to distinguish POEMS syndrome from MGUS, smoldering MM, MM or solitary plasmacytoma, since the treatment and supportive therapy strategies are very different [19].

Bone marrow biopsy reveals megakaryocyte hyperplasia, which resembles myeloproliferative diseases, but it is not detected during the JAK2V617F mutation testing [19].

In one third of patients, the biopsy of the iliac bone does not reveal clonal plasma cells - most often in solitary plasmacytoma. The other two-thirds of patients have clonal plasma cells in the bone marrow and, in 91 % of cases, with lambda chain secretion [20]. The average percentage of detected plasma cells is less than 5 %. In this case, immunohistochemical staining is used, since it is most sensitive, as it provides information about the architecture of the bone marrow, which is the key one in making the diagnosis in almost half of the cases. Overall, only 8/67 (12 %) cases of POEMS syndrome had normal bone marrow biopsy data from the iliac bone, that is, no clonal plasma cells, lymphoid accumulations, and megakaryocyte hyperplasia were found [20].

Making a diagnosis may be challenging, but an accurate medical history, physical examination followed by skeletal radiography, and bone marrow biopsy can help in the differential diagnosis with other conditions such as plasma cell dyscrasia, light chain amyloidosis, and polyneuropathy in MGUS [20].

Conclusion

In the past decade, much attention has been paid to the understanding of the mechanisms regulating tumor development that promote progression and metastasis. It is becoming increasingly apparent that the interaction between tumor cells and the bone marrow microenvironment plays a significant role in tumor spread, survival, and drug resistance. Tumor development and progression are complexly linked chains of internal and external factors. Studying the role of the tumor microenvironment promotes better understanding of tumor biology.

In this review, we presented data on the role of the bone marrow microenvironment in various plasma cell dyscrasias.

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