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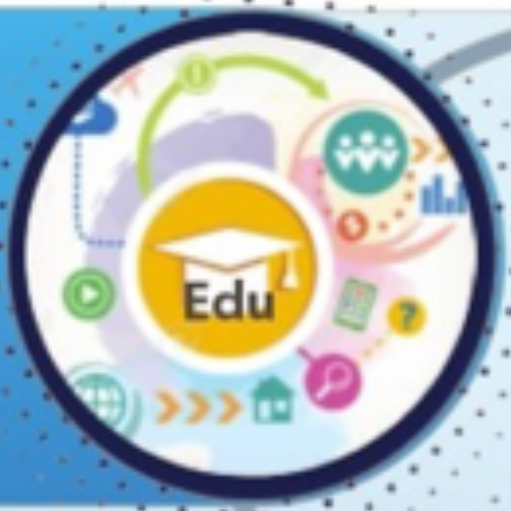

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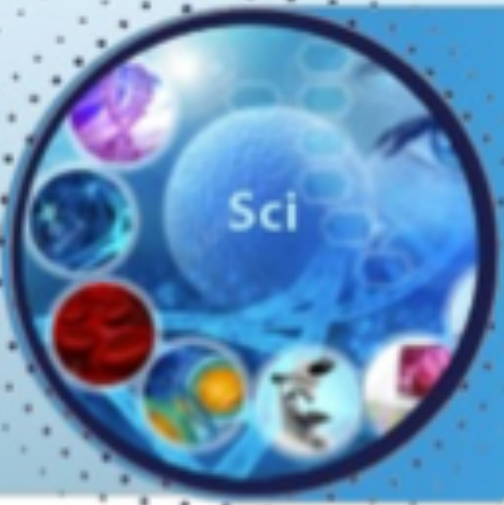

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Review Article

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The Role and Place of Cellular Immunity in Bone Regeneration

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ABSTRACT

The immune system is actively involved in bone regeneration. This reasoning may stem from the peculiarities of immune cell populations, which are known to be diverse and heterogeneous. Such functional and cytological versatility of bone tissue, to a certain extent, may indicate the similarity of their natural relationship. The basis of this connection is regenerative processes, which we decided to describe in this review article.

Keywords: Bone tissue regeneration, role of cellular immunity, callus, bone marrow

Fundamental information about the cellular system of bone tissue points to the fact that the monocyte line of bone marrow stem cells is considered to be the matrix for the formation of macrophages. At the same time, it is this ancestral cell line that acts as the basis for the regeneration of skeletal bones – osteoclasts [8].

It is known that macrophages, participating in the pathological process, contribute to the destruction of tissues and thereby provoke the development of the next, main response stage - repair. Osteoclasts have identical properties in bone tissue regeneration. These, in turn, stimulate the production of osteoblasts, i.e. cells whose origin comes from mesenchymal cells [57].

Osteoblasts develop along the path of osteoclastogenesis, which is expressed by stromal cells [67]. Such an origin of cells is considered to be natural physiological, as it reflects the entire nature of the hematopoietic process [9]. It is in this natural way that osteoblasts develop [64].

This conclusion is based on several experimental and clinical studies, which have studied various aspects of both the hematopoietic cycle and the influence of the immune system on the process of bone tissue regeneration.

In the 90s of the last century, several studies revealed patterns in the cellular regulation of the regenerative process in bone tissue. This structural-functional relationship has been termed a continuous system of mononuclear and bone cells [38]. Hematopoietic cells mature mononuclear phagocytes, blood monocytes, and bone marrow fibroblasts play an important role in the process of consolidation of destroyed bones [52]. Subsequently, inducers, both local and systemic, and modulators of bone formation, begin to be activated in bone formation. This mechanism is considered to be the most

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acceptable in terms of interpreting the mechanisms of regulation of distraction osteogenesis.

The regulation of distraction osteogenesis by lymphocytic and macrophage interconnection is determined by both qualitative and quantitative changes in the immunocompetent cytological system. Such a relationship has the possibility of vector designation, determining the variant of the course of the regenerative process in bone tissue. There are two options for assessing and predicting the outcome of the regenerative process in the form of its favourable course and/or delayed bone tissue recovery.

Empirical conclusions about the important role of lymphocytes in bone tissue regeneration were carried out through banal experimental studies, by assessing the course of the pathological process after removing the thymus gland, researchers stated a slowdown in the process of bone regeneration.

It was assumed that the deficiency of T-cells leads to a slowdown in regenerative processes in bone tissue. Further studies have shown that the process of bone regeneration is not controlled by all types of lymphocytes in the same way. Thus, according to European researchers, the cytological picture of the bone tissue regeneration zone was characterized by a wide range of immune cells of various types. Low values of the number of T-lymphocytes and mast cells were revealed. Against this background, the predominance of mononuclear cells and fibroblasts was noted [31].

Severe traumatic tissue injuries, polytrauma, traumatic shock – all of them are accompanied by pronounced disorders in the cellular link of immunity. The severity of these processes was determined by the suppression of CD2+ receptor expression. Against this background, scientists have identified a decrease in the number of cells with CD4+ and CD8+ phenotypes.

Carl J. Hauser et al. published the results of studies to assess the activity of natural killer cells in patients with injuries [60]. They put forward a hypothesis about the possibility of the participation of natural killer cells in traumatic injuries, since in such conditions there is a high concentration of cytokines in the blood and, possibly, they regulate the activity of these cells. The study involved patients with fixed bone fragments. For comparison, blood samples from healthy volunteers were examined.

The next stage of the study was the evaluation of changes in natural killer cells and mononuclear cells in the supernatant of the bone fracture zone, which was obtained during surgery. At the same time, bone fracture supernatants and peripheral plasma were collected during the fixation of the open fracture. Voluntary mononuclear cells were used as effector sources (natural killer cells). Mononuclear cells were pre-incubated with fracture supernatants, paired peripheral plasma, or normal plasma under various conditions.

Fracture supernatants have been shown to suppress the function of natural killer cells faster than peripheral plasma. Fracture supernatants 1 to 4 days after injury were the most overwhelming. Inactivation of complementary and reactive oxygen species failed to restore lysis.

Neutralization of antibodies to the cytokines IL-4 and IL-10 further suppresses lysis. Antibodies to transforming growth factor β1 failed to restore lysis. The addition of INF-γ did not restore lysis, but the addition of IL-12 resulted in the restoration of lysis. In conclusion, it was stated that the supernatant obtained in the fracture zone and the examined blood plasma in patients with fractures suppress natural killer cells. Responsible mediators may be focused on soft tissue fractures/injuries. Responses to manipulation of the cytokine medium suggest that fracture cytokines may impair cooperation between natural killer cells and accessory cells. There are also experimental studies proving the high role of B-lymphocytes in the formation of bone tissue [41].

Although there may be a close relationship between B lymphocytes and osteoclasts, or bone resorbent cells, little is known about the role of B lymphocytes in bone formation. Many researchers have compared the novel in vivo bone induction in mice homozygous for gene silencing with B cell deficiency that lacks functional B lymphocytes with bone induction in wild-type control mice.

The immune system, in particular the hematopoietic system, and bone have a close relationship that can be both functional and anatomical. In particular, osteoclasts, which resorb bone tissue, develop from precursors found in hematopoietic bone marrow [51].

At the same time, osteoblasts, which are bone-forming cells, may differ from bone stroma [24]. This, in turn, can be considered a basic requirement for normal hematopoiesis [20].

Many of the agents produced or acting on immune/hematopoietic cells have potent effects on bones, and vice versa. However, much of the in vivo evidence on bone turnover in immunocompromised animals is contradictory. A marked decrease in bone formation and resorption has been observed in mice with a preliminary

thymus gland and, accordingly, in which T-lymphocytes are lacking [69], although other studies in mice with a similar model [1] or rats [12] have shown that the physiological turnover of bone tissue in these animals is comparable to the physiological turnover of hematopoiesis.

In studies by A. Marusic et al., it was proved that in rats in which the thymus gland had previously been removed, cellular immunity depression had higher rates of new bone induction by demineralized bone matrix than in control rats [39]. They also proved that mice with β2-microglobulin gene suppression, which do not have functional molecules of class I of the tissue compatibility complex and have a disturbed cellular immune response, have physiological bone regeneration [39].

Other studies have demonstrated that B-lymphocytes can be an important regulator of both normal and abnormal bone resorption. In particular, estrogen is a powerful regulator of bone mass, which is actively involved in the differentiation of the B-cell hematopoietic line [59] and the increased formation of B-lymphocytes may be involved in the mechanism of stimulated bone resorption, which is observed in estrogen deficiency [26].

In mice with a suppressed gene for nuclear transcription factor, which is involved in the survival of osteoclasts [6], both B-lymphocytes and mature osteoclasts cannot be generated [50]. At the same time, transgenic mice with T-cell lymphotropic human virus type I, which is usually associated with T-cell leukaemia, myelopathy, and arthropathy, have an increase in the number of progenitor cells for both osteoclasts and B-lymphocytes [71].

Under the condition that IL-7 receptors are suppressed in mice and there is a lack of B cells due to the cessation of B-lymphatic hematopoiesis at the stage of pro-B-cell maturation, there is an increase in the volume of the internal septa of the tubular bones [42]. Although the concurrent changes in osteoclastogenesis and B-lymphopoiesis described in these reports may not be related, recent work on the regulation of B-lymphoid line adherence has provided direct evidence that B-lymphocyte precursor cells can differentiate into osteoclasts in vitro and in vivo [13].

In contrast to the growing experimental support for the close connection between B lymphocytes and osteoclasts, the role of B lymphocytes in osteoblast proliferation and differentiation has not been investigated. Based on evidence that osteoclast differentiation is regulated by factors produced or transduced by osteoblasts (stromal cells), it is suggested that B-lymphocytes should be involved not only in the differentiation of osteoclasts but also in the regulation of bone formation by osteoblasts [46].

To confirm this hypothesis, a group of scientists led by D. Kitamura studied the formation of new bone tissue in mice with a deficiency of B-lymphocytes caused by a purposeful disruption of the μ-chain, which stops the development of B-lymphocytes at the stage before B-cell maturation [37].

In M.R. Urist's studies, new bone formation was evaluated using two well-defined in vivo models: ectopic bone induction by morphogenetic bone proteins, which recapitulates cellular events in endochondral bone formation and bone regeneration after fracture repair, and bone regeneration after bone marrow injury. synchronous bone formation at a well-defined anatomical location [68]. The popularity of such experimental models for the study of bone regeneration has also been proven by the studies of T. Shimizu et al. [56], L.J. Suva et al. [48], and Tanaka et al. [62].

Strong evidence was presented that mice lacking functional B lymphocytes responded to an osteoinductive stimulus by producing a greater volume of new bone, which was morphologically similar to that of nature-type control groups. These changes were accompanied by changes in the expression of bone-related markers and inflammatory/immunomodulatory cytokines.

Because bone can develop along two differentiation patterns, the researchers presented an analysis of bone formation in vivo in two models: one involving osteogenesis through cartilaginous bridges, and the other, with osteoblasts that differed directly from mesenchymal progenitors.

The epiphyseal cell cascade that was induced by a recombinant human morphogenetic protein in a blood clot as a carrier in nature-type mice was similar to that described in many scientific papers using recombinant morphogenetic bone proteins or bone matrix gelatin [40].

Chemotaxis and proliferation of mesenchymal cells, which are precursors to cartilage, led to cartilage differentiation and hypertrophy, angiogenesis, and invasion of bone marrow cells. The differentiation of osteoblasts and the final formation of new bone, in the form of remodelling, was represented by its filling with bone marrow.

Researchers usually select two time points in a given cell cascade for histological analysis of newly formed tissues: at the beginning of cell proliferation and differentiation, and when the bone is fully organized. The first point was noted 7 days after implantation of recombinant human bone morphogenetic protein when a blood clot as a source of recombinant human bone morphogenetic pro-

tein was surrounded by a large mass of proliferating mesenchyme with very little newly induced cartilage or bone. The relative volumes of blood clots, mesenchyme, cartilage, bone, or bone marrow in the implants were similar in wild-type mice.

It is important to emphasize that histomorphometric analysis is always performed on successive implant sites, which allows researchers to conclude. The volume and mass of whole implants or newly induced tissue in mice with B-lymphocyte suppression were greater than in intact mice.

In the bone marrow injury model, there is an orderly process of bone marrow regeneration after bone marrow ablation, which includes capillary invasion of the bone marrow cavity, appearance of mesenchymal cells, osteoblast proliferation, cancellous bone formation, reappearance of hematopoietic tissue, and osteoclastic resorption, resulting in the final regeneration of normal bone marrow.

B lymphocytes may play a role in regulating the induction and regeneration of new bone in vivo. In a model of epiphyseal osteogenesis induced by recombinant human bone morphogenetic protein, newly formed bone cells were significantly larger in mice without functional B lymphocytes than in animal controls.

The similarity between the relative volumes of newly induced cartilage and bone in the two groups of mice indicates that the absence of B lymphocytes did not affect the potential for osteoprogenitor cell differentiation in the newly induced tissue, but rather the recruitment and proliferation of chondrogenic and osteogenic progenitors in response to implanted recombinant human bone morphogenetic protein.

Macrophages accumulate near the demineralized bone matrix early after in vivo implantation can induce directed monocyte migration at femtomolar concentrations in vitro [17], suggesting that monocyte chemotaxis is a key step in bone induction. Studies by N.D. Cunningham et al. [17] have shown that morphogenetic cells also stimulate the expression of TGF-β in monocytes, which in turn stimulates bone formation and additional expression of the cells themselves. Similar results were obtained by J.M. Wozney and V. Rosen [70].

Hematopoietic cells carry specific receptors and thus can participate in bone morphogenesis [11]. Evidence of the importance of lymphocytes in the early phases of bone regeneration is also described in studies of progressive fibrous dysplasia. In one study, disabling ectopic osteogenesis was associated with overexpression of lymphocytes [47], and in another, the earliest lesions were characterized by acute infiltration of both B-lymphocytes and T-lymphocytes [7].

Многие исследования проведенные in vitro задокументировали важность отдельных цитокинов и местных факторов роста для функции как остеокластов, так и остеобластов. IL-1 и TNF-α являются мощными стимуляторами резорбции костей, а также участвуют в регуляции образования костей [34]. IL-6 действует как нижестоящий цитокин, индуцированный IL-1 и TNF-α, и стимулирует как остеокластогенез [33], так и остеобластогенез [5].

In an in vivo situation, there are likely to be very complex interactions between immunological and bone cells, and it is difficult to understand the contribution of individual factors. For this reason, many analytical comparisons of researchers disagree on the role of immunological indicators in bone regeneration.

Currently, most often, researchers do not analyze the expression of individual cytokines but rather monitor the cytokine profile and bone-related factors expressed during bone regeneration.

The pattern of cytokine expression during both types of osteogenesis changes in the absence of B lymphocytes. During epiphyseal osteogenesis induced by recombinant human bone morphogenetic protein, the expression of IL-1α and IL-1β, TNF-α and IL-6 increases with bone cell differentiation in intact mice but decreases in immunosuppressed mice.

Because these cytokines can play a role in both initial cellular chemotaxis during osteogenesis and osteoclastic resorption, which finally remodels bone tissue, the differences observed in the cytokine expression pattern may be due to a change in one or both of these processes in immune cell-suppressed mice.

The altered pattern of cytokine expression in mice with immune cell suppression during the early phases of bone induction may be a reflection of an altered immunological environment that promotes early attraction and proliferation of cartilage and/or bone cells. The role of these cytokines in the differentiation and activation of osteoclasts at later stages of the osteoinduction sequence requires further study.

The change in the cytokine expression model during osteogenic regeneration after bone marrow ablation in immunosuppressed mice is in the opposite direction than in the epiphyseal osteogenesis model. This is not surprising because the local immunological, and in this case,

the hematopoietic environment in the bone marrow is different from that of the subcutaneous tissue, where epiphyseal osteogenesis is induced by a recombinant morphogenetic protein of human bone.

Cell-suppressed mice showed a consistent increase in IL-1α and IL-1β expression and a slight change in TNF-α expression during the first 10 days after bone marrow ablation compared to unchanged or decreasing expression of these cytokines in the wild-type control.

In studies by C.A. Dinarello, it was shown that since the isoforms IL-1 and TNF-α were implicated in normal hematopoiesis [21], the changes observed in mice with cell suppression may reflect altered bone marrow regeneration, which repopulates into the reabsorb trabecular meshwork in the diaphysis, compensating for the absence of B-lymphopoiesis.

M. Bhatia et al. found that the differences between non-laboratory mice and those with cellular suppression in early period expression were similar to those in the expression of cytokines, and could reflect their involvement in hematopoiesis. It is also possible that a change in cytokine expression patterns in mice with cell suppression was due to altered osteoclast differentiation and activation during bone marrow regeneration. Most of the studies focused mainly on bone formation because the amount of bone 10 days after bone marrow ablation, the last point in time that followed in the studies, did not change from the earlier dates of the experiments, and extensive resorption was still not apparent.

However, the change from thick and less separated trabeculae at day 6 after ablation to more numerous, but thinner, trabeculae at day 10 after ablation, as well as reduced expression of bone-specific markers at later time points in mice with cell suppression compared to control, states that these mice may also differ in resorption and remodelling of the trabecular meshwork.

The results of the study by L.J. Suva et al., as well as H. Tanaka, showed that such studies should assess the number of osteoclasts and their resorption activity at later points in time. All of this occurs when the diaphyseal bone marrow space is restored by complete resorption of the trabecular meshwork.

The induction of new bone formation in the adult body in vivo has an important immunological aspect related to B lymphocytes. The stimulation of the initial steps in the cellular sequence of osteoinduction observed in mice with cell suppression may be explained by a general imbalance of the immunological system in the absence of B lymphocytes because it is well known that depletion of B lymphocytes reduces humoral (Th2) immunity and shifts the immune response towards an inflammatory and cell-mediated (Th1) response [4].

This alteration of local populations of lymphocytes and other immune cells and their activity may promote the migration and proliferation of mesenchymal precursors in response to an osteoinductive stimulus. Further studies at the molecular level in vivo will be important to elucidate the possible roles and interactions of B lymphocytes with other cell populations in bone mass regulation.

Understanding these processes will be an important step in identifying molecular defects in many pathological conditions related to the hematopoietic and skeletal systems, such as hematologic malignancies, immunodeficiency disorders, and osteoporosis.

Physiological metabolism in bone tissue can also occur in conditions of a lack of mature T-lymphocytes [10].

Meanwhile, as the results of the studies indicate, under the condition of modelling the pathological process in the form of a bone fracture or performing surgical interventions on bone tissue, the deficiency of mature forms of T-lymphocytes was accompanied by a violation of the consolidation of bone fragments with the formation of an inferior callus.

The results of clinical observations presented by F.J. Buchinsky et al. also confirm the important role of T-lymphocytes in the regulation of bone density [61].

Several scientific studies have proven the leading role of changes in the absolute number of T-lymphocytes and B-lymphocytes and their populations in other pathological conditions that have the basis of hormonal dysfunction. These research results were similar to each other. For example, a group of scientists led by C.J. Rosen proved a significant decrease in the absolute number of CD4+ and CD8+ lymphocytes in women with osteoporosis due to menopause with climacteric syndrome [65].

B. Abrahamsen et al. noted a significant increase in the CD4+/CD8+ ratio in this pathological condition [18], and the results of S. Epstein's studies showed an increase in the absolute number of CD3+ and CD56+ T-lymphocytes in women with this manifestation of the pathological process [25].

In the study by E.M. Shevach et al. [16] and D.P. Huston [30] on the effect of immunological control on osteoclastogenesis, it was found that classes of T-lymphocytes, such as CD4+ and CD8+, act as the main levers for triggering this process. Similar results have been obtained by other scientists [34, 35]. All of them indicate that the formation of bone cells and the resorp-

tion of its minerals can be inhibited by T lymphocytes. At the same time, studies by H. Takayanagi and N. Udagawa [35] showed that suppression of osteoclastogenesis is possible under the condition of the production of γ-interferon.

Stimulation of the formation of bone cells, in particular osteoclasts, was achieved in experimental studies outside the living organism by a group of scientists led by V. John [2]. In these studies, CD8+ T lymphocytes were removed from cell culture. All of them contained osteoclast procells and bone pulp procells. As a result, there is an increased formation of mature osteoclasts.

D. Greevise et al. proved that these changes occur by a mechanism with the active participation of prostaglandins [19].

P. Sallusto proved that not only the varieties of T-lymphocyte populations play a role in bone regeneration, but also the variant of their influence in combination with local cytokine secretion [54]. A corresponding vicious circle is formed, in which the destruction of bone tissue is compensated by its increased osteosclerosis. In this process, cytokines, which are produced by T-lymphocytes, take the starting position. Bone metabolism increases with increased bone formation [23].

Lymphocytes, especially T-lymphocytes, can also affect the regeneration of cartilage tissue. Such results of experimental studies were obtained by a group of scientists led by A. Marusise [44].

Thus, the discoveries made about the role of T-lymphocytes in the regeneration of bone and cartilage tissue indicate the existence of a relationship between the immune and bone systems of the body. However, as the researchers themselves point out, there are still several other studies that could reveal the whole picture of the ongoing processes. All these studies are at the stage of continuation, and today they have also made it possible to determine the role of B-lymphocytes in bone tissue regeneration.

Back in 2001, P.A. Koni published an article describing the role and place of B-lymphocytes in the regulation of bone tissue regeneration [15]. His theory boiled down to the topical affiliation of B-lymphocyte types, which are known to be at the stage of early precursors and mature lymphocytes. Early B lymphocytes are located in close contact with the endosteal bone surface and determine their role in traumatic bone injury. As they mature, B-lymphocytes move to the central zone of the bone marrow, which exerts their influence through increased production of immature cells and, accordingly, have a stimulating effect on regenerative processes in bone tissue.

A mechanism has been described in which immature B-lymphocytes adhere to the vascular wall in the bone marrow similar to intercellular adhesion molecules, and are expressed on the surface of stromal cells, directly binding to immature forms of B-lymphocytes [3]. This phenomenon was described in detail by a group of scientists led by P.A. Koni in the Journal of Experimental Medicine in 2021 [15]. According to the phenomenon of homing, such molecules play a leading role in the migration of lymphocytes to the bone marrow. The regenerative properties of B-lymphocytes in bone healing are also determined by a B-cell-specific activator. This assumption was made in the works of S.L. Nutt et al. [45] and M. Sigvardsson [58].

Its presence promotes the maturation of B-lymphocytes and vice versa, the lack of B-cell specific activator, this process is suppressed or does not occur at all. Along with this, on the part of G. Smithson et al. It has been demonstrated that immature B lymphocytes under such conditions can easily pass into sources of other cells (macrophages or osteoclasts), which by nature originate from the bone marrow pool [66].

The intraaxial dividing part of the bone increases in volume, which can also reliably indicate the suppression of the maturation processes of B-lymphocytes in the bone marrow [32].

M. Kanematsu et al. [49], as well as Y. Onoe et al. [14] almost simultaneously described the results of experiments where an artificial deficiency of mature B-lymphocytes was created in animals without any experimental models of the pathological state. Such a deficiency of B-lymphocytes did not affect the metabolism in the bone tissue to any extent.

Also in 2000, a group of scientists led by J.A. Lorenzo published an article in the Journal of Bone and Mineral Research, where researchers conducted the same experiments, but in the process of ontogeny. The results of these experiments also showed that (we quote) "under the conditions of ontogenesis, the lack of mature B-lymphocytes practically does not affect the cellular balance and metabolism in bone tissue" [43].

Only under the conditions of reproduction of experimental models of pathological processes in the form of various deformities or even bone fractures, does the lack of B-lymphocytes have an impressive effect on the course of bone tissue regeneration processes. Such results were described based on the results of experimental studies conducted by a group of scientists led by A. Marusise et al. [53].

The participation of neutrophils in influencing the healing process of bone tissue was described in the

monograph by I.I. Dolgushin "Immunology of Trauma" 35 years ago. Under the influence of a traumatic agent, a local inflammatory reaction develops. Such a reaction can be exudative, destructive, or purulent-infectious overnight. As a severe form of the inflammatory process develops, the role of neutrophils becomes more pronounced. It is on them, in particular on their reactivity, that the outcome of any inflammatory process depends. However, their direct role in bone repair has not yet been revealed. The available data in the literature describe the effector effect of neutrophils in the subsequent phases of the ongoing inflammatory process. It should be noted here that the severity of the inflammatory process determines the course of collagenosis through the production of factors that activate fibroblasts and several regenerative enzymes, such as collagenase, gelatinase and stromalizin. These, in turn, play an important and direct role in the remodelling of the pericellular matrix.

The main manifestation of neutrophil disorders in traumatic injury is determined by their functional inferiority. Such neutrophil changes occur in any type of injury and do not depend on the severity of the injury or the traumatic agent. Accordingly, the development of traumatic shock also cannot indicate specific changes in this cellular immune response system.

There is information about the peculiarities of changes in the cell population, immunological response to various volumes and forms of traumatic injuries to soft tissues and internal organs.

However, along with this, the literature describes the results of scientific studies that demonstrate an increase in the migratory ability of polymorphonuclear neutrophils, especially in traumatic bone injury.

The mechanisms by which neutrophil migration is impaired in the event of traumatic injuries are still unclear. Researchers only state a decrease in this ability of neutrophils, but the causal effect has not yet been identified [63].

In his studies, B. Grogaard proved that the decrease in the strength of bone tissue consolidation depended on the degree of reduction in the number of polymorphonuclear leukocytes [29].

In some cases, abnormalities of this level could be significant, especially in the case of the development of a hematoma around the area of the bone fracture. In such cases, neutrophils migrated and concentrated in the zone of revascularization. At the same time, a large number of inflammatory mediators, such as serotonin, bradykinins, and histamines, are released. They subsequently disrupt the process of bone tissue regeneration and the formation of calluses.

As a result of impaired revascularization, there is a decrease in the mechanical strength of the callus in the area of the bone fracture.

In bone tissue regeneration after traumatic injuries, adhesion, migration and differentiation of osteogenic cell fibroblasts occur. The substrate for such receptors is the proteins of the extracellular matrix. In the literature, they are known as integrins or heterodimeric transmembrane receptors [36]. They take an active part in the regulation of bone tissue regenerative processes. These regulatory mechanisms ultimately affect gene expression. It is based on a certain relationship between bone tissue cells and the extracellular matrix [28].

Receptors transmit information about the traction or distraction of bone fragments across the cell membrane. In skeletal traction, this mechanism is considered to be the basis for predicting the process of bone tissue regeneration [55].

O. Nakade et al. Studies were conducted to assess the effect of extracellular calcium on the expression of protein immunogens from bone tissue extract [22]. The morphogenetic characteristics of a specific protein both under normal conditions and under conditions of traumatic injury are presented.

Immunocompetent cells can change their direction of action as a result of activating a combination of a signal with receptors, which in turn are antigen-recognizing. At the same time, in the process of recirculation, there is a migration of immune system cells through tissues that are involved in the regenerative process [27].

In the case of impaired bone tissue regeneration, in particular, unhealed fractures of the lower jaw, there is a postoperative decrease in the number of lymphocytes expressing CD3+, CD4+, CD8+, and CD20+ markers.

Thus, in the study of cellular immunity indicators in regenerative bone tissue repair, the available data are ambiguous. Some authors present information about the active role of T-lymphocytes, others about B-lymphocytes. Both play a role in bone regenerative processes to a certain extent. However, to what extent can the nature of the traumatic agent and the severity of the injury itself influence the changes in these cells? What is the role of immune cells in the development of adverse disease outcomes?

Unfortunately, many scientists still give contradictory answers to these questions. Most of the available information on the mechanisms of callus formation does not

provide the context that could be applied in clinical practice.

Nevertheless, some authors, in particular T.V. Melenberg and A.B. Zhestkov, proposed to use the data obtained as a result of immunological studies to predict the course of osteogenesis. In their studies, they found that depression of the main links of the immune system during the first week after injury may indicate a violation of the processes of reparative osteogenesis [67].

We believe that research in this area will be very productive for clinical practice.

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REFERENCE:

1. A comparison of bone turnover in athymic (nude) and euthymic mice: biochemical, histomorphometric, bone ash and in vitro studies / L.K. McCauley, T.J. Rosol, C.C. Capen, J.E. Horton // J. Bone. – 1989;10:P.29-34.

2. A role for CD8+ T-lymphocytes in osteoclast differentiation in vitro / V. John, J.M. Hock, L.L. Short, et al. // J. Endocrinology. – 2016;137:P.2457-2463.

3. A VCAM-like adhesion molecule on murine bone marrow stromal cells mediates binding of lymphocyte precursors in culture / K. Miyake, K. Medina, K. Ishihara, et al // J . Cell. Biol. – 2021;114:P.557-565.

4. Abbas A.K., Murphy K.M., Sher A. Functional diversity of helper T lymphocytes // Nature, 2016;381:787-793.

5. Activation of JAK/STAT signal transduction by IL-6 type cytokines promotes osteoblast differentiation / T. Bellido, V.Z. Borba, P. Robertson, S.C. Manolagas // Endocrinology, 2017;138:3666-3676.

6. Activation of NF-kappaB is involved in the survival of osteoclasts promoted by interleukin-1 / E. Jimi, I. Nakamura, T. Ikebe, et al. // J Biol Chem, 15 (1998), pp. 8799-8805.

7. Acute lymphocytic infiltration in an extremely early lesion of fibrodysplasia ossificans progressiva / F.H. Gannon, B.A. Valentine, E.M. Shore, M.A. Zasloff, et al. // Clin. Orthop., 2018;346:19-25.

8. An adherent condition is required for the formation of multinuclear osteoclasts in the presence of macrophage colony-stimulating factor and receptor activator of nuclear factor B ligand / T. Miyamoto, P. Aral, O. Ohneda et al. // L. Blood. – 2000;96:P.4335-4343.

9. Bianco P., Robey P.G. Marrow stromal stem cells // J. Clin. Invest. – 2000;l: P.1663-1668.

10. Bone mineral metabolism in T-lymphocyte-deficient and - replete strains of rat / F.J. Buchinsky, Y. Ma, G.N. Mann et al. //J. Bone Miner. Res. – 1995;10:P.1556-1565.

11. Bone morphogenetic proteins regulate the developmental program of human hematopoietic stem cells / M. Bhatia, D. Bonnet, D. Wu, et al. // J. Exp. Med., 2019;189:1139-1148.

12. Buchinsky F.J., Ma Y., Mann G.N. Bone mineral metabolism in T lymphocyte-deficient and -replete strains of rat // J Bone Miner Res, 10 (1995), pp. 1556-1565.

13. Commitment to the B-lymphoid lineage depends on the transcription factor Pax5 / S.L. Nutt, B. Heavey, A.G. Rolink, M. Busslinger // J. Nature. – 2009;401:P.556-562.

14. Comparative effects of estrogen and raloxifene on B-lymphopoiesis and bone loss induced by sex steroid deficiency in mice / Y. Onoe, C. Miyaura, M. Ito, et al. // J. Bone Miner. Res. – 2000;15:P.541-549.

15. Conditional vascular cell adhesion molecule 1 deletion in mice: Impaired lymphocyte migration to bone marrow / P.A. Koni, S.K. Joshi, U.A. Temann, et al. // J. Exp. Med. – 2021;193:P.741-753.

16. Control of T-cell activation by CD4+ CD25+ suppressor T-cells / E.M. Shevach, R.S. McHugh, C.A. Piccirillo, A.M. Thornton // J. Immunol. Rev. – 2021;182:P.58-67.

17. Cunningham N.D., Paralkar V., Reddi A.H. Osteogenin and recombinant bone morphogenetic protein 2B are chemotactic for human monocytes and stimulate transforming growth factor β1 mRNA expression // Proc. Natl. Acad. Sci. USA, 2022;89:11740-11744.

18. Cytokines and T-lymphocytes subsets in healthy post menopausal woman: estrogen retards bone loss without affecting the release of IL-1 or IL-IRA / B. Abrahamsen, K. Bendtzen, H. Beck-Nielsen // J. Bone. – 2017;20:P.251-258.

19. Depletion of CD4+ and CD8+ T-lymphocytes in mice in vivo enhances 1,25- dihydroxy vitamin D3-stimulated osteoclast-like cell formation in vitro by a mechanism that is dependent on prostaglandin synthesis / D. Greevise, S-K. Lee, A. Marusiae, J.A. Lorenzo // J.Immunol. – 2020;165:P.4231-4238.

20. Dexter T.M., Allen T.D., Lajtha L.G. Conditions controlling the proliferation of hematopoietic stem cells in vitro // J Cell Physiol, 91 (1977), pp. 335-344.

21. Dinarello C.A. Interleukin-1 and interleukin-1 antagonism // Blood, 2021;77:1627-1652.

22. Effect of extracellular calcium on the gene expression of bone morphogenetic protein-2 and -4 of normal human bone cells / O. Nakade, K. Takahashi, T. Takuma, et al. // J. Bone Miner.Metab. – 2021;19:P.13-19.

23. Effects of interleukin 1 on bone turnover in normal mice / B.F. Boyce, T.B. Aufdemorte, R. Garret, et al. // J. Endocrinology. – 2019;125:P.1142-1150.

24. Encina N.R., Billotte W.G., Hofmann M.C. Immunomagnetic isolation of osteoprogenitors from human bone marrow stroma // Lab Invest, 79 (1999), pp. 449-457.

25. Epstein S. Post-transplantation bone disease: a role of immunosuppressive agents and the skeleton // J. Bone Miner. Res. – 2016;11:R.l-7.

26. Estrogen deficiency stimulates B-lymphopoiesis in mouse bone marrow / T. Masuzawa, C. Miyaura, Y. Onoe, et al. // J Clin Invest, 94 (1994), pp. 1090-1097.

27. Expression of mRNAs encoding for a and ß integrin subunits, MMPs, TIMPs in stretched human periodontal ligament and gingival fibroblasts / A.L. Bolcato-Bellemin, R. Elkaim, A . Abehsera, et al. // J. Dent. Res. - 2020;79:P.1712-1716.

28. Giancotti P.G., Ruoslahti E. Integrin signaling // Science. – 2019;285:P.1028-1032.

29. Grogaard B. The polymorphonuclear leukocyte: Has it a role in fracture healing? // J. Arch.Orthop.-Traum. Surg. – 2000;109(5):P.261-271.

30. Huston D.P. The biology of the immune system // JAMA. – 2017;278:P.1804-1814.

31. Immunologic studies of nonunited fractures / S. Santavirta, Y.T. Konttinen, D. Nordstrom et al. // J. Acta Orthop. Scand. – 1992;63(6):P.579-586.

32. Increased B-lymphopoiesis by interleukin 7 induces bone loss in mice with intact ovarian function: Similarity to estrogen deficiency / C. Miyaura, Y. Onoe, M. Inada, et al. // J. Proc. Natl. Acad. Sci. USA. – 2017;94:P.9360-9365.

33. Increased osteoclast development after estrogen loss: Mediation by interleukin-6 / R.L. Jilka, G. Hangoc, G. Girasole, G. Passeri, et al. // Science, 2022;257:88-91.

34. Inflammatory cytokines regulate the proliferation of cultured human osteoblasts / A. Frost, K.B. Jonsson, O. Nilsson, O. Ljunggren // Acta Orthop. Scand., 2017;68:91-96.

35. Interleukin-18 (interferon-gamma-producing factor) is produced by osteoblasts and acts via granulocyte/macrophage colony-stimulating factor and not via interferon to inhibit osteoclast formation / N. Udagawa, N.J. Horwood, J. Elliott, et al. // J. Exp. Med. – 2017;185:P.1005-1012.

36. Kapila Y.L., Lancero H., Johnson P.W. The response of periodontal ligament cells to fibronectin // J. Periodontol.- 2018;69:P.1008-1019.

37. Kitamura D., Roes J., Kuehn R., Rajewsky K. A B-cell deficient mouse by targeted disruption of the membrane exon of the immunoglobulin μ chain gene // Nature, 2021;350:423-426.

38. Lorenzo J.A. Interactions between immune and bone cells: new insights with many remaining questions // J. Clin. Invest. – 2000;106:P.749-752.

39. Marusic A., Dikic I., Vukicevic S. New bone induction by demineralized bone matrix in immunosuppressed rats // Experientia, 48 (1992), pp. 783-785.

40. Marusic A., Grcevic D., Katavic V. New bone induction by bone matrix and recombinant human bone morphogenetic protein-2 in the mouse // Croat. Med. J., 2016;37:237-244.

41. Marusic A., Grcevic D., Katavic V. Role of B Lymphocytes in New Bone Formation. // Laboratory Investigation, Volume 80, Issue 11, 2000, Pages 1761-1774.

42. Miyaura C., Onoe Y., Inada M. Increased B-lymphopoiesis by interleukin-7 induces bone loss in mice with intact ovarian function: Similarity to estrogen deficiency // Proc Natl Acad Sci USA, 94 (1997), pp. 9360-9365.

43. Murine osteoclasts and B-lymphocytes share a common progenitor cell whose abundance in bone marrow is regulated by estrogen / J.A. Lorenzo, D. Greevi, S. Lee, et al. // J. Bone Miner. Res. – 2000;15:P.1176.

44. New bone induction by bone matrix and recombinant human bone morphogenetic protein-2 in the mouse / A. Marusise, D. Greevias, V. Katavi, et al. // Croat. Med. J.- 2016;37:P.237-244.

45. Nutt S.L., Heavey B., Rolink A.G., Busslinger M. Commitment to the B-lymphoid lineage depends on the transcription factor Pax5 // Nature, 401 (1999), pp. 556-562.

46. Osteoclast differentiation factor is a ligand for osteoprotegerin/osteoclastogenesis-inhibitory factor and is identical to TRANCE/RANKL / H. Yasuda, N. Shima, N. Nakagawa, K. Yamaguchi, et al. // Proc. Natl. Acad. Sci. USA,2018; 95:3597-3602.

47. Overexpression of an osteogenic morphogen in fibrodysplasia ossificans progressiva / A.B. Shafritz, E.M. Shore, F.H. Gannon, M.A. Zasloff, et al. // N. Engl. J. Med., 2016;335:555-561.

48. The pattern of gene expression following rat tibial marrow ablation / L.J. Suva, J.G. Seedor, N. Endo, H.A. Quartuccio, et al. // J. Bone Miner. Res., 2023;8:379-387.

49. Prostaglandin E2 induces expression of receptor activator of nuclear factor-kappa B ligand/osteoprotegerin ligand on pre-B cells: implications for accelerated osteoclastogenesis in estrogen deficiency / M. Kanematsu, T. Sato, H. Takai, et al. // J. Bone Miner. Res. – 2000;15:P.1321-1329.

50. Requirement for NF-kappaB in osteoclast and B-cell development / G. Franzoso, L. Carlson, L. Xing, L. Poljak, et al. // Genes Dev, 11 (1997), pp. 3482-3496.

51. Rifas L. Bone and cytokines: Beyond IL-1, IL-6 and TNF-α // Calcif. Tissue Int., 2019;64:1-7.

52. Rodan G.A., Martin T.J. Therapeutic approaches to bone diseases // J. Science. – 2000;289:P.1508-1514.

53. Role of B-lymphocytes in new bone formation / A. Marusise, D. Greevij, E.V. Katavie, et al. // J. Lab. Invest. – 2000;80:P.1761-1774.

54. Sallusto P., Lanzavecchia C., Mackay R. Chemokines and chemokine receptors in T-cell priming and Thl/Th2-mediated responses // J. Immunol Today. – 2018;19:P.568-574.

55. Schoenwaelder S.M., Burridge K. Bidirectional signalling between the cytoskeleton and integrins // J. Curr. Opin. Cell Biol. – 2019;11:P.274-286.

56. Sequential expression of bone morphogenetic protein, tumour necrosis factor, and their receptors in bone-forming reaction after mouse femoral marrow ablation / T. Shimizu, R. Mehdi, Y. Yoshimura, H. Yoshikawa, et al. // Bone, 2018;23:127-133.

57. Sharrock W.J. Bone and the hematopoietic and immune systems: A report of the proceedings of a scientific workshop // J Bone Miner Res, 13 (1998), pp. 537-543.

58. Sigvardsson M. EBP and E47 collaborate to induce expression of the endogenous immunoglobulin surrogate light chain genes // J. Immunity. – 2007;7:P.25-36.

59. Smitson G., Medina K., Ponting I. Estrogen suppresses stromal cell-dependent lymphopoiesis in culture // J Immunol, 155 (1995), pp. 3409-3417.

60. Suppression of natural killer cell activity in patients with fracture/soft tissue injury / C.J. Hauser, P. Joshi, Q. Jones et al. // J. Arch. Surg. – 1997;132(12):P.1326-1330.

61. T-lymphocytes play a critical role in developing cyclosporin A-induced osteopenia / F.J. Buchinsky, Y.Ma, G.N. Mann, et al. // J. Endocrinology. – 2016;137:P.2278-2285.

62. Tanaka H., Barnes J., Liang C.T. Effect of age on the expression of insulin-like growth factor-I, interleukin-6, and transforming growth factor-β mRNAs in rat femurs following marrow ablation // Bone, 2016;18:473-478.

63. The influence of trauma on changes in neutrophil granulocyte function assessed by an analysis of granulocyte migration / H.P. Hofer, G. Egger, E.M. Kukovetz, et al. // J. Langenbecks Arch. Chir. – 2016;381(3):P.148-154.

64. The osteoblasts: a sophisticated fibroblast under central surveillance / P. Ducy, T. Schinke, G. Karsenty et al. // J. Science. – 2000;289:P.1501-1504.

65. The predictive value of biochemical markers of bone turnover for bone mineral density in early postmenopausal women treated with hormone replacement or calcium supplementation / C.J. Rosen, C.H. Chesnut, N.J.S. Mallinak, et al. // J. Clin. Endocrinol. Metab.- 2017;82:P.1904-1910.

66. The role of estrogen receptors and androgen receptors in sex steroid regulation of B-lymphopoiesis / G. Smithson, J.F. Couse, D.B. Lubahn [et al] / / J . Immunol. - 1998. - No 161. -P.27-34.

67. The roles of osteoprotegerin and osteoprotegerin ligand in the paracrine regulation of bone resoфtion / E.G. Hofbauer, S. Khosla, C.R. Dunstan et al. // J. Bone Miner. Res. – 2000;15:P.3-12.

68. Urist M.R. The first three decades of bone morphogenetic protein research // Osteologie, 2015;4:207-223.

69. Vignery A., Silvergate A., Horowitz M. Abnormal remodelling activity in the immunodeficient (nu/nu) and motheaten (me/me) mutant mice // Calcif Tissue Int, 33 (1981), p. 301.

70. Wozney J.M., Rosen V. Bone morphogenetic protein and bone morphogenetic protein gene family in bone formation and repair // Clin. Orthop., 2018;346:26-37.

71. Yamazaki H., Kunisada T., Ishuzu A. Promotion of early osteoclastogenesis and B lymphopoiesis in the bone marrow of transgenic rats with the env-pX gene of human T-cell lymphotropic virus type I // Oncogene, 17 (1998), pp. 2955-2960.

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SUYAK TO'QIMALARINING REGENERATSIYASIDA HUJAYRAVIY IMMUNITETNING O'RNI

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ABSTRAKT

Immun tizimi suyuk regeneratsiyasida faol ishtirok etadi. Ushbu mulohaza turli xil va heterogen ekanligi ma'lum bo'lgan immun hujayra populyatsiyalarining o'ziga xos xususiyatlaridan kelib chiqishi mumkin. Suyak to'qimalarining bunday funktsional va sitologik ko'p qirraliligi, ma'lum darajada, ularning tabiiy munosabatlarining o'xshashligini ko'rsatishi mumkin. Ushbu ulanishning asosi regenerativ jarayonlar bo'lib, biz ushbu maqolada tasvirlashga qaror qildik.

Tayanch iboralar: Suyak to'qimalarining regeneratsiyasi, hujayraviy immunitetning roli, kalla, suyak iligi

РОЛЬ И МЕСТО КЛЕТОЧНОГО ИММУНИТЕТА В РЕГЕНЕРАЦИИ КОСТНОЙ ТКАНИ

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АБСТРАКТ

Иммунная система принимает активное участие в регенерации костной ткани. Данное рассуждение может исходить из особенность популяций иммунных клеток, которые, как известно, многообразны и гетерогенны. Подобная функциональная и цитологическая многогранность костной ткани, в определенной степени, может свидетельствует о схожести их природной взаимосвязи. Основу данной связи составляют регенераторные процессы, о которых мы решили изложить в данной обзорной статье.

Ключевые слова: Регенерация костной ткани, роль клеточного иммунитета, костная мозоль, костный мозг