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Stromal-Hematopoietic Interrelationships: Maximov's Ideas and Modern Models

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The idea of stromal-hematopoietic cell interactions was the essential part of Alexander Maximov's theory of hematopoiesis, which he proposed more than 60 years ago. According to Maximov (see Figs. 1–4), committed hematopoietic precursors descend from the hematopoietic stem cells due to local impacts generated by marrow stroma; this creates the conditions for hematopoietic cell differentiation [1]. Maximov's theory was far ahead of his time, and, though Maximov was highly respected in the scientific community, his concept of local "differentiation conditions" operative in hematopoiesis was met with particular skepticism. Today, Maximov's idea raises no doubt; in fact, it constitutes the essence of the problem of hematopoietic microenvironment (HME). What provokes discussions in modern hematology is the exact types of stromal cells responsible for HME and the mechanisms of stromal-hematopoietic cell interactions. Maximov assumed that the stromal cells in question were stromal fibroblasts (reticular cells), but for a long time many experimental hematologists denied this. Only recently has it been possible to apply two experimental models for checking the microenvironmental functions of marrow fibroblasts. The first model is the transfer of HME by heterotopic transplantation of marrow cells; the sccond is the establishment of HME in vitro by stromal cell underlayers in Dexter cultures.

Heterotopic transplantation of marrow cells results in the formation of marrow organs covered by a bone capsule [2–5]. Their hematopoietic cells are of the recipient origin [6], indicating that engraftment of some category of marrow cells results in the formation of bone and an HME suitable for population by hematopoietic cells and for their proliferation and differentiation. Heterotopic marrow can be retransplanted repeatedly with similar results, provided the recipients are compatible with H-2 antigens of the initial donor, not of the intermediate recipients [7,8]. This means that HME is transferred by engraftment of the marrow cells which remain unreplaced by the recipient cells. Chromosome typing of clonogenic stromal fibroblasts (CFUf) of the heterotopic marrow confirmed their donor origin [9,10], and the problem was to check whether stromal fibroblasts were able to transfer HME when grafted heterotopically.

The in vitro descendents of CFUf after several passages compose diploid fibroblast culturcs [11–13]. Tested by heterotopic transplantation, they were found to form bone marrow organs, while engraftment of cultured spleen fibroblasts (the descendents of spleen CFUf) produced lymphoid organs [14,15]. Thus, cultured marrow fibroblasts appear to be able to transfer bone marrow HME. Depending on the origin of marrow fibroblast cultures (the source CFUf being from red or yellow marrow), their engraftment transferred not only the general pattern of HME, but also such details as the density of hematopoietic cells in a would-be marrow [16].

Cultured marrow fibroblasts produce hematopoietic growth factor (M-CSF, G CFS, GM-CFS, BFUf- and mixed-colony-CSF) which can be detected in the culture medium [17–20]. They regulate proliferation and differentiation of GMCFU: their stimulatory effects were noted when the target marrow contained few spontaneous colonies, the inhibitory effects when large numbers of spontaneous GM-CFU were present [21]. Hematopoietic growth factors are also produced by cloned lines of marrow fibroblasts [22]. However, the direct proof of in vitro microenvironmental competence of marrow fibroblasts was their ability to establish HME in Dexter-type cultures. It has been shown [23] that when used as underlayers, the passaged murine marrow fibroblasts, free from macro phages and endothelial cells, supported hematopoiesis if seeded with stromal cell-depleted marrow suspensions.

Thus, cultured marrow fibroblasts transfer HME, release hematopoietic growth factors in vitro, and are capable of presenting them in a proper way to support hematopoiesis in cultures. This confirms Maximov's hypothesis of the role of marrow fibroblasts in hematopoiesis.

The population of marrow fibroblasts is probably a heterogeneous one, and there is no evidence that marrow fibroblasts which produce or present hematopoietic growth factors are the same cells which transfer HME, and vice versa. It may well be that there are several subpopulations of marrow fibroblasts with different microenvironmental functions. At present, fibroblasts including those from nonhematopoietic and hematopoietic organs look much alike, reminiscent of the situation with lymphocytes in Maximov's time. The main and most conclusive sine of fibroblasts (mechanocytes) is interstitial collagen types I and III synthesis, and few markers of their phenotype and genetic diversity have been so far ascertained. The diversity does exist, for instance, between marrow as compared with spleen fibroblasts, which is proved by the results of their heterotopic transplantation. The next question regarding HME seems to be the diversity of marrow fibroblasts including their clonogenic precursor cells.

In primary cultures of marrow cell suspensions the CFUf (CFCf) form adherent-cell colonies which are cell clones [24,25]. The colonies are composed of fibroblasts which synthesize type-I

and -III collagen and fibronectin and lack macrophage markers and VIII-factor-associated antigen [26–30]. Morphologically, the colonies are distinctly heterogeneous within each culture. Some are composed of elongated or blanket-like fibroblasts or of a mixture of both; the colonies may include fat cells or have a mineralized intercellular matrix [39]. These differences can hardly be regarded as markers of CFCf, the diversity not beeing stable at passaging and recloning.

In situ CFCf are outside the cycle arrested in G0 [31]. Marrow fibroblasts possess PDGF receptors [32] and in medium with platelet-poor plasma their proliferation and the CFUf colony formation requires PDGF [33,34]. It is believed that serum growth factors, which include PDGF, are sufficient for recruitment of CFCf into the cycle and that CFUf colony formation in serum-supplemented medium does not require additional growth stimulation. Yet this is probably not the case.

The efficiency of CFUf colony formation (CFEf) drops close to zero in low-density marrow cultures if they are depleted of nonadherent cells: 85% of CFCf do not proliferate at all or pass through one to three cell doublings (Fig. 1). On the other hand, the CFEf increases dramatically when such adherent marrow cell cultures are supplemented with irradiated marrow feeder cells or with platelets. This colony-stimulating activity is not replaced by additional PDGF and is expressed only in the serum-rich medium. Being stimulated by platelets each fibroblast precursor present in marrow cell suspensions turns out to be a clonogenic stromal cell (Fig. 1).

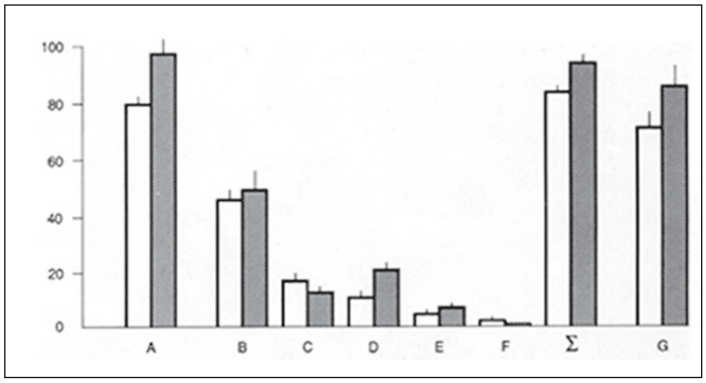


Figure 1. CFUf colony formation in mice adherent marrow cell cultures

Cultures were initiated by injecting 5×10^5 mechanically (white columns) or 5×10^4 trypzinised (black columns) marrow cells per culture flask (25 cm^2). Two hours after explantation the nonadherent cells were decanted from all cultures and further cultivation accomplished in aMEM medium plus 20% embryonal calf serum, part of the cultures (G) being additionally suplemented with 107 irradiated (60 Gy) marrow cells. Abscissa: A – E – fibroblast foci, fibroblast colonies and single fibroblasts in feeder non-supplemented cultures. A – single fibroblasts in one day cultures; B – F – 10 day cultures. B – single fibroblasts, C – two fibroblasts foci, D – three-eight fibroblasts foci, E – nine-forty nine fibroblasts foci, F – fibroblast colonies composed of 50 and more fibroblasts, Σ-sum of B, C, D, E and F per culture. G – fibroblasts colonies in 10 days feeder-supplemented cultures. Ordinate: mean numbers (M±m) of single fibroblasts, fibroblast foci and fibroblast colonies for 3–5 cultures.

Thus, nonstromal marrow cells which accompany CFCf in marrow cultures (probably megakaryocytes) provide growth-stimulating factors for CFUf colony formation. There are indications that CFCf are sensitive also to other growth-stimulating factors which induce the formation of fibroblast colonies with a different composition of matrix proteins. It has been reported [35] that marrow cells cultured in methylcelluloseclotted plasma with cortisone and PHA-stimulated leukocyte-conditioned medium produced fibroblast colonies with collagen type IV and laminin, in addition to collagen types I and III and fibronectin present in CFUf colonies, in liquid cultures with the serum-supplemented medium. The differences suggest either that there is a diversity of CFCf, which also require different colony-stillulating factors, or that the same CFCf can generate different descendents, depending on the stimulating factors used to induce colony formation.

Marrow CFCf diversity was demonstrated with regard to their proliferative and differentiative potencies. Only a small portion (10%) of single CFUf colonies transferred HME when grafted heterotopically, i. e., formed bone marrow organs [36]. At least 30% of CFCf appeared to be highly proliferative cells which provide single-colony-derived fibroblast cultures with 20–30 population doublings. When tested by transplantation of cells in diffusion chambers, 20% of these cultures formed simultaneously bone, cartilage, and reticular-like tissue, 30% formed only bone, and 27% only reticular-like tissue. The number of osteogenic units in late passages of cultured fibroblasts exeeded by far the total numbers of the initially explanted marrow cells, indicating that osteogenic precursors intensively multiplied within cultures [37]. There are reasons to consider CFCf with osteochondrogenic potencies as being osteogenic stem cells [38,39]. One can assume that some of them are the progenitors of a marrow stromallineage which includes committed osteogenic precursors, mature bone cells, and microenvironmentally competent fibroblasts (reticular cells).

The assumption is backed up by the obligatory association of HME transfer with bone formation, which applies to heterotopic transplantation of both freshly isolated marrow and single-CFUf-derived fibroblast colonies. In the heterotopic marrow the CFUf are of donor origin [9,10], and it is reasonable to assume that the same applies to the microenvironmentally competent reticular cells. However, the ability of fibroblasts from single CFUf-colony-derived heterotopic bone marrow organs to support hematopoiesis in vitro, and their donor origin (which would be the proof of the above speculation) was not tested up to now. Anyway, the hierarchy of marrow precursors awaits further studies.

As far as Maximow's contribution to the problems of HME is concerned, it is impossible to omit his last work, entitled "Cultures of blood leukocytes. From lymphocyte and monocyte to connective tissue." [40]. It describes the formation of fibroblasts in plasma-clot cultures of guinea-pig blood cells. Subsequently, his results were put in question on the grounds of two possible objections, namely that the source of fibroblasts might be fragments of vessel walls which contaminate the blood during sampling, and that the cells in question were not fibroblasts (for references, see [41]).

The first objection proved to be invalid when a CFUf colony assay was carried out with blood cells. It turned out that the incidence of CFUf colonies in guinea-pig and rabbit leukocyte cultures did not change with the number of punctures performed for blood sampling [42]. It has also been shown that fibroblasts in

blood-derived CFUf colonies synthesize collagen type I [43] and lack VIII-factor-associated antigen and macrophage determinant MacI [44], which confirms their fibroblast nature (Fig. 2, 3).

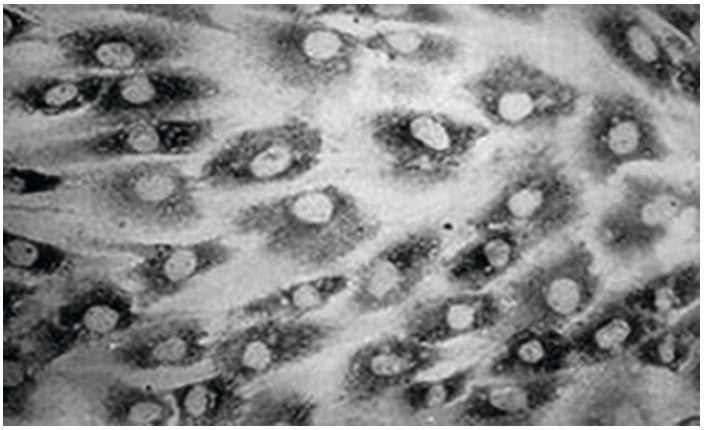
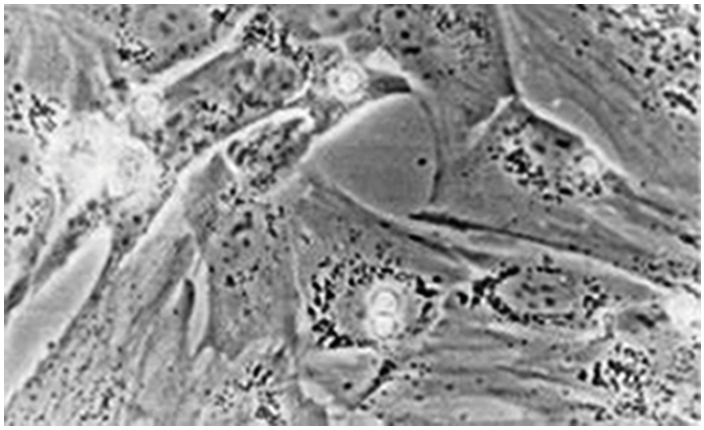
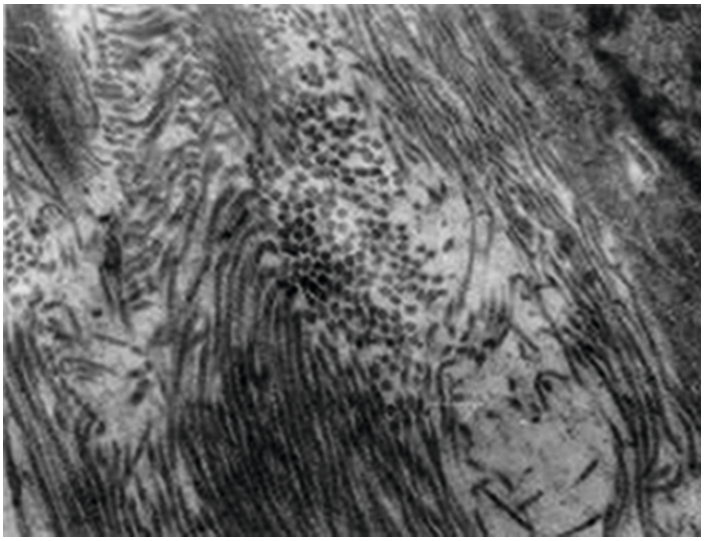


Figure 2. Type I collagen in 12 day CFUf colony of guinea pig periferal blood leukocytes.
A. Anticollagen antiserum, immunoperoxidase reaction



B. Live culture



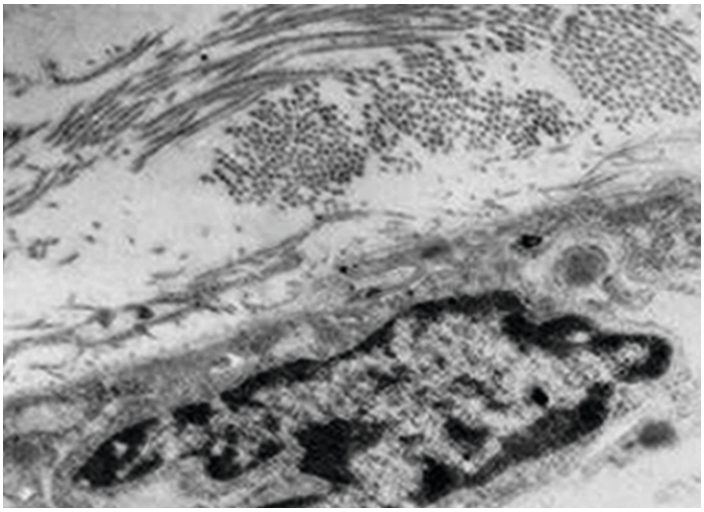


Figure 3 A, B. Fibroblasts and collagen fibrils in 16 day CTUf colonies of rabbit periferal blood leukocytes. E. M.

It remains unknown from where CFUf migrate into blood, where they settle (if they do), and why blood-derived CFUf are not detectable in some mammals, including human beings. The presence of fibroblast precursors in blood discovered by Maximov is related to many unsolved problems of HME, in particular, to the possibility of CFUf repopulation; CFUf circulation in blood does not prove it at all.

Figure 4.
Professor Alexander Maximov

The story of the circulating fibroblast precursor cells demonstrates once again that not only Maximov's ideas, but also his experimental results are so topical that Professor Alexander Maximov almost remains a participant of present-day research (Fig. 5).

Figure 5. Maximov in his tissue culture laboratory in the Military Medical Academy in Petersburg (1915).

A. Preparation of plasma for plasma-clot cultures

Figure 5. B. Placing tissue fragments in culture medium

Figure 5. C. Kaissug hangrug-drop cultures in hallow-ground microscope slides

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От редакции

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Взаимоотношения между гемопоэтическими стволовыми клетками и клетками стромы: идеи Максимова и современные модели

А.Я. Фриденштейн

Резюме/ От редакции

Если А.А. Максимова считают первооткрывателем гемопоэтических стволовых клеток, то А.Я. Фриденштейна можно смело назвать первооткрывателем мезенхимальных (или, как их позднее стали называть, стромальных) клеток костного мозга. К сожалению, должный резонанс его работы вызывали

только спустя несколько десятков лет, но и в тот момент современники смогли по достоинству оценить их основополагающий характер.

С конца 60х годов Фриденштейн и его сотрудники проводили глубокие исследования в области стромальных клеток костного мозга различных видов животных, включая человека. При этом были разработаны методы, практически не претерпевшие изменений с того времени, включая анализ формирования колоний стромальных клеток костного мозга, образование штаммов и трансплантация стромальных клеток in vivo. Фриденштейн описал дифференциацию стволовых клеток костного мозга в клетки костной ткани, хряща и жировой ткани, а также в клетки стромы костного мозга. Кроме того, он был основоположником теории, согласно которой стромальные клетки костного мозга являются полипотентными клетками-предшественницами.

Эксперименты Фриденштейна впоследствии были повторены другими исследователями, в частности Weissman и соавт. (Irving L. Weissman et al. Endochondral ossification is required for haematopoietic stem-cell niche formation. Nature 457, 490-494, 2009) и Bianco и соавт. (Paolo Bianco et al. Self-Renewing Osteoprogenitors in Bone Marrow Sinusoids Can Organize a Hematopoietic Microenvironment. Cell, Volume 131, Issue 2, 324-336, 2007).

Особое внимание в своей работе Фриденштейн уделял исследованиям Максимова и развитию его идей. Анализируя его данные в статьях, докладах и лекциях, сопоставляя их с результатами, полученными к тому времени на моделях селезеночных и агаровых колоний, он возродил (сформировал) у своих современников интерес к научным работам и проблемам, поднятых в них, а понятие «стволовые клетки» широко вошло в научную терминологию. Ярким примером тому является его статья «Взаимоотношения между гемопоэтическими стволовыми клетками и клетками стромы: идеи Максимова и современные модели» (Friedenstein A.J. Stromal-hematopoietic interrelationships: Maximov‘s ideas and modem models. Haematol. Blood Transfus. 1989; 32: 1 59-67).

Эта работа посвящена оценке взаимодействий между гемопоэтическими и стромальными клетками костного мозга, а также определению гистологического типа этих „стромальных клеток“.

Идея такого взаимодействия была ключевым моментом теории гемопоэза, разработанной А.А.Максимовым в начала XX века. Согласно этой теории, коммитированные предшественники гемопоэтических клеток образуются из стволовой клетки под действием локальных стимулов со стороны стромы костного мозга, которые создают условия для их дифференцировки. Работы Максимова намного опередили свое время и были встречены современниками достаточно скептически. Сегодня идеи Максимова признаны мировой наукой. В своей статье, опубликованной в данном номере журнала, Фриденштейн пытается ответить на вопрос, к какому именно гистологическому типу принадлежат эти стромальные клетки, играющие столь существенную роль в гемопоэзе а также установить механизм их взаимодействия с гемопоэтическими клетками в костном мозге. Как и Максимов, Фриденштейн особое внимание уделяет фибробластам, доказывая их роль в качестве важнейшего элемента микроокружения в костном мозге. Свои заключения он сопровождает результатами, полученными на двух экспериментальных моделях: гетеротопической трансплантации клеток костного мозга и фидерных эффектах стромальных клеток в культурах Декстера. Фриденштейн также подтверждает образование фибробластов при культивировании сгустка, получаемого при свертывании плазмы. Впервые это явление было описано Максимовым, однако подверглось значительной критике и не было воспринято всерьез. Фриденштейн же доказал, что формирование фибробластов в культуре не связано с изначальным присутствием в плазме фрагментов сосудистой стенки, которые могли быть их источником, а также доказал гистологическую принадлежность образующихся de novo клеток к классу фибробластов.

Рассматриваемая статья представляет собой своеобразное связующее звено между идеями Максимова и современными подходами, которые развивали А.Я.Фриденштейн и его научная школа. Представленная работа является по сей день актуальной и важной для специалистов в области гематологии и трансплантологии.