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Macrophagal Polykaryocytes in Inflammation, Tumor Growth, and Tissue Remodeling

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Abstract Macrophagal polykaryocytes (MPs) are terminally differentiated multinuclear macrophage cells responsible for remodeling and resorption of bone, foreign body, and tissue depositions in inflammation. MPs are encountered only in bone and cartilagenous tissues, in which they are referred to as osteoclasts, odontoclasts, and septoclasts. Depending on the disease, the MPs differentiate into many morphological variants that include foreign-body giant cells, Langhans-type cells, and Touton-type cells. Morphological heterogeneity of MPs could reflect the giant cell formation from phenotypically different macrophage precursors by the process of fusion. At present, many cytokines, adhesion/fusion molecules, and other factors of the microenvironment have been discovered that influence the multinucleation process. Many evidences suggest that conditions in giant cell fibrohistiocytomas, which facilitate MP formation, are similar to the inflammation site of granulomatosis. MPs in the giant cell tumors and granulomatosis foci are formed in response to the factors secreted by mesenchymal cells. It is proposed that one of the first steps in vertebrate evolution could be the organization of skeleton remodeling, in which osteoclasts play a major role. In this step, the same mechanism of regulations served as a basis for the development of both osteoclast and inflammatory forms of MPs.

Key words: Macrophages, multinucleation, osteoclasts, granuloma, giant cell tumor, bone resorption

Study of macrophagal polykaryocytes (MPs) dates back to more than 100 years when Langhans [51] discovered polynuclear cells in tuberculosis granulomas in 1868. In 1885, Touton described a new type of giant cells in xanthomas for the first time. Metchnikoff [63] noted that the appearance of giant MPs in the organism has an adaptive role for increasing the effectiveness of phagocytosis. In the same years, Podvisotskii [80] published work about the important role of giant polynuclear cells, "necrophages," during the resorption process of the liver necrotic foci. Contemporary studies testify that the MPs are formed as a result of cell fusion, and are one of the variants of the terminal differentiation of macrophages [111]. Normally, MPs are encountered only in bone and cartilagenous tissues, in which they are referred to as osteoclasts, odontoclasts, and polynuclear chondroclasts (septoclasts) [60]. The MP formation in the nonskeletal tissues of senile organisms can be the usual reaction to the appearance of cellular decay products. Although the occurrence of MPs have been described in the middle of the nineteenth century, a lot of research activity is still focused to understanding their roles in inflammatory reactions and in giant cell tumors. In this article, the roles of MPs in inflammation, autoimmune processes, and tumor growth are reviewed.

Morphological Variants of MPs

Depending on the arrangement of organelles and their quantitative composition, MPs have been classified into several morphological variants that include foreign-body giant cells, Langhans-type cells, Touton-type cells, osteoclast-like cells, and osteoclasts.

In foreign-body giant cells, the nuclei (up to 100–200) are arranged in a diffusive manner, while those in Langhans-type ones are located on the periphery around the Golgi complex and other organelles. Some authors consider that the formation of Langhans-type cells is a result of maturation of foreign-body giant cells [58], and others are of the opinion that the Langhans-type cells are their precursors [110]. Most likely, Langhans-type cells are formed from the foreign-body giant cell as a result of functional organelle integration. In the course of this process, the undivided, self-organized Golgi complex shifts the nuclei to the periphery of the cell and unites the activity of all cellular territories [38]. The microtubulin system plays an important role in the mechanism of cellular territory association. It was shown that colchicine suppresses the formation of Langhans-type cells but not foreign-body

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giant cells on the surface of the implanted material [25]. Many researchers noted the morphological similarity of the MPs and their mononuclear precursors, especially the epithelioid cells [10, 92]. Epithelioid cells are the macrophages, which differentiate into the secretory cells in inflammatory foci. Extracellular release of lysosomes is the normal merocrine function of epithelioid cells [103]. The foreign-body giant cells might have formed as a result of epithelioid cell fusion. Attached to the substratum foreign-body giant cells, just as osteoclasts, are the heteropolar cells. The Golgi complex, mitochondrion, and the nuclei are located in the basal region [109, 111]. The surface, inverted to the foreign body or to the resorbed site, usually has a folded structure.

In the Touton-type cells, the nuclei are located in the center and are surrounded by foamy cytoplasm. These cells are usually arranged to the foam macrophages from which they might have formed as a result of fusion [47]. The Touton-type cells are most frequently formed in the xanthogranulomas and also in the foci of cholesterol depositions during different pathologic processes.

The appearance of epithelioid macrophage cells, their fusion, and formation of the Langhans-type cells, and then the morphological transformation of the Langhans-type cells into the Touton-type cells were observed during the hypodermic implantation of cellophane film to rats. Both variants of MPs fused with each other forming super giant MPs with a diameter of up to 1 mm [97]. In certain cases, 3 to 4 morphological variants of MPs were found in the inflammation foci [97, 121] (Fig. 1A).

In the morphology, the osteoclasts are closer to the foreign-body giant cells, although they have considerably smaller quantity of nuclei. The ruffled border in osteoclasts is observed only when they attach to the substratum (bone matrix). The basic physiological role of these MPs is extracellular resorption of mineral and organic bone matrix components (Fig. 1C). In the description of the histological structure of tumors, the term "osteoclast-like cell" is often used. This term is applied on the basis of morphological similarities of these MPs and osteoclasts, although usually in the osteoclast-like cells, an average quantity of nuclei is more than those in osteoclasts [124].

Thus, the morphological heterogeneity of MPs reflects both the stages of maturation and formation of these giant cells from the phenotypically different macrophage precursors.

Macrophage Multinucleation

According to Metchnikoff, Podvisotskii, and Maximoff, the formation of MPs can occur through fusion of cells and amitosis with equal probabilty (see [118]). Recent studies of three decades showed that the MPs are formed as a result of fusion [45, 52, 81]. This is evident from the incorporation of ^{3}H-thymidine in DNA as a consequence of fusion of macrophages, one with the active and other

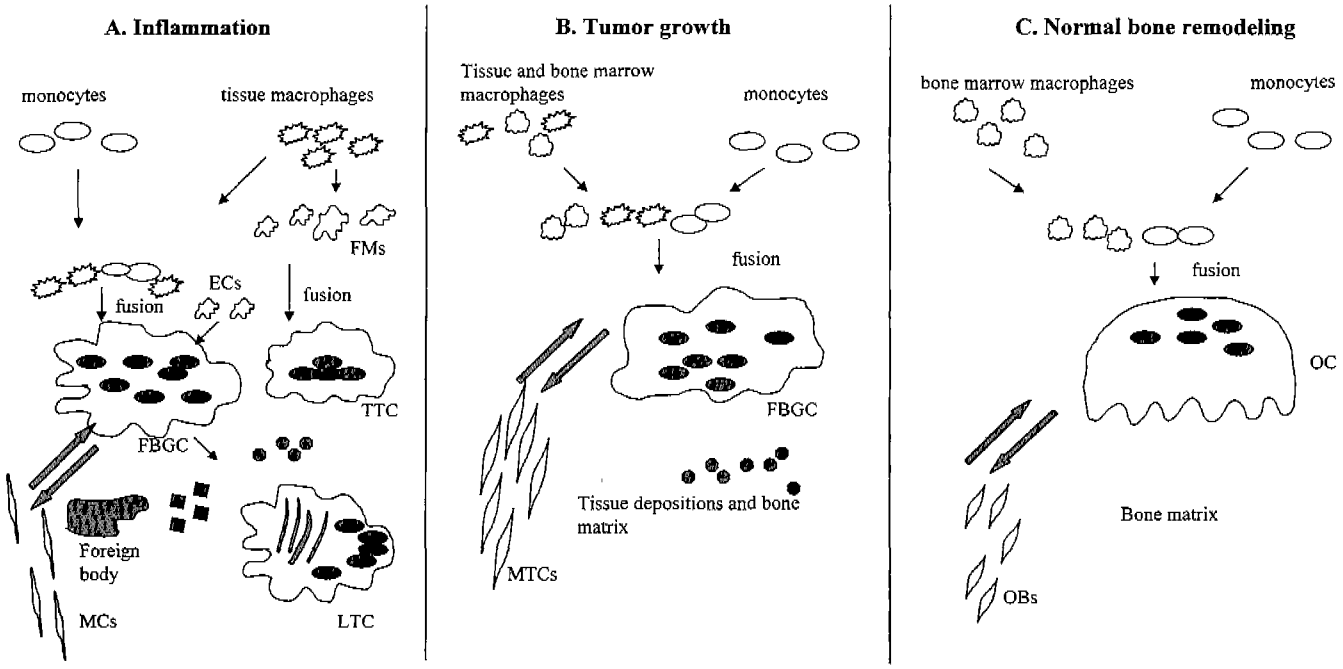

Fig. 1. Schematic representation of MP formation in inflammation (A), tumor growth (B), and normal bone remodeling (C).
FBGC - foreign-body giant cell, TTC - Touton-type cells, LTC - Langhans-type cells, OC - osteoclasts, ECs - epithelioid cells, FMs - foam macrophages, MCs - mesenchymal cells, MTCs - mesenchymal tumor cells, OBs - osteoblasts; little circles - tissue depositions (lipids, hemosiderin, fibrinoid substances), little squares - microbes or foreign particles; broad arrows - bidirectional modulation interactions between MPs and mesenchymal cells, thin arrows - directions of cell migration and differentiation.

with inactive DNA synthesis. Furthermore, it is known that the artificial fusion of two cells, one of which is capable of synthesizing DNA, but the other is incapable of synthesizing DNA, formed a heterokaryon in which the DNA synthesis can be activated in the inactive cellular territory of the second cell as a result of positive control from the cellular territory of the first cell [32].

Monocytes, recently recruited into the inflammation or tumor growth foci, play a dominant role in MP formation *in vivo*, and the process of homotypic fusion of the mature macrophages (histiocytes) occurs in an inactive manner [68]. Other researchers suggest that multinucleation is a result of histiocyte and monocyte fusion [18, 58]. The microenvironmental factors at pathologic foci determine the cell combination.

For macrophage fusion, as in other types of cells, at least two conditions are to be satisfied. First, cells must overcome electrostatic repulsion and enter into close contact, and second, intermembrane hydrophobic interactions must exist at the contact site. During the fusion process, the numerous interpenetrating digitiform outgrowths, which considerably increase the surface area of cellular contact, were observed [112]. Subsequently, the outgrowths of membranes disappear as a result of vesicular transformation of dual intercellular membranes [18, 102]. Many cytokines, adhesion/fusion molecules, physico-chemical properties of substratum (foreign body, bone matrix), pH, hydrolytic enzymes, and other factors have an influence on macrophage multinucleation [22, 103]. An increase in the concentration of the intracellular Ca^{2+} is necessary for macrophage fusion and activation of second mediators of the protein kinase C system [77].

Soon after their accumulation, at the site of production of chemotactic factors for cell fusion, monocytes/ macrophages undergo a number of differential changes which may contribute to or prevent the fusion process. The multinucleation process could be hindered by 1) the decrease in the mobility of plasma membrane, 2) the decreased expression of adhesion/fusion receptors as a result of reduction in their synthesis or recycling, 3) exhaustion of functional cellular reserve as a result of secretory activity, 4) regulatory influence of systemic and local factors, and 5) reaching dynamic equilibrium between MP formation and decomposition to oligonuclear macrophages [98]. The lifetime of the foreign-body giant cells in the inflammation foci, according to the estimation by Papadimituio *et al.* [78], is not more than 10 days. The final phase of the vital activity of MPs could be the death of entire cell or budding of cellular territories [118].

Regulatory Mechanisms in Multinucleation and Maturation of MPs

At present, it is known that all stages of MP formation, including migration, aggregation, spreading, and fusion, depend on the cellular cooperation factors, namely cytokines and fusion/adhesion molecules.

The combination of cytokines rather than their individual application gives the best result for *in vitro* stimulation of macrophage multinucleation. This is connected with the influence of cytokines on the different stages of MP formation. For example, the active multinucleation is observed during the application of granulocyte macrophage colony-stimulating factor (GM-CSF) and interleukin-4: GM-CSF stimulates monocyte differentiation while interleukin-4 activates the fusion process [16, 61]. The important regulators of MP formation are oncostatin, interferon-γ, and interleukin-4 and -6. Oncostatin was found to enhance the MP formation by 2–5-folds in the culture of human bone marrow cells [35]. Interleukin-4 and interferon-γ can both activate and inhibit MP formation [5, 43, 105].

Chemotactic activity with respect to macrophages is detected in the macrophage colony-stimulation factor (M-CSF), the tumor necrosis factor-α (TNF-α), interferon-γ, interleukin-1, monocyte chemoattractant protein-1, and the transforming growth factor-β1 (TGF-β1) [46, 104, 111, 123]. The chemotactic mechanism of these factors is related to cell-matrix or cell-cell adhesion. Osteopontin renders direct adhesive action on the macrophages. Based on the experimental model of nephritis, it was shown that an increase in osteopontin expression leads to macrophage infiltration and subsequent MP formation in the inflammation site [50].

Expression of adhesion molecules (ICAM-1), such as integrins (LFA-1, $\alpha_v\beta_3$), is necessary for macrophage fusion [7, 43]. Monoclonal antibodies to α- and β-chains of LFA-1 integrin almost completely block the MP formation [67]. Action of cytokines and hormones on multinucleation could be related to the regulation of these fusion/adhesion molecules in macrophages. For example, the activation effect of interferon-γ and calcitriol on MP formation is caused by its ability to increase the expressions of ICAM-1, LFA-1, and $\alpha_v\beta_3$ in the MP precursors [7, 67]. Interleukin-13 resulted in increased expression of mannose receptors which has a direct relation to the macrophage multinucleation process [15].

Saginario *et al.* [88] established the possibility of blocking the macrophage fusion with the aid of antibodies to fusion proteins, without disrupting the cell aggregation process. The fusion proteins were expressed only on the mononuclear macrophages and downregulated on the MPs. Among other proteins that can function as fusion factors, researchers have identified P2Z/$P2X_7$, an extracellular ATP receptor capable of forming nonselective transmembrane channels for hydrophilic molecules with a molecular weight up to 900 daltons [12].

Two pathways to osteoclast-like cells formation have recently been reported: osteoclast differentiation factor (ODF)-mediated and CD98-mediated osteoclastogenesis.

ODF (also called OPGL/RANKL/TRANCE) was shown to directly stimulate osteoclastogenesis in the presence of M-CSF [66]. ODF activity is neutralized by binding to the soluble decoy receptor, osteoprotegerin (OPG) [31]. The CD98 molecule has been demonstrated to function as an amino acid transporter. However, the implication of amino acid transporter activity with respect to MP formation remains unclear.

Thus, cytokines cause differentiation of macrophages to the phenotype, which is characterized by expression of specific adhesion/fusion molecules on the surface of the plasma membrane. This is a necessary condition for the onset of fusion process. In MP formation, from migration to fusion, a number of factors play crucial roles. The communication of adhesion molecules with the cytoskeleton can, to a certain degree, cause redistribution of organelles and nuclei after the aggregation of MPs. Hence, the cytokine spectrum and the expression of adhesion/fusion molecules could determine the formation of different morphological variants of MPs. For example, interleukin-4 in combination with GM-CSF or interleukin-3 caused MP formations that were morphologically similar to foreign-body giant cells, and the presence of interferon-γ in the medium stimulated the Langhans-type cell formation [61]. On the other hand, MPs are an active source of inflammatory cytokines, which could contribute to the initiation, maintenance, and downregulation of granulomatous inflammation induced by immunological and inert substances [34].

The basic regulatory mechanisms of foreign-body giant cells do not evidently differ from those of osteoclasts [111]. Opinion about the fact that, among MPs, the expression of the calcitonin receptors is characteristic of only the osteoclasts [56] is not confirmed by other researchers [113]. The high expression of calcitonin receptors in the alveolar MPs gave basis for the assumption that calcitonin could regulate immune reactions in the inflammation foci. Other endocrine hormones that regulate MP formation and activity include calcitonin gene-related peptide, calcitriol, $17\beta_2$-estradiol and retinoic acid [113, 115].

MPs in the Inflammation

A number of pathological processes like inflammation, autoimmunity, and tumor genesis are accompanied by reactive histiocytosis. The term "reactive histiocytosis" usually implies the recruition of monocytes/macrophages into the pathologic foci and their subsequent *in situ* differentiation to the more mature forms, including MPs. The reactive histiocytosis is the necessary condition for the appearance of MPs in the pathologic foci.

In human beings, MPs are found in 1–10% of cases of granulomas and lymph nodes during the inflammatory processes of different origin [6]. MPs are formed in autoimmune diseases such as Crohn's disease, rheumatoid arthritis, giant cell arteritis, sarcoidosis, and some diseases of unknown genesis such as Erdheim-Chester disease [10]. Their appearance is part of the normal spectrum of tissue reaction to the stroke [90]. They surround the foreign inorganic particles like metals (Co, Al, Ba, Be, Zr), minerals (Si, talc, asbest), and also the aggregations of endogenous uric acids, keratin, and insoluble fat deposits [6]. Usually, these cells are encountered in the granuloma sections with infectious diseases such as tularemia, tuberculosis, leprosy, syphilis, leishmaniosis, trypanosomiasis, paragonimiasis, ascaridosis, toxocariasis, filyariasis, wusheriasis, and different micoses [100].

The granuloma is a protective inflammatory fibrohistiocytosis process that plays a significant role in bacterial growth control and in blockade of bacterial dissemination [37]. Tissue macrophages, including MPs, are implicated in the production of growth factors for fibroblasts and adhesion/fusion cytokines [54]. In particular, it is shown that cells of granuloma tissue, surrounding *Schistosome m.* eggs, produce cytokines for the macrophage fusion [83]. MPs are observed in large quantities in mature (more than 8 weeks) Be- and Zr-granulomas with the foci of necrosis, which confirms their direct relation to the necrobiotic process. Cellular debris and fibrinoid materials are observed at places adjoining the necrotic masses between cytoplasmic outgrowths of these cells [6, 92]. The MP formation in granulomas around the uninfected particles could be correlated with new antigenic structures, formed as a result of interaction between self-macromolecules with the surface of the implanted material and/or the charge characteristics of the foreign surface. Apparently, this mechanism is the basis of the process of granuloma formation and reactive histiocytosis in the regional lymph nodes around the endoprostheses and other metal-polymer implants [42, 69, 70, 114]. *Kao et al.* [40, 41] detected an increase in adhesion of macrophage cells and rate of formation of foreign-body giant cells with an increase in hardness and hydrophobicity of the surface of implanted polymers (polyurethanes, low-weight polyethylene and polydimethylsiloxane). The dependence of the resorption speed of foreign material on the physico-chemical properties of the latter was investigated, in particular, for the calcium-phosphate materials utilized in medicine for bone substitution [53, 117].

MPs play an important role in the pathogenesis of autoimmune processes such as rheumatoid disease and giant cell arteritis, and central giant cell granuloma, a disease of unknown genesis.

Rheumatoid disease. In rheumatic Aschoff nodules, the necrotic focus is delimited by MPs. Talalayev, as early as in 1929, observed that this process was necessary as a reaction of reparative nature, and the emergent polynuclear cells are as the foreign-body giant cells [106]. A recent study showed expression of macrophage markers in Anitschkow-

and Aschoff-type giant cells that participate in the resorption of necrotic masses and fibrinoid substance of rheumatoid nodules [23]. Formation of these cells could be stimulated by polypeptide factors of rheumatoid synovial cells [14]. In the opinion of Russu [87], the functional activity of MPs of the Aschoff nodules is directed towards synthesis and secretion of hydrolytic enzymes for digesting the matrix material.

Giant cell arteritis. The histological study of the vessels usually reveals two morphological variants of MPs, namely, the foreign-body giant cells and the Langhans-type cells. The inflammation begins from the reaction of foreign-body giant cells against calcified internal elastic membrane in the atrophic arterial foci. Subsequent diffusive attack of mononuclear macrophages on the vascular wall result in the formation of Langhans-type giant cells [72]. Electron-microscopic examination showed that the foreign-body giant cells adjoining to calcified tissue contain fragments of internal elastic membrane with different degrees of disintegration [73]. The experimental models of arteritis confirm the participation of MPs in the pathogenesis of giant cell arteritis. The introduction of elastase into the vessel leads to the appearance of multinuclear giant cells, which results in hydrolysis of extra- or intracellular elastin [94]. Peptides formed as a result of elastolisis activity as autoimmune targets for the T-cells [27]. Mono- and polynuclear macrophages are the basic sources of the platelet-derived growth factor (PDGF), which stimulates the proliferation of the endothelial cells of vessel intima [39]. Besides macrophage markers, A-actin is expressed in the foreign-body giant cells. Nevertheless, Langhans-type cells, which are formed in all layers of arterial wall, manifest strong immunoreactivity with respect to macrophage markers but they were not stained for A-actin. This gave the basis to Nordborg *et al.* [73] to assert their opinion that foreign-body giant cells in arteritis have nonmacrophagal origin. However, it is most likely that the foreign-body giant cells, in the process of maturation into the Langhans-type ones, lose their ability to phagocytose A-actin. In the opinion of Nordborg, giant cells can present antigen, thereby initiating the subsequent diffusion of lymphocyte attack, leading to severe destruction and dilation of the arterial walls [74].

Central giant cell reparative granuloma. The central giant cell granuloma of jaws could be the version of giant cell tumor of bone, which has a certain specificity for this localization [4]. Nevertheless, the application of calcitonin successfully prevents relapses of granuloma after its surgical treatment [85], which can testify for the nontumor genesis of this disease. Among the possible reasons for the development of central giant cell granuloma, local injury was implicated with the reactive response to hemorrhage and Peget disease [108]. Histological study of the pathological section of granuloma showed fibrillar connective tissue, packed in locks, containing a large quantity of fibroblast-like mononuclear ovoid or spindel cells with elongated nuclei. In the stroma, a many small capillaries with frequent hemorrhages and rare lymphocytes are observed. Numerous osteoclast-like giant cells usually form clusters around the hemorrhagic foci and they also possess the ability of bone resorption [20].

Thus, the physiological role of MPs in the inflammation include the remodeling of extracellular matrix of granulomas and resorption of foreign particles and organic insoluble tissue deposits. Furthermore, they can participate in processes of utilization of apoptotic and necrotic cells during some infections, including viral ones [86]. Intracellular bactericidal activity could be elicited during phagocytosis of microbes by mononuclear macrophages following their fusion [68].

Giant Cell Tumors

In the international classification of tumor diseases, the giant cell tumors are placed in a separate division that includes giant cell tumors of bone and soft tissues. Nevertheless, all these diseases are the giant cell versions of reactive histiocytosis, which appear in a number of cases in mesenchymal tumors.

Giant cell tumor of bone. The basic cellular components of giant cell tumor of bone are osteoclast-like giant cells, mononuclear tumor stromal fibroblast-like cells, and histiocytes [125]. Tumor shows characteristic intensive capillarogenesis and extravascular arrangement of erythrocytes with the deposition of hemosiderin. Histological findings from the sections of metastastic spreading (for example, from the lungs) are usually identical to the primary focus of damage and contain MPs [11]. Mononuclear tumor cells, apparently, occur from the undifferentiated mesenchymal cells of bone marrow. The prolonged cultivation of cells, explanted from the giant cell tumor of bone (48 passages during 1 year) showed that, after only several passages, the culture consisted of fibroblast-like mesenchymal tumor cells, and macrophage cells disappeared after 1–3 weeks [55]. Thus, the assumption of Yoshida *et al.* [116] that the giant cell tumor of bone could be the tumor of the system of mononuclear phagocytes is of historical interest at present.

The osteoclast-like cells of giant cell tumor of bone are capable of forming resorption pits on the surface of a calcified matrix [28]. Roessner *et al.* [84] noted that the MPs of giant cell tumor of bone were analogous to the giant cells of granulomas in morphology. The difference in the expression of some antigens makes it possible to divide the giant cells of this tumor into two subgroups: (1) insensitive to calcitonin with the phenotype HLA-DR$^+$, and (2) sensitive to calcitonin with the phenotype HLA-DR$^-$ [82]. Insensitivity to calcitonin is determined by the disturbance of post-receptor events, which can lead to uncontrollable resorption of bone tissue and local osteolysis. MPs with this type of tumor are the reactive cellular elements, formed

Table 1. Tumorous and reactive cells of giant cell tumors.

Tumor	Tumorous cells	Reactive cells	Typical tissue depositions	References
Giant cell tumor of bone	Fibroblast-like cells	Histiocytes, osteoclast-like cells	Hemosiderin	[125]
Giant cell tumor of tendon	Unmaturate mesenchymal cells (fibroblast-like cells)	Histiocytes, giant MPs	Hemosiderin and lipids depositions	[8, 26]
Parosteal osteosarcoma	Fibroblast-like or osteoblast-like cells	Osteoclast-like cells	Hemosiderin	[91]
Chondroblastoma	Chondroblast-like cells	Osteoclast-like cells	Hemosiderin	[24, 49]
Giant cell tumors of skin	Fibroblast-like cells	MPs	Hemosiderin	[48]
Giant cell tumors of larynx	Fibroblast-like cells	Histiocytes, osteoclast-like cells	Not determined	[36]

in response to the cytokines secreted by tumor cells [33]. The supernatant of giant cell tumor of bone cultures possesses chemotactic activity against osteoclast precursors [124]. Cytokines such as M-CSF, ODF, TNF-α, interferon-γ, interleukin-1, -6, -11, -17, and TGF-β are found in giant cell tumor of bone [3, 46, 89, 99, 123, 124]. TGF-β, which is expressed by both tumor cells and reactive macrophage cells, plays a key role in recruiting osteoclasts and their precursors into the tumor. Bioactivation of TGF-β could be achieved by a plasmin proteolytic system, and the secreted tumor cell by matrix metal proteinase-2 and -3 [89]. TGF-β, in turn, increases the level of expression of monocyte chemoattractant protein-1 in the mesenchymal tumor cells [123]. Osteoclast-like cells have receptors to interleukin-6 and, furthermore, they themselves are capable of the producing this factor [75].

Chambers *et al.* [10] considered that the appearance of a large quantity of osteoclast-like cells in the giant cell tumor of bone is the result of macrophagal reaction to the abnormal bone matrix. In fact, the irregularity of microtopography on the surface of a bone matrix can induce fusion of macrophage precursors and MP formation [29]. The additional reason for the appearance of MPs in the giant cell tumor of bone, as in the case of a number of other tumors and fibro-inflammatory diseases, could lead to destructive processes in the extracellular matrix and diapedesis of erythrocytes [95]. Histologically, the giant cell tumor of bone has a structure similar to malignant fibrohistiocytoma [71]. Malignant fibrohistiocytoma, in turn, could be the variant of the fibrosarcoma, accompanied by reactive histiocytosis [59]. Thus, giant cell tumors of bone are localized in the bone fibroma or the fibrosarcoma (depending on the degree of the malignancy of process), accompanied by reactive histiocytosis with MP formation. The karyotypical analysis of tumor cells of giant cell tumor of bone and malignant fibrohistiocytoma reveals similar chromosomal disturbances/breakdowns: telomeric associations, change in the loci of 8p11, 19q13, and 20q13, and also the deletion of gene RB1 [2, 13, 57, 65, 91].

MPs in other giant cell tumors. Examination of the histological structure of giant cell tumors of other tissue localizations showed characteristic features of appearance of MPs (Table 1) [8, 24, 26, 36, 48, 49, 91, 125]: 1) MPs in the tumors are reactive cellular elements; 2) MPs are usually arranged next to the sinus-like blood vessels in the foci of hemorrhages and hemosiderin deposits. The development of sinus-like blood vessels (micro-aneurysms) is the consequence of resorption activity of MPs; 3) neoplastic cells are the cells of local mesenchyma with the phenotype of immature fibroblast-, chondroblast-, or osteoblast-like cells. The last assertion gives grounds for assumption that, in the giant cell fibrohistiocytomas, conditions, which facilitate the MP formation, are created that are probably similar to the ones in the granulomatous inflammation site (Figs. 1A and 1B).

MPs in Phylo- and Ontogenesis

Formation of MPs was observed upon introduction of foreign bodies in different classes of multicellular organisms. Metchnikoff, in his classical studies about the inflammation, observed MP formation as a result of fusion of phagocytes around the foreign body, introduced into the organism of the sea-star *Bipinnari asterigera* and also the adult form of the *Phyllirrhoe bucephala* [64]. Metalnikoff and Chorin detected the hemocyte fusion and the formation of giant cells around the tuberculosis bacillus inoculated to the caterpillars of *Pyrausta nubilalis* [62]. After 1–2 days, hemocytes were fused to the giant cells forming similar granulomas around the bacillus. In earthworms, at the site of the foreign body introduction, the appearance of "polynuclear plasmodiums" was observed by Zavarzin that occurred as a result of phagocyte fusion on the boundary of the necrotic zone. The encapsulated accumulation of foreign particles remained in the worm only in such a case, when capsule grew together with the body well. But, in the case of foreign particles surrounded by fibrous tissue, no union was observed and the particles were ejected through the spinal pore [119]. Garshin showed that the tuberculosis nodules could be ejected by the same pathway in human beings (see [96]). Hence, in insects, worms, and vertebrates, the polynuclear cells (derivatives of hemocytes and macrophages) can participate not only in the resorption

of foreign body but also in the process of resorption of their own tissues for the elimination of foreign body.

Ebergardt in 1907 described the accumulation of giant polynuclear cells around celloidin, implanted into the tortoise body. Polykaryons did not manifest the phagocytic activity, as they were located closely to the necrotic masses and the places of limited hemorrhage, and participated in the process of their resorption, and cells with a smaller quantity of nuclei (3–4 nuclei) were Podvisotskii-type necrophages [17].

The MP formation as a result of fusion of mononuclear cells could be an adaptive passage from the intracellular (dependent on the endocytosis) to extracellular (dependent on exocytosis) digestion for the more effective fulfillment of resorptive function. This functional self-organization of cells could be considered as recapitulation of the phylogenetic process of primary multicellular organism formation (polynuclear plasmodium). This is in correspondence with the hypothesis about the association of the clone of unicellular organisms into a complex polynuclear organism around the food object [102].

Participation of MPs in the physiological processes of resorption is an important component of the destructive phase of morphogenesis and is extended both to the provisory (for example, cartilage) and definitive (bone tissue) structures of the organism [60]. In this aspect, the fibrous tissue of inflammatory granuloma can be considered as the provisory structure, which is one of the substratum of MPs.

Formation of MPs both in the inflammation and during bone remodeling gives grounds to formulate the hypothesis that the inflammation participates in the physiological resorption of the bone and, generally, in the morphogenetic processes. Studitskaya [101], and also Chambers [10], noted that different agents and conditions (parathyroid hormone, mechanical pressure) can produce a change in the physico-chemical properties of bone tissue. In the opinion of Studitskaya, the development of osteoclasts in the ontogenesis is the manifestation of an inflammatory reaction [101]. A similar idea that "bone remodeling results from a microinflammatory reaction," was reported recently by Vignery [111] (see Fig. 1A and 1C). Alyoshin in 1941 reported that "an inflammation taking part in the formation of the definite structure of an organism is turned out to be a morphogenetic factor" [1]. From an evolutionary point of view, it appears that cellular and tissue processes, named inflammation, are the basis of a number of formatting processes both in embryogenesis and the development of adult vertebrates [107]. One of the first steps in vertebrate evolution could be the organization of highly-adjustable mechanisms of "incessant metamorphosis" of the skeleton, in which osteoclasts play a dominant role. The same regulatory mechanisms (for instance, the reactive mechanism of polynuclear plasmodius formation) could serve in the phylogenesis as a basis for the development of both the normal remodeling (osteoclastic bone resorption in the ontogenesis) and the inflammation processes (resorption of foreign body and/or tissues of its own organism in the focus of inflammation).

In 1911, Ebner [44] noted for the first time that biological structures, performing same functions, usually have certain similarities. In particular, the yolk epithelium of fish embryo has a structure of heteropolar polynuclear symplast, whose basal surface is extremely closely related to the thick network of blood vessels, and the apical is found in direct contact with the yolk. This symplastic structure of the yolk epithelium, adequate of its function, is connected with the resorption of the overall undifferentiated mass of yolk [93]. Zavarzin studied the structures of the human syncytiotrophoblast and arrived at a conclusion that the characteristic property of this polynuclear formation is the high erosional activity, which ensures the destruction of maternal tissues and the utilization of the products of their decomposition in the region of the developing embryo (histiotrophic nutrition) [120]. Contact with the maternal blood is necessary for retaining the usual morphological and functional properties of syncytiotrophoblast [122]. The surface of syncytiotrophoblast takes the form of a ruffled border, whose formation is caused by the need for an increase in the resorbing surface of the trophoblast.

In the polyploid cells with several nuclei (syncytiotrophoblast) or one segmented nucleus (megakaryocyte), the ratio of the overall surface of nuclei to their volume is more favorable for fulfilling the secretory function than in the mononuclear cell of the same ploidy [9]. The secretory activity of these cells could be considered as a process of 1) liberating ferments from MPs or syncytiotrophoblasts, 2) splitting entire plasma non-nucleate fragments (formation of thrombocytes from the megakaryocyte), or 3) splitting multinuclear cells, for example, trophoblastic cells, from the syncytiotrophoblast or the oligonuclear macrophages from the MPs [98, 102, 122]. Thus, MP formation could be referred to as a process of natural hybridization of cells directed towards the activation of synthetic and secretor functions of macrophages.

Interaction of MPs and Mesenchymal Cells

Cell-to-cell interaction between osteoblasts and osteoclast progenitors are essential for osteoclastogenesis. Cooperation of other mesenchymal cells and mononuclear macrophages is also indispensable for MP formation at inflammation and tumor growth. An examination of tumor and fibro-inflammatory diseases showed that the appearance of MPs is accompanied by the functional activation of mesenchymal cells (Fig. 1). The phenomenon of association of mesenchymal and macrophagal cells in the tumors of soft tissues is a reflection of the close functional relation between these two types of cells, as was also noted earlier by Chambers [10]. This phenomenon might be related to the removal of

necrotic (in inflammation process) or apoptotic (in normal morphogenetic process) cells by macrophages and the remodeling of extracellular matrix. The majority of tumor processes with the MPs could be described as the diverse variants of fibrohistiocytomas, from the benign to the malignant forms. Mesenchymal cells are tumor cells in fibrohistiocytomas. Depending on the tissue in which fibrohistiocytoma is developed, the frequency of detecting osteoclast-like cells varies [21, 30]. At present, a few reports support the fact that MPs in the giant cell tumors are formed in response to many factors like cytokines secreted by mesenchymal tumor cells [19, 33]. On the other hand, in granulomatous inflammations that could lead to the appearance of tumor-like formations, the proliferation of mesenchymal cells in the pathologic focus is supported by the factors of macrophagal origin [100]. On the basis of these ideas about the morphogenesis of tumor and fibro-inflammatory processes, with MPs, it could be assumed that there are bidirectional regulatory interactions in the system, "mesenchymal cell - macrophage," that participate in the formation of similar histological structures (for example, central giant cell granuloma and giant cell tumor of bone). These regulatory interactions result in macrophagal modulation of mesenchymal cells or in the modulation of the functional activity of macrophages and MPs by mesenchymal cells. The proliferation of mesenchymal tumor cells are determined by somatic mutations, or other factors as in the case of giant cell tumors. The cooperation of mesenchymal cells and macrophages observed with these diseases is the result of phylogenesis of both normal morphogenetic processes, and the reactions of tissues of the organism to the damage [76]. In the course of osteogenesis, positive signals for activating the osteoclast can proceed from osteocytes, which are in preapoptosis and apoptosis states. Resorption of bone tissue is the mechanism for deleting the nonfunctioning osteocytes, which were previously "embedded" into the bone tissue.

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References

1. Alyoshin, B. V. 1936. Investigation of an amphibian methamorphosis. 1. Resorption of larva tail as inflammation process. *Arch. Anat. Histol. Embriol.* (Rus.) **15:** 9–70.
2. Araki, N., U. Atsumasa, T. Kimura, H. Yoshikawa, Y. Aoki, T. Ueda, S. Takai, T. Miki, and K. Ono. 1991. Involvement of the retinoblastoma gene in primary osteosarcoma and other bone and soft tissue tumors. *Clin. Orthop.* **270:** 271–277.
3. Atkins, G. J., D. R. Haynes, S. E. Graves, A. Evdokiou, S. Hay, S. Bouralexis, and D. M. Findlay. 2000. Expression of osteoclast differentiation signals by stromal elements of giant cell tumors. *J. Bone Miner. Res.* **15:** 640–649.
4. Auclair, P. L., P. Cuenin, F. J. Kratochvil, L. J. Slater, and G. L. Ellis. 1988. A clinical and histomorphologic comparison of the central giant cell granuloma and the giant cell tumor. *Oral Surg. Oral Med. Oral Pathol.* **66:** 197–208.
5. Belosevic, M., D. S. Finbloom, P. H. Van der Meide, M. V. Slayter, and C. A. Nacy. 1989. Administration of monoclonal anti-IFN-γ antibodies *in vivo* abrogates natural resistance of C3H/HeN mice to infection with *Leishmania major*. *J. Immunol.* **143:** 266–274.
6. Black, M. M. and W.L. Epstein. 1974. Formation of giant cells in organized epithelioid cell granulomas. *Am. J. Pathol.* **74:** 263–274.
7. Boissy, P., I. Machuca, M. Pfaff, D. Ficheux, and P. Jurdic. 1998. Aggregation of mononucleated precursors triggers cell surface expression of $\alpha_v\beta_3$ integrin, essential to formation of osteoclast-like multinucleated cells. *J. Cell Sci.* **111:** 2563–2574.
8. Booth, K. C., G. S. Campbell, D. R. Chase, and L. Linda. 1995. Giant cell tumor of tendon sheath with intraosseous invasion: a case report. *J. Hand Surg.* **20A:** 1000–1002.
9. Brodskii, V. Ya. 1966. *Cellular Trophicity*, Nauka, Moscow, Russia.
10. Chambers, T. J. 1978. Multinucleated giant cells. *J. Pathol.* **126:** 125–148.
11. Cheng, J. C. and J. O. Johnston. 1997. Giant cell tumor of bone. Prognosis and treatment of pulmonary metastases. *Clin. Orthop.* **338:** 205–214.
12. Chiozzi, P., J. M. Sanz, D. Ferrari, S. Falzoni, A. Aleotti, G. N. Buell, G. Collo, and F. Di Virgilio. 1997. Spontaneous cell fusion in macrophage cultures expressing high levels of the P2Z/P2X7 receptor. *J. Cell Biol.* **138:** 697–706.
13. Choong, P. F. M., A. Rydholm, F. Mertens, and N. Mandahl. 1997. Musculoskeletal oncology. Advances in cytogenetics and molecular genetics and their clinical implications. *Acta Oncol.* **36:** 245–254.
14. Clarris, B. J., J. R. Fraser, C. J. Moran, and K. D. Muirden. 1977. Rheumatoid synovial cells from intact joints. Morphology, growth, and polykaryocytosis. *Ann. Rheum. Dis.* **36:** 293–301.
15. De Fife, K. M., C. R. Jenney, A. K. McNally, E. Colton, and J. M. Anderson. 1997. Interleukin-13 induces human monocyte/macrophage mannose receptor expression. *J. Immunol.* **158:** 3385–3390.
16. Dugast, C., A. Gaudin, and L. Toujas. 1997. Generation of multinucleated giant cells by culture of monocyte-derived macrophages with IL-4. *J. Leukoc. Biol.* **61:** 517–521.
17. Ebergard, I. I. 1907. The blood and connect tissue cells in tortoise in normal and inflammation conditions. Reprint, St.-Peterburg, Russia.
18. Erokhin, V. V. 1978. Morphofunctional state of the cellular elements of a tuberculous granuloma. *Arch. Pathol.* (Rus.) **40(6):** 37–44.

19. Flanagan, A. M. and T. J. Chambers. 1989. Osteoclasts are present in the giant cell variant of malignant fibrous histiocytoma. *J. Pathol.* **159:** 53–57.
20. Flanagan, A. M., B. Nui, S. M. Tinkler, M. A. Horton, D. M. Williams, and T. J. Chambers. 1988. The multinucleate cells in giant cell granulomas of the jaw are osteoclasts. *Cancer* **62:** 1139–1145.
21. Fletcher, C. D. M. 1990. Benign fibrous histiocytoma of subcutaneous and deep soft tissue: A clinicopathologic analysis of 21 cases. *Am. J. Surg. Pathol.* **14:** 801–809.
22. Franklin, R. M. 1958. Some observations on the formation of giant cells in tissue cultures of chicken macrophages. *Z. Natur. Forsch.* **13:** 213.
23. Fraser, W. J., Z. Haffeju, and K. Cooper. 1995. Rheumatic Aschoff nodules revisited: An immunohistological reappraisal of the cellular component. *Histopathology* **27:** 457–461.
24. Fukuda, T., M. Saito, and T. Nakajima. 1998. Imrint cytology of chondroblastoma of bone. A case report. *Acta Cytol.* **42:** 403–406.
25. Gadde, P. S. and E. A. Moscovic. 1994. Asteroid bodies: Products of unusual microtubule dynamics in monocyte-derived giant cells. An immunohistochemical study. *Histol. Histopathol.* **9:** 633–642.
26. Galliani, I., G. Cassiani, A. Valmori, and E. Falcieri. 2000. Giant cell tumor of tendon sheath: A light and electron microscopic study. *J. Submicrosc. Cytol. Pathol.* **2:** 69–76
27. Gillot, J. M., E. Masy, M. Davril, E. Hachulla, P. Y. Hatron, B. Devulder, and J. P. Dessaint. 1997. Elastase derived elastin peptides: Putative autoimmune targets in giant cell arteritis. *J. Rheumatol.* **24:** 677–682.
28. Goldring, S. R., S. F. Kroop, and A. H. Gorn. 1990. Stromal cells from human giant cell tumors of bone; production of factors involved in recruitment and differentiation of osteoclasts. *J. Bone Mineral Res.* **5:** 79.
29. Gomi, K., B. Lowenberg, G. Shapiro, and J. E. Davies. 1993. Resorption of sintered synthetic hydroxyapatite by osteoclasts *in vitro*. *Biomaterials* **14:** 91–96.
30. Gonzalez, S. and I. Duarte. 1982. Bening fibrous histiocytoma of the skin. A morphologic study of 290 cases. *Pathol. Res. Pract.* **174:** 379–391.
31. Gori, F., L. C. Hofbauer, C. R. Dunstan, T. C. Spelsberg, S. Khosla, and B. L. Riggs. 2000. The expression of osteoprotegerin and RANK ligand and the support of osteoclast formation by stromal-osteoblast lineage cells is developmentally regulated. *Endocrinology* **41:** 4768–4776.
32. Harris, H. 1974. *Nucleus and Cytoplasm.* Oxford Univ. Press, Oxford, U.K.
33. Hasegawa, T., T. Hirose, K. Seki, T. Sano, and K. Hizawa. 1993. Transforming growth factor alpha and CD68 immunoreactivity in giant cell tumors of bone: A study on the nature of stromal and giant cells, and their interrelations. *J. Pathol.* **170:** 305–310.
34. Hernandez-Pando, R., Q. L. Bornstein, D. Aguilar Leon, E. H. Orozco, V. K. Madrigal, and E. Martinez Cordero. 2000. Inflammatory cytokine production by immunological and foreign body multinucleated giant cells. *Immunology* **100:** 352–358.
35. Heymann, D., J. Guicheux, F. Gouin, M. Cottrel, and G. Daculsi. 1998. Oncostatin M stimulates macrophage-polykaryon formation in long-term human bone-marrow cultures. *Cytokine* **10:** 98–109.
36. Hinni, M. L. 2000. Giant cell tumor of the larynx. *Ann. Otol. Rhinol. Laryngol.* **109:** 63–66.
37. Hogan, L. H., W. Markofski, A. Bock, B. Barger, J. D. Morrissey, and M. Sandor. 2001. Mycobacterium bovis BCG-induced granuloma formation depends on gamma interferon and CD40 ligand but does not require CD28. *Infect Immun.* **69:** 2596–2603.
38. Ilina, K. B. 1972. The dynamics of macrophage development under the prolonged influence of environmental factors. *Arch. Anat. Histol. Embriol.* (Rus.) **63(12):** 98–110.
39. Kaiser, M., C. M. Weyand, J. Bjornsson, and J. J. Goronzy. 1998. Platelet-derived growth factor, intimal hyperplasia, and ischemic complications in giant cell arteritis. *Arthritis Rheum.* **41:** 623–633.
40. Kao, W. J., Q. H. Zhaao, A. Hiltner, and J. M. Anderson. 1994. Theoretical analysis of *in vivo* macrophage adhesion and foreign body giant cell formation on polydimethyloxane, low density polyethylene, and polyetherurethanes. *J. Biomed. Mater. Res.* **28:** 73–79.
41. Kao, W. J. 1999. Evaluation of protein-modulated macrophage behavior on biomaterials: Designing biomimetic materials for cellular engineering. *Biomaterials* **20:** 2213–2221.
42. Kazachkov, E. L., A. B. Fridman, and S. A. Friss. 1998. Granulomatous pleurisy after mammaplasty, induced by polyacrylamide gel. *Arch. Pathol.* (Rus.) **60(3):** 58–61.
43. Kazazi, F., J. Chang, A. Lopez, M. Vadas, and A. L. Cunningham. 1994. Interleukin 4 and human immunodeficiency virus stimulate LFA-1-ICAM-1-mediated aggregation of monocytes and subsequent giant cell formation. *J. Gen. Virol.* **75:** 2795–2802.
44. Khlopin, N. G. 1946. *The General Biological and Experimental Principles of Histology*, Acad. Nauk USSR, Moscow, Russia.
45. Khrushchov, N. G., M. A. Lange, and G. P. Satdykova. 1978. Electron-microscopic and autoradiographic study of giant cells of foreign bodies in the focus of aseptic inflammation. *Arch. Anat. Histol. Embriol.* (Rus.) **75(8):** 43–49.
46. Kito, M., H. Moriya, A. Mikata, K. Harigaya, T. Takenouchi, N. Takada, S. Tatezaki, and T. Umeda. 1993. Establishment of a cell line from a human giant cell tumor of bone. *Clin. Orthop.* **294:** 353–360.
47. Kodama, H., H. Akiyama, Y. Nagao, O. Akagi, and N. Nohara. 1988. Persistence of foam cells in rabbit xanthoma after normalization of serum cholesterol level. *Arch. Derm. Res.* **280:** 108–113.
48. Kutchemeshgi, M., R. J. Barr, and C. D. Henderson. 1992. Dermatofibroma with osteoclast-like giant cells. *Am. J. Dermatopathol.* **14:** 397–401.
49. Kyriakos, M., V. J. Land, L. Penning, and S. G. Parker. 1985. Metastatic chondroblastoma. Report of a fatal case with a review of the literature on atypical, aggressive, and malignant chondroblastoma. *Cancer* **55:** 1770–1789.
50. Lan, H. Y., X. Q. Yu, N. Yang, D. J. Nikolic-Paterson, W. Mu, R. Pichler, R. J. Johnson, and R. C. Atkins. 1998. *De*

novo glomerular osteopontin expression in rat crescentic glomerulonephritis. *Kidney Int.* **53:** 136–145.
51. Langhans, T. 1947. Uber reizenzellen mit wandstandingen kernen in tuberkeln und die fibrose form des tuberkels. *Arch. Pathol. Anat.* **42:** 332.
52. Lazarus, D., M. Yamin, K. McCarthy, E. E. Schneeberger, and R. Kradin. 1990. Anti-RMA, a murine monoclonal antibody, activates rat macrophages: II. Induction of DNA synthesis and formation of multinucleated cells. *Am. J. Respir. Cell Mol. Biol.* **3:** 103–111.
53. Leeuwenburgh, S., P. Layrolle, F. Barrere, J. de Bruijn, J. Schoonman, C. A. van Blitterswijk, and K. de Groot. 2001. Osteoclastic resorption of biomimetic calcium phosphate coatings *in vitro*. *J. Biomed. Mater. Res.* **56:** 208–215.
54. Leibovich, S. J. and R. Ross. 1975. The macrophage and the fibroblast, pp. 45–50. *In* R. van Furth (ed.), *Mononuclear Phagocytes in Immunity, Infection and Pathology*, Blackwell, Oxford, U.K.
55. Liu, T.-C., Z.-M. Ji, and L.-T. Wang, 1989. Giant cell tumors of bone: An immunohistochemical study. *Path. Res. Pract.* **185:** 448–453.
56. Lomri, A. and R. Baron. 1992. 1,25-Dihydroxyvitamin D_3 regulates the transcription of carbonic anhydrase II mRNA in avian myelomonocytes. *Proc. Natl. Acad. Sci USA* **89:** 4688–4692.
57. Mandahl, N., S. Heim, K. Arheden, A. Rydholm, H. Willen, and F. Mitelman. 1988. Rings, dicentrics, and telomeric association in histiocytomas. *Cancer Genet. Cytogenet.* **30:** 23–33.
58. Mariano, M. and W. G. Spector. 1974. The formation and properties of macrophage polykaryons inflammatory giant cells. *J. Pathol.* **113:** 1–19.
59. Martorell, M., C. Calabuig, A. Peydro-Olaya, A. Llombart-Bosch, M. J. Terrier-Lacombe, and G. Contesso. 1989. Fibroblast and myofibroblast participation in malignant fibrous histiocytoma of bone. Ultrastructural study of eight cases with immunohistochemical support. *Pathol. Res. Pract.* **184:** 582–590.
60. Mazhuga, P. M. 1995. The mononuclear and multinuclear cells of tissue resorption and their functional characteristics. *Cytol. Genet.* (Rus.) **29(1):** 9–18.
61. McNally, A. K. and J. M. Anderson. 1995. Interleukin-4 induces foreign body giant cells from human monocyte/ macrophages. Differential lymphokine regulation of macrophage fusion leads to morphological variants of multinucleated giant cells. *Am. J. Pathol.* **147:** 1487–1499.
62. Metalnikoff, V. S. and V. Chorin. 1929. On the natural and acquired immunity of *Pyrausta nubilalis*. *Intern. Corn. Borer. Invest. Sci. Repts.* **2:** 22–38.
63. Metchnikoff, I. I. 1888. Uber die phagocytäre rolle der tuberkelriesenzellen. *Virch. Arch. Pathol. Anat.* **113:** 63–69.
64. Metchnikoff, I. I 1968. *Lectures on the Comparative Pathology of Inflammation: Delivered at the Pasteur Institute in 1891*. Dover Pub. New York, U.S.A.
65. Molenaar, W. M., E. van den Berg, R. P. Veth, T. Dijkhuizen, and E. G. de Vries. 1994. Tumor progression in a giant cell type malignant fibrous histiocytoma of bone: Clinical, radiologic, histologic, and cytogenetic evidence. *Genes Chromosomes Cancer.* **10:** 66–70.
66. ori, K., N. Miyamoto, Y. Higuchi, K. Nanba, M. Ito, M. Tsurudome, M. Nishio, M. Kawano, A. Uchida, and Y. Ito. 2001. Cross-talk between RANKL and FRP-1/CD98 systems: RANKL-mediated osteoclastogenesis is suppressed by an inhibitory anti-CD98 heavy chain mAb and CD98-mediated osteoclastogenesis is suppressed by osteoclastogenesis inhibitory factor. *Cell Immunol.* **207:** 118–126.
67. Most, J., H. P. Neumaer, and M. P. Dierich. 1990. Cytokine-induced generation of multinucleated giant cells *in vitro* requires interferon-gamma and expression of LFA-1. *Eur. J. Immunol.* **20:** 1661–1667.
68. Most, J., L. Spotl, G. Mayr, A. Gasser, A. Sarti, and M. P. Dierich. 1997. Formation of multinucleated giant cells *in vitro* is dependent on the stage of monocyte to macrophage maturation. *Blood* **89:** 662–671.
69. Neale, S. D. and N. A. Athanasou. 1999. Cytokine receptor profile of arthroplasty macrophages, foreign body giant cells and mature osteoclasts. *Acta Orthop. Scand.* **70:** 452–458.
70. Nishii, T., N. Sugano, K. Masuhara, and K. Takaoka. 1995. Bipolar cup design may lead to osteolysis around the uncemented femoral component. *Clin Orthop.* **316:** 112–120.
71. Noguera, R., A. Llombart-Bosch, C. Lopez-Gines, C. Carda, and C. Fernandez. 1989. Giant-cell tumor of bone, stage II, displaying translocation t12;19. q13;q13. *Virch. Archiv A Pathol. Anat.* **415:** 377–382.
72. Nordborg, E., B. A. Bengtsson, and C. Nordborg. 1991. Temporal artery morphology and morphometry in giant cell arteritis. *APMIS* **99:** 1013–1023.
73. Nordborg, E., B. A. Bengtsson, and C. Nordborg. 1997. Morphological aspects of giant cells in giant cell arteritis: An electron-microscopic and immunocytochemical study. *Clin. Exper. Rheumatol.* **15:** 129–134.
74. Nordborg, E. 2000. Epidemiology of biopsy-positive giant cell arteritis: An overview. *Clin. Exp. Rheumatol.* **18(Suppl 20):** S15–S17.
75. Ohsaki, Y., S. Takahashi, T. Scarcez, A. Demulder, T. Nishihara, R. Williams, and G. D. Roodman. 1992. Evidence for an autocrine/paracrine role for interleukin-6 in bone resorption by giant cells from giant cell tumors of bone. *Endocrinology* **131:** 2229–2234.
76. Okulov, V. B. 1997. Current issues in immunotherapy of tumors in the context of macrophage reaction to tissue damage fixed through evolution. *Vopr. Onkol.* (Rus.) **43:** 102–106.
77. Orentas, R. J., L. Reinlib, and J. E. Hildret. 1992. Anti-class II MHC antibody induces multinucleated giant cell formation from peripheral blood monocytes. *J. Leukoc. Biol.* **51:** 199–209.
78. Papadimitiou, J. M., D. Sforcina, and L. Papaelias. 1973. Kinetics of multinucleated giant cell formation and their modification by various agents in foreign body reaction. *Am. J. Pathol.* **73:** 349–363.
79. Papadimitriou, J. M. and M. N. Walters. 1979. Macrophage polykarya. *CRC Crit. Rev. Toxicol.* **6:** 211–255.

80. Podvisotskii, V. V. 1889. The resorption of necrotic foci of liver tissue by giant cells, hepatophages. *Vrach* (Rus.) **3:** 1–12.
81. Prieditis, H. and I. Y. Adamson. 1996. Alveolar macrophage kinetics and multinucleated giant cell formation after lung injury. *J. Leukoc. Biol.* **59:** 534–538.
82. Rathod, H., A. J. Malcolm, J. I. Gillespie, V. Berry, J. Pooley, N. H. Piggott, and H. K Datta. 1994. Characterization of a subtype of primary osteoclastoma: extracellular calcium but not calcitonin inhibits aggressive HLA-DR-positive osteoclastoma possessing "functional" calcitonin receptors. *J. Pathol.* **175:** 293–299.
83. Rodrigues-Acosta, A., M. E. Giron, and I. Aguilar. 1992. Secretion of macrophage fusion factor MFF by schistosome egg granulomas maintained *in vitro*. *Scand. J. Immunol.* **35:** 633–636.
84. Roessner, A., D. B. V. Bassewitz, W. Schlake, G. Thorwesten, and E. Grundmann. 1984. Biologic characterization of human bone tumors. III. Giant cell tumor of bone. A combined electron microscopical histochemical, and autoradiographical study. *Pathol. Res. Pract.* **178:** 431–440.
85. Rosenberg, A. J., A. N. Bosschaart, J. W. Jacobs, J. J. Wirds, and R. Koole. 1997. Calcitonin therapy in large or recurrent central giant cell granuloma of the lower jaw. *Ned. Tijdschr. Geneeskd.* **141:** 335–339.
86. Ruibal-Ares, B., N. E. Riera, and M. M. E. de Bracco. 1997. Macrophages, multinucleated giant cells, and apoptosis in HIV+ patients and normal blood donors. *Clin. Immun. Immunopathol.* **82:** 102–116.
87. Russu, V. G. 1974. The functional role of Aschoff-Talalaevs granuloma cells. *Publ. Health Kishinev.* (Rus.) **2:** 37–41.
88. Saginario, C., H.-Y. Qian, and A. Vignery. 1995. Identification of an inducible surface molecules specific to fusion macrophages. *Proc. Natl. Acad. Sci. USA* **92:** 12210–12214.
89. Sakaguri, Y., S. Komiya, K. Sugama, K. Suzuki, A. Inoue, M. Morimatsu, and H. Nagase. 1992. Production of matrix metalloproteinases 2 and 3 stromelysin by stromal cells of giant cell tumor of bone. *Am. J. Pathol.* **141:** 611–621.
90. Savage, N. W. and P. A. Monsour. 1985. Oral fibrous hyperplasias and the giant cell fibroma. *Aust. Dent. J.* **30:** 405–409.
91. Sciot, R., I. Samson, P. Dal Cin, L. Lateur, B. van Damme, H. van den Berghe, and V. Desmet. 1995. Giant cell rich parosteal osteosarcoma. *Histopathology* **27:** 51–55.
92. Seitzer, U., H. Haas, and J. Gerdes. 2001. A human *in vitro* granuloma model for the investigation of multinucleated giant cell and granuloma formation. *Histol. Histopathol.* **16:** 645–563.
93. Shchelkunov, S. I. 1958. *Cellular Theory and Doctrine about Tissues*, Med. State Edit., Moscow, Russia.
94. Shionoya, S., S. Tsunekawa, and K. Kamiya. 1965. Elastolysis and giant cell reaction against disintegrated elastic fibres. *Nature* **207(4994):** 311–312.
95. Sidoni, A., S. Monico, P. D'Errico, and C. Simoncelli. 1994. Giant cell reparative granuloma of the maxillary bone: Case report and review of diagnostic criteria. *Pathologic* **86:** 552–556.
96. Sirotinin, N. N. 1981. *Evolution of Resistance and the Reactivity of Organism.* Medicine, Moscow, Russia.
97. Smetana, K. Jr. 1987. Multinucleated foreign-body giant cell formation. *Exp. Mol. Pathol.* **46:** 258–265.
98. Solari, F., C. Domenget, V. Gire, C. Woods, E. Lazarides, B. Rousset, and P. Jurdic P. 1995. Multinucleated cells can continuously generate mononucleated cells in the absence of mitosis: A study of cells of the avian osteoclast lineage. *J. Cell. Sci.* **108:** 3233–3241.
99. Sorimachi, K., K. Akimoto, K. Tsuru, T. Ieiri, and A. Niwa. 1995. The involvement of tumor necrosis factor in the multinucleation of macrophages. *Cell Biol. Intern.* **19:** 547–549.
100. Strukov, A. I. and O. Y. Kaufman. 1989. *Granulomatosis Inflammation and Granulomatosis Diseases.* Medicine, Moscow, Russia.
101. Studitskaia, A. 1936. The osteoclast formation in skeletogenic tissue in allantois. *Dokl. Acad. Sci. USSR* (Rus.) **4:** 329–332.
102. Studitskii, A. N. 1981. *Evolutional Morphology of Cell.* Nauka, Moscow, Russia.
103. Sutton, J. S. and L. Weiss. 1966. Transformation of monocytes in tissue culture into macrophages, epitheloid cells, and multinucleated giant cells. *J. Cell Biol.* **28:** 303–332.
104. Takahashi, N., G. R. Mundy, and G. D. Roodman. 1986. Recombinant human interferon-gamma inhibits formation of human osteoclast-like cells. *J. Immunol.* **137:** 3544–3552.
105. Takashima, T., K. Ohnishi, I. Tsuyuguchi, and S. Kishimoto. 1993. Differential regulation of formation of multinucleated giant cells from concanavalin A-stimulated human blood monocytes by IFN-γ and IL-4. *J. Immunol.* **150:** 3002–3010.
106. Talalaev, V. T. 1929. *Acute Rheumatism: Pathology, Pathologic Anatomy, and Clinical-Anatomical Classification.* State Med. Edit., Leningrad, Russia.
107. Tokin, B.P. 1955. *Immunity of the Embryos*, Leningrad State Univ., Leningrad, Russia.
108. Upchurch, K. S., L. S. Simon, A. L. Schiller, D. I. Rosenthal, E. W. Campion, and S. M. Krane. 1983. Giant cell reparative granuloma of Paget's disease of bone: A unique clinical entity. *Ann. Intern. Med.* **98:** 35–40.
109. Vaananen, H. K., H. Zhao, M. Mulari, and J. M. Halleen. 2000. The cell biology of osteoclast function. *J. Cell Sci.* **113:** 377–381.
110. Van der Rhee, H. J., C. P. M. de Winter, and W. T. Daems. 1979. The differentiation of monocytes into macrophages, epithelioid cells, and multinucleated giant cells in subcutaneous granulomas: Fine structure. *Cell Tissue Res.* **197:** 355–378.
111. Vignery, A. 2000. Osteoclasts and giant cells: Macrophage-macrophage fusion mechanism. *Int. J. Exp. Pathol.* **81:** 291–304.
112. Vignery, A., T. Niven-Fairchild, D. Ingbar, and M. Caplan. 1989. Polarized distribution of Na^+/K^+-ATPase in giant cells elicited *in vivo* and *in vitro*. *J. Histochem. Cytochem.* **35:** 1265–1271.

113. Vignery, A., M. Raymond, H.-Y. Qian, F. Wang, and S.A. Rosenzweig. 1991. Multinucleated rat alveolar macrophages express functional receptors for calcitonin. *Am. J. Physiol.* **261:** F1026–F1032.
114. Wolter, J. R. 1985. Cytopathology of intraocular lens implantation. *Ophthalmology* **92:** 135–142.
115. Woods, C., C. Domenget, F. Solari, O. Gandrillon, E. Lazarides, and P. Jurdic. 1995. Antagonistic role of vitamin D3 and retinoic acid on the differentiation of chicken hematopoietic macrophages into osteoclast precursor cells. *Endocrinology* **136:** 85–95.
116. Yoshida, H., M. Akeho, and T. Yumoto. 1982. Giant cell tumor of bone. Enzyme histochemical, biochemical and tissue culture studies. *Virch. Archiv A Path. Anat.* **395:** 319–330.
117. Yuasa, T., Y. Miyamoto, K. Ishikawa, M. Takechi, M. Nagayama, and K. Suzuki. 2001. *In vitro* resorption of three apatite cements with osteoclasts. *J. Biomed. Mater. Res.* **54:** 344–350.
118. Zakhar'evskaia, M. 1937. The changes and destination of the foreign-body giant cells. *Arch. Biol. Nauk.* (Rus.) **47:** 100–109.
119. Zavarzin, A. A. 1935. To comparative histology of blood and connect tissue. XI. The inflammatory formation of the connect tissue in the earthworm *Allobophora Calliginosa*. *Arch. Biol. Nauk.* (Rus.) **37:** 527–551.
120. Zavarzin, A. A. 1967. *The DNA Synthesis and Kinetic of Cellular Populations in Mammalians*, Nauka, Leningrad, Russia.
121. Zelger, B., R. Cerio, G. Orchard, and E. Wilson-Jones. 1994. Juvenile and adult xanthogranuloma. A histological and immunohistochemical comparison. *Am. J. Surg. Pathol.* **18:** 2126–2135.
122. Zemkova, Z. P. 1957. The growth of trophoblast in fibrinoid substance of human placenta. *Dokl. Acad. Nauk. USSR* (Rus.) **114:** 893–895.
123. Zheng, M. H., Y. Fan, A. Smith, S. Wysocki, J. M. Papadimitriou, and D. J. Wood. 1998. Gene expression of monocyte chemoattractant protein-1 in giant cell tumors of bone osteoclastoma: Possible involvement in CD68+ macrophage-like cell migration. *J. Biol. Biochem.* **70:** 121–129.
124. Zheng, M. H., Y. Fan, S. J. Wysocki, A. T. Lau, T. Robertson, M. Beilharz, D. J. Wood, and J. M. Papadimitriou. 1994. Gene expression of transforming growth factor-betta1 and its type II receptor in giant cell tumors of bone. *Am. J. Pathol.* **145:** 1095–1104.
125. Zheng, M. H., P. Robbins, J. Xu, L. Huang, D. J. Wood, J. M. Papadimitriou. 2001. The histogenesis of giant cell tumour of bone: A model of interaction between neoplastic cells and osteoclasts. *Histol. Histopathol.* **16:** 297–307.