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STUDY OF MORPHOCYTOCHEMICAL AND IMMUNOPHENOTYPIC FEATURES OF ACUTE LEUKEMIA STEM CELLS

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The immunophenotypic profile of hematopoietic stem cells (HSC) and hematopoietic precursor cells as well as leukemic stem cells (LSC) has been extensively studied in several laboratories worldwide. The results of our studies suggest that the standard panel for classification of acute leukemias should be supplemented with several new markers allowing us to identify more precisely the different forms of the leukemias being of the closely related origin, for example AML M6b and AML M7. The common bipotent LSC in AML M7 of low grade and AML M6b may exist analogous to precursor cell common for megakaryocytopoiesis and erythropoiesis. We have also found the similarity between blast cells in pro-B-ALL [t (4;11), 11q23] and AML M5a [t (9;11), 11q23]. Such similarity of immunophenotype and cytogenetic abnormalities in blast cells in pro-B-ALL and AML M5a may be considered as hint explaining the cases of AML M5a as a recurrence of leukemia in children with originally diagnosed pro-B-ALL.
Key Words: **leukemic stem cell, acute leukemia, classification, immunophenotype.**

The characterization of leukemic stem cells (LSC) and their potential differences as compared to normal hematopoietic stem cells (HSC) are important for understanding the process of malignant transformation.

The multistage process of hematopoiesis resulting in the appearance of the mature cells of the peripheral blood (erythrocytes, leukocytes, platelets) is maintained by HSC. The existence of the common multipotent hematopoietic stem cell (MHSC) is a fundamental principle of the modern unipotent scheme of hematopoiesis [1–3]. MHSCs possess the self-renewal abilities, high proliferative potential and are capable for maintaining myelo- and lymphopoiesis.

As early as in 1961, Till and McCulloch [4] elaborated the technique for cloning the hematopoietic cells in the spleen of lethally irradiated mouse and gave the first experimental evidence that HSC in fact exist. Since that time, the particular progress has been made in defining the role of factors produced by stromal microenvironment (cytokines and interleukins) in controlling proliferation and differentiation of hematopoietic progenitor cells.

The HSC population is a heterogeneous one subdividing into long-term HSCs (LT-HSCs) and short-term HSCs (ST-HSCs). While ST-HSCs have limited self-renewal capacity giving rise to myeloid and lymphoid lineages within about 8 weeks, LT-HSCs are capable of self-renewal giving rise to long-term bone marrow culture capable of differentiating to myeloid and lymphoid lineages. HSC gives rise to oligolineage-restricted progenitors with limited ability of self-renewal: the common progenitor cell of myelopoiesis and the common progenitor cell of lymphopoiesis. The progenitor cells in turn give rise to the cells with most limited differentiation potential and finally to the functionally mature cells.

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Abbreviatios used: HSC – hematopoietic stem cells; LSC – leukemic stem cells; LT-HSC – long-term HSC; MHSC – multipotent HSC; ST-HSC – short-term HSC.

In the generally recognized scheme of the hematopoiesis [2], HSC as well as progenitor cells class II and III were depicted as the empty circles. Chertkov and Vorobiov [3] in their scheme of the hematopoiesis predicted that depending on the phase of cell cycle HSC and progenitor cells possess the cytomorphological features of blasts or lymphocyte-like cells.

Cytomorphological and cytochemical features of HSC and hematopoietic progenitors. Besides the analysis of cell population in splenic colonies developed in the lethally irradiated mouse upon grafting the bone marrow cells and the study of the least differentiated cells in granulocytic and monocytic-macrophage colonies and clusters *in vitro*, another approach turned out to be promising.

Prof. Butenko in the monograph "Hematopoietic stem cells and leukemia" published in Ukraine [5] presented the cytomorphological features of the presumable "candidates" for hematopoietic stem cells. In R.E. Kavetsky Institute of Oncology Problems (Kyiv, Ukraine), the cytological and cytochemical study of HSC and progenitor cells has been performed. In particular, the early stages of the embryonic hematopoiesis in human and mouse were studied, especially the early hematopoietic cells in the yolk sac, which later migrate to liver and populate bone marrow, spleen, thymus, and lymph nodes [6].

Earlier we have demonstrated that the hematopoietic progenitor cells of classes II–III (according to Chertkov and Vorobiov's scheme of hematopoiesis) regarded earlier as morphologically non-distinguishable turned out to possess some marker cytochemical features pertinent to more mature cells of granulocytic lineage (positive peroxidase and chloracetate esterase activity); monocytic-macrophage lineage (high non-specific alpha-naphtyl acetate esterase activity); megakaryocytic lineage (positive acetylcholin esterase activity) and T-lymphocyte lineage (granular or dot-like acid phosphatase reaction) [6]. Our findings together with the results of several biochemical studies performed in former USSR may be regarded as the retrospective rationale substantiating the use of the cytochemical techniques

for delineating the various forms and cytological variants of the acute myeloid and lymphoid leukemias originating from the transformation and the clonal proliferation of various types of the hematopoietic progenitor cells.

Recently, the immunophenotypic profile of HSC and hematopoietic progenitor cells has been extensively studied. In particular, the phenotype of the pluripotent stem cell is now delineated as $CD34^+$, $CD90^+$, $CD172a^+$, $CD173^+$, $CD174^+$, $CD175^+$, $CD176^+$, $CD224^+$, $CD227^+$, $CD239^+$, $HLA\text{-}DR^+$. Accordingly, the phenotype of myeloid stem cells is $CD33^+$, $CD34^+$, $CD38^+$, $CD117^+$, $CD123^+$, $CD133^+$, $HLA\text{-}DR^+$, $TdT^{+/-}$, $CD13^{+/-}$, $CD7^{+/-}$, $CD230^+$; the phenotype of lymphoid stem cells is $CD10^+$, $CD34^+$, $CD38^+$, $CD117^{+/-}$, $CD124^+$, $CD127^+$, $HLA\text{-}DR^+$, TdT^+. In fact, only identified markers are given in the listed phenotypes above, and the exact sets of the phenotypic markers of HSC and hematopoietic progenitor cells in all lineages are still to be elucidated [7, 11–13].

Leukemic stem cells. Leukemias as well as other cancers represent the clonal processes. The leukemic cells infiltrating the bone marrow as well as the leukemic cells detected in the blood and in the organs of the body are the descendents of the single cell undergoing the malignant transformation (HSC or committed progenitor cell). There are many functional similarities between the LSC and solid tumor stem cells. The milestones of the study of HSC and cancer stem cells are summarized chronologically in Table 1.

The experimental evidence for the existence of clonogenic or LSC was obtained in 1997 in heterotransplantation experiments in SCID mouse with severe combined immunodeficiency (lack of B- and T-cells) and NOD/SCID (nonobese diabetic x SCID) mouse (in addition to SCID mouse NK cells are lacking, the macrophage activity is not detected neither the complement activation) [12].

Table 1. Milestones of the studies developing the concept of cancer stem cell

1961	Experimental evidence of polypotent hematopoietic stem cells	Till and McCulloch, 1961 [4]
1967–1981	Evidence of CML and AML clonality	Fialkow et al., 1967; Fialkow, 1981 [8, 9]
1972–1973	Elaboration of modern unipotent scheme of hematopoiesis	Mathe et al., 1972; Chertkov and Vorobiov, 1973 [2, 3]
1975–1990	The technology for production of monoclonal antibodies against lineage-specific and differentiation antigens of leukocytes	Kohler, Milstein, 1975 [10]
1988	Use of mouse with severe combined immunodeficiency (SCID) for studying human hematopoietic cells	Weissman (ref. Passegue et al., 2003) [11]
1989–1994	Use of SCID mouse and mouse with SCID and non-obese diabetes (NOD/SCID) for studying leukemic cells	Dick et al., 1996 [12] Passegue et al., 2003 [11] Huntly, Gilliland, 2005 [13]
1997	Identification of leukemic stem cell	Dick et al., 1996 [12]
2003	Identification of stem cell in breast cancer	Al-Hajj et al., 2003 [14]
2004	Identification of human brain tumor initiating cells	Singh et al., 2004 [15]
2005	Prostate cancer stem cells	Collins and Maitland, 2005 [16]
2005	Epithelial ovarian cancer stem cells	Bapat et al., 2005 [17]
2005	Osteogenic sarcoma stem cells	Gibbs et al., 2005 [18]
2005	Melanoma stem cells	Fang et al., 2005 [19]
2007	Neuroblastoma stem cells	Ross, Spengler, 2007 [20]
2008	Lung cancer stem cells	Eramo et al., 2008 [21]

Upon transplantation of leukemic cells from bone marrow and peripheral blood of AML patients (regardless FAB type), most leukemic blasts are not capable to proliferate. Only a small subset of leukemic cells in the

Table 2. Markers of normal and transformed hematopoietic stem cells and progenitor cells.

Antigen	Structure and function	Normal expression	Expression in hematoblastoses
CD19	Belongs to IgSF family, takes part in signal transduction controlling B-cell activation and differentiation	B-cell progenitors; mature B-cells	B-cell leukemias and lymphomas
CD34	Sialomucin involved in intercellular adhesion	Hematopoietic stem cells and progenitor cells	AML and ALL; leukemic stem cells
CD38	ADP-ribosyl cyclase; takes part in the control of cell activation and proliferation	Progenitor cells of myelopoiesis, T and B cells, monocytes, activated T and B cells, plasma cells	Non-clonogenic cells in AML, cells in multiple myeloma
CD45RA	Common leukocyte antigen, regulator of leukocyte activation	B cells, activated T cells, monocytes, macrophages	B cell leukemia
CD90 (Thy-1)	Participate in differentiation of HSC and neuronal cells	HSC, T cells, fibroblasts, stromal cells	Blasts in several forms of AML, rare cases of ALL
CD123 (IL-3Rα)	α-subunit of IL-3 receptor	Progenitor cells, endothelial cells, stromal cells	Blasts in AML; leukemic stem cells
HLA-DR	Histocompatibility antigen class II	B cells, antigen-presenting cells, progenitor myeloid cells	Blasts in various forms of AML except for AML M3, most B cell tumors
CD172a	SIRP-1α, belongs to Ig superfamily	$CD34^+$ HSC, hemopoietic progenitor cells, monocytes, macrophages, granulocytes, dendritic cells	–*
CD173	Antigen H (glycotop Fucα1–2Galβ1-4GlcNAcβ), progenitor of group A and B antigens	Subpopulation of $CD34^+$ HSC, erythrocytes, platelets, endothelial cells	–*
CD174	Lewis Y antigen	Subpopulation of $CD34^+$ HSC, new marker of hemopoietic progenitor cells, epithelial cells	–*
CD175	Tn antigen (epitope GalNAcα1-, *O*-linked with serine or threonine	Subpopulation of HSC, tumors of epithelial origin	AML cell lines (HG-1a, HL-60), K-562, B-cell leukemia (REH, Nalm-6), T-cell leukemia (Jurkat)
CD176	TF antigen (epitope Gal β1-3GalNAcα1-, *O*-linked with serine or threonine	Subpopulation of HSC, different types of cancer cells	–*
CD213a1	Low affinity receptor α1 IL-13	Hemopoietic progenitor cells, subpopulation of peripheral blood leukocytes, B-cells, monocytes, endothelial cells, fibroblasts	–*
CD224	Ectoenzyme γ-glutamyl transpeptidase	HSC, subpopulation of B-cells, $CD45RO^+$ T-cells, macrophages	–*
CD227	Polymorphic transmembrane epithelial mucine (MUC-1)	Subpopulation of HSC, B-cells, monocytes, follicular dendritic cells, glandular and tubular epithelial cells	–*
CD230	PrP-sialoglycoprotein	Hemopoietic progenitor cells, lymphocytes, monocytes, neurons	–*
CD239	B-CAM glycoprotein, belongs to Ig superfamily	Subpopulation of HSC, erythrocytes, endothelial cells, basal membrane epithelial cells	–*

*Data on expression of CD172a, CD173, CD174, CD175, CD176, CD213a1, CD224, CD227, CD230, CD239 were not found in available literature.

fraction of $CD34^+CD38^-$ cells was capable of extensive proliferation (from 0.2 to 1%).

The recent data suggest that the majority of AML (except for AML M3) as well as CML develop as a result of mutations accumulated in HSC.

Several markers of normal HSC and progenitor cells are expressed also in leukemic cells. The data on the expression, structure, and function of several antigens expressing on the surface of HSC and progenitor cells as compared with their expression in various forms of the malignancies of hematopoietic and lymphoid tissues are summarized in Table 2.

The immunophenotype of MHSC and LSC in different leukemias was delineated [11, 12]. In particular, the immunophenotype of MHSC in normal hematopoiesis has been suggested as $CD34^+CD38^-CD90^+CD123^-CD117^+$. The suggested immunophenotype of LSC in acute myelogenous leukemia is $CD34^+CD38^-CD90^-CD123^+CD117^-$ $CD71^-$HLA-DR^-, while in acute lymphoblastic leukemia the suggested immunophenotype of LSC is $CD34^+CD38^-$ $Lin^-CD10^-CD19^-$. Moreover, in contrast to the normal HSC, a universal phenotype for LSC may not exist, and patient-to-patient variations in cell surface antigen expression may be the rule.

Various cytological forms of acute myeloid leukemia (M0–M7) are believed to originate from a hierarchy of leukemic stem cell classes that differ in self-renewal capacities, molecular and cellular features [12].

The results of our studies suggest that the standard panel for classification of acute leukemias [24] should be supplemented with several new markers allowing us to identify more precisely the different forms of leukemias being of the closely related origin, for example AML M6b (MPO^-, HLA-$DR^{+/-}$, $CD34^+$, $CD117^-$, $CD71^+$, $CD33^{-/+}$ and $CD13^{-/+}$, $CD36^+$) *vs* AML M7 (MPO^-, HLA-$DR^{+/-}$, $CD34^{-/+}$, $CD117^-$, $CD71^{-/+}$, $CD33^{+/-}$ or $CD13^{+/-}$, $CD36^{+/-}$) (Table 3). We suggest the existence of the common bipotent LSC in AML M7 of low grade and AML M6b, which is analogous to precursor cell common for megakaryocytopoiesis and erythropoiesis. We have also found the similarity between the blast cells in pro-B-ALL [MPO^-, HLA-DR^+, $CD34^+$ (less than 50% of cells), $CD19^+$ and $CD33^-$ (or their co-expression), t (4;11), 11q23] and AML M5a [MPO^-, HLA-$DR^{+/-}$, $CD34^{+/-}$, $CD33^+$ and $CD19^-$ (or their co-expression), t (9;11), 11q23] (Table 4). The similarity of immunophenotype and cytogenetic abnormalities in blast cells in pro-B-ALL and AML M5a seems to be the hint explaining the cases of AML M5a as a recurrence of leukemia in children with originally diagnosed pro-B-ALL. Moreover, the common LSC for pro-B-ALL and AML M5a further suggest the analogous precursor cell for the normal hematopoiesis. Therefore, the modern concept of LSC allows one to analyze in more depth the mechanisms of leukemic transformation of target cells in acute leukemias of the closely related origin such as AML M6 *vs* AML M7; AML M5a *vs* pro-B-ALL.

Based on the consistency of $CD34^+CD38^-$ cell surface immunophenotype in different AML subtypes except for M3 and their similarity to the phenotype of normal HSC, a model of leukemogenesis was proposed [22] suggesting that the transformation genetic events occur in primitive stem cells. According to the alternative point of view, that cells of origin for AML M0–M7 are the lineage committed hematopoietic progenitors [23, 24]. As was stated by Weissman [11], the mechanisms of leukemic transformation involve the increased cell survival, the increased proliferative potential, the increased self-renewal capability, the genome instability, and the disordered differentiation.

Table 3. Immunophenotype of blasts in AML M6b and AML M7

Acute erythroleukemia (AML M6b)	Acute megakaryoblastic leukemia (AML M7)
MPO^-	MPO^-
HLA-$DR^{+/-}$	HLA-$DR^{+/-}$
$CD34^+$	$CD34^{-/+}$
$CD117^-$	$CD117^-$
$CD71^+$	$CD71^+$
$CD33^-$ and $CD13^-$	$CD33^{+/-}$ or $CD13^{+/-}$
$CD36^+$	$CD36^+$

Table 4. Immunophenotype of blasts in pro-B-ALL and AML M5a

Pro-B-ALL	AML M5a
MPO^-	MPO^-
HLA-DR^+	HLA-DR^+
$CD34^+$ (90–100% cells)	$CD34^{+/-}$ (less than 50% cells)
$CD19^+CD33^-$ (co-expression is possible)	$CD33^+CD19^-$ (co-expression is possible)
t (4;11), 11q23	t (9;11), 11q23

The recent data on the presumptive target cells for leukemic transformations and the candidates LSC in various hematopoietic malignancies delineated in accordance with the recent WHO classification [25] are summarized in Table 5.

Table 5. Candidate LSC in the tumors of hematopoietic and lymphoid tissues [25]

Chronic myeloproliferative diseases	
Chronic myelogenous leukemia	Pluripotent bone marrow SC
Chronic eosinophilic leukemia	Pluripotent SC in case of t (8;13); multipotent HSC or committed eosinophil precursor cell
Polycythemia vera	Multipotent HSC
Chronic idiopathic myelofibrosis	Multipotent HSC
Essential thrombocytemia	Bone marrow SC with variable lineage potential
Myelodysplastic/myeloproliferative diseases	
Chronic myelomonocytic leukemia	HSC
Atypical chronic myeloid leukemia	Bone marrow myeloid SC
Juvenile myelomonocytic leukemia	Multipotent or pluripotent HSC
Myelodysplastic syndromes	
Refractory anemia (RA)	HSC
Refractory anemia with ringed sideroblasts (RARS)	HSC
Refractory cytopenia with multilineage dysplasia (RCMD)	Myeloid SC
Refractory anemia with excess blast (RAEB)	Myeloid SC
Unclassifiable	Myeloid SC
Associated with del (5q)-	HSC
Acute myeloid leukemias	
AML with recurrent cytogenetic abnormalities	Myeloid SC with potential to granulocytic differentiation
AML with 11q23 (MLL)	HSC with multilineage potential
AML with multilineage dysplasia	HSC
Therapy-related AML	HSC
AML not otherwise characterized	
AML minimally differentiated and AML with maturation	Precursor HSC at early stage of myeloid differentiation
Acute myelomonocytic leukemia	HSC with potential to differentiate into granulocytic and monocytic lineages
Acute monoblastic and monocytic leukemia	HSC with some commitment to monocytic differentiation
Acute erythroid leukemia	Multipotent HSC with myeloid potential
Acute megakaryoblastic leukemia	Precursor cell committed to megakaryocytic and possibly erythroid differentiation
Acute lymphoblastic leukemias	
Precursor B-lymphoblastic leukemia/lymphoma	Precursor B-lymphoblast
Precursor T-lymphoblastic leukemia/lymphoma	Precursor T-lymphoblast

CONCLUSION

The identification of LSC in specified types and variants of the diseases should be an important task in the routine diagnostic research in leukemia patients. The identification of LSC and gene expression in heterogeneous forms of hemoblastoses differed by cytological, cytochemical features as well as by immunophenotype is advantageous for studying in depth molecular and genetic mechanisms of leukemogenesis. LSC and not the usual blasts should be regarded as the major targets for the novel therapeutic modalities.

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ИЗУЧЕНИЕ МОРФОЦИТОХИМИЧЕСКИХ И ИММУНОФЕНОТИПИЧЕСКИХ ПРИЗНАКОВ СТВОЛОВЫХ КЛЕТОК ПРИ ОСТРЫХ ЛЕЙКОЗАХ

Иммунофенотипический профиль стволовых лейкемических клеток (СЛК) интенсивно изучают в ряде лабораторий мира. Результаты данного исследования подтверждают, что стандартная панель для классификации острых лейкозов (ОЛ) должна быть дополнена рядом новых маркеров. Это позволяет более точно идентифицировать близкие по происхождению формы ОЛ, например ОМЛ М6b и ОМЛ М7. Предполагается существование общей низкодифференцированной бипотентной ЛСК при ОМЛ М7 и ОМЛ М6b, подобной нормальной общей клетке-предшественнице мегакариоцитопоэза и эритропоэза. Установлено также сходство бластных клеток при про-В-ОЛЛ с перестройкой хромосомного участка 11q23 и транслокацией (4;11) и бластных клеток при ОМЛ М5а с перестройкой того же хромосомного участка 11q23 и транслокацией (9;11). Подобное сходство иммунофенотипа и цитогенетических аномалий при указанных 2 формах ОЛ объясняет появление бластов с фенотипом ОМЛ М5а при рецидиве заболевания у детей, у которых ранее был диагностирован про-В-ОЛЛ.

***Ключевые слова*: стволовая лейкемическая клетка, острые лейкозы, классификация, иммунофенотип.**