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On Possible Approaches to Supplementing Classical Scheme of Hematopoiesis Based on Immunocytochemical Analysis of Leukemic Blast Cells

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The multistage process of hematopoiesis resulting in appearance of the mature cells of the peripheral blood (erythrocytes, granulocytes, monocytes, platelets, lymphocytes) is maintained by pluripotent hematopoietic stem cells (HSC). The first experimental evidence that HSC in fact exist was presented by Till and McCulloch [1] who elaborated the technique for cloning hematopoietic cells in the spleen of lethally irradiated mouse. The existence of HSC is a fundamental principle of the modern classical unipotent scheme of hematopoiesis.

HSC population is heterogeneous one subdividing into long-term HSCs (LT-HSCs) and short-term HSCs (ST-HSCs). While ST-HSCs have only limited self-renewal capacity giving rise to myeloid and lymphoid lineages within about 8 weeks, LT-HSCs are capable of self-renewal for life generating long-term bone marrow culture capable of differentiating to myeloid and lymphoid lineages [2-4].

HSC and progenitor cells depending on the phase of cell cycle possess the cytomorphological features of blasts or lymphocyte-like cells. Earlier we have attempted to study HSC and progenitor cells using cytological and cytochemical approach. In particular, the early stages of human and mouse embryonic hematopoiesis were observed as the early hematopoietic blast-like cells in the yolk sac which later migrate to the liver and repopulate bone marrow, spleen, thymus and lymph nodes [5]. The morphological and cytochemical features of hematopoietic cells of adult patients in colonies in semisolid media and cells repopulating the bone marrow after chemotherapy and radiation therapy were studied. We have demonstrated that some unipotent progenitor cells regarded earlier as morphologically indistinguishable turned out to possess some marker cytochemical features pertinent to more mature cells of granulocyte lineage (positive myeloperoxidase and naphthol-AS-D-chloracetatesterase activities), monocyte-macrophage lineage (high non-specific esterase activity), megakaryocytic lineage (positive acetyl cholinesterase activity) and T lymphocyte lineage (granular or dot-like acid phosphatase reaction) [5].

The key postulate of the first classical model of hematopoiesis [3] is that loss of the self-renewal capacity during differentiation precedes lineage commitment. According to current models of lineage determination in the adult human hematopoietic hierarchies [6], differentiation of HSC gives rise to multipotent progenitors (MPPs). MPPs have very limited or no self-renewal ability but retain the potential for multilineage differentiation. MPP in its turn gives rise to common myeloid progenitors (CMPs) and population of immature lymphoid progenitors (MLPs). CMPs produce GMPs, which become committed to granulocyte-monocyte pathway and MEP, which produce only erythroid and megakaryocytic (E-MK) cells. MLPs are the origin of B cell precursors and the earliest thymic progenitors (ETPs) committed to T and NK lineages.

While in several studies, the existence of common lymphoid progenitor cells (CLPs) committed to B, T and NK lineages was predicted and demonstrated [7-9], in modified classical model a common myelo-lymphoid progenitor (CMLP) was placed between HSC and CLP [10]. The postulated CMLP generates T and B cell progenitors through bipotential myeloid-T progenitor and myeloid B-progenitor stages, respectively.

While both classical and modified schemes of hematopoiesis which have entered into textbooks [11-13] are based predominantly on study of normal hematopoiesis, the approach based on studying cytochemical and immunophenotype features of leukemic blast cells seems to be advantageous for supplementing further the classical model of normal hematopoiesis for defining more precisely several pathways in differentiation and commitment of progenitor cells.

The clones of leukemic blasts of different origin and levels of maturation represent the progenies of leukemic stem cells (LSC) sharing some common phenotypic features and functional properties with normal HSC [4,14,15]. Our analysis of these features in leukemic cells of large population of patients with different biological subtypes of leukemia studied in Ukrainian Reference laboratory [16] proved to be useful to put forward several suggestions as to the possible links between progenitor cells in the conventional scheme of hematopoiesis. Some controversial pathways in modern scheme of hematopoiesis are discussed below based on our own data as well as data of other studies.

For immunocytochemical study of leukemic blast cells (APAAP and LSAB-AP methods) we used panel of monoclonal antibodies (MoAbs) proposed by WHO experts for classification of acute leukemias that includes markers of hematopoietic progenitor cells (CD34, HLA-DR, TdT, CD45), B-lineage markers (CD19, CD20, CD22, CD79a), T-lineage markers (CD2, CD3, CD5, CD7), markers of myeloid lineage (CD13, CD33, CD15, MPO, CD117), and megakaryoblasts (CD41, CD61).

The results of our study suggest the similarity between 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 acute monoblastic leukemia (AML M5a) [MPO-, HLA-DR+/-,CD34+/-, CD33+ and CD19- (or their co-expression), t (9;11), 11q23]. Such similarities of immunophenotype and cytogenetic abnormalities in blast cells in pro-B-ALL and AML M5a seem to be the hint explaining for us three cases of AML M5a that were presented as a recurrence of

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leukemia in children originally diagnosed as pro-B-ALL that were in fact observed in our laboratory. On the other hand, the possible existence of the common LSC for pro-B-ALL and AML M5a further suggests the analogous progenitor of B cells and monocytes-macrophages in normal human hematopoiesis.

The use of the standard panel of MoAbs has allowed us to identify more precisely the different forms of acute leukemias being of closely related origin. For example, we have diagnosed 12 patients with acute erythroid leukemia (AML M6b) with immunophenotype of leukemic cells being MPO-, HLA-DR+/-, CD34+, CD117-, CD71+, CD33-/+ CD36+, and CD13-/+. At the same time, in 9 our patients acute megakaryoblastic leukemia (AML M7) was diagnosed with immunophenotype of MPO-, HLA-DR+/-, CD34-/+, CD117-, CD71-/+, CD33+/- or CD13+/-, CD36+/-. Based on these similarities, we suggest the existence of the common bipotent progenitor cell in AML M7 and AML M6b, which is analogous to precursor cell common for megakaryocytopoiesis and erythropoiesis.

In some cases of acute leukemia, the co-expression of the markers characteristic of NK cells and monoblasts has been found out. In our experience, the aberrant expression of CD7 and CD56 observed in 32% cases of acute monoblastic leukemia was indicative of unfavorable course of the disease.

In our practice, we have identified four cases of blastic plasmacytoid dendritic cell neoplasm considered according to novel WHO classification of 2008 as a new entity of acute myeloid leukemias and related precursor neoplasms with the expression of CD33 on cells of CD4, CD56 – negative lineage. Therefore, one may suggest that the normal counterpart of malignant cells in this clinically aggressive tumor is the progenitor of the plasmacytoid dendritic cells.

In myeloid blast phase (BP) of chronic myelogenous leukemia (CML) accounting for about 70% of cases, blast cells have strong or weak myeloperoxidase activity and express antigens associated with granulocyte, monocyte, and megakaryoblast and/or erythroid differentiation. In most cases of lymphoblastic BP (20 patients), cells of B-cell lineage are observed sometimes with co-expression of myeloid antigens, but no proved co-expression of B- and T-cell lineage antigens has been ever reported.

The important data for understanding normal human hematopoiesis were obtained in studying some types of acute leukemias of ambiguous lineage (acute undifferentiated leukemia, mixed phenotypic acute leukemias – B/myeloid and T/myeloid). The postulated normal counterpart in these types of acute leukemias is polypotent hematopoietic stem cell. The growing evidence is accumulating on a possible relationship between B-cell and myeloid development and T-cell and myeloid development, respectively, suggesting either involvement of common progenitor or progenitor of one of the lineage that has reactivated the differentiation program of the other lineage [17,18].

It should be noted that in ALL from earlier B cell progenitors (pro-ALL, common ALL) in some cases co-expression of myeloid markers (CD33, CD13, CD15) is observed. However, we have never seen T cell lineage associated antigens in B-ALL leukemic blasts. As a rule, in ALL of T cell origin, we do not find out the expression of B cell differentiation antigens. This holds true for other neoplasms from

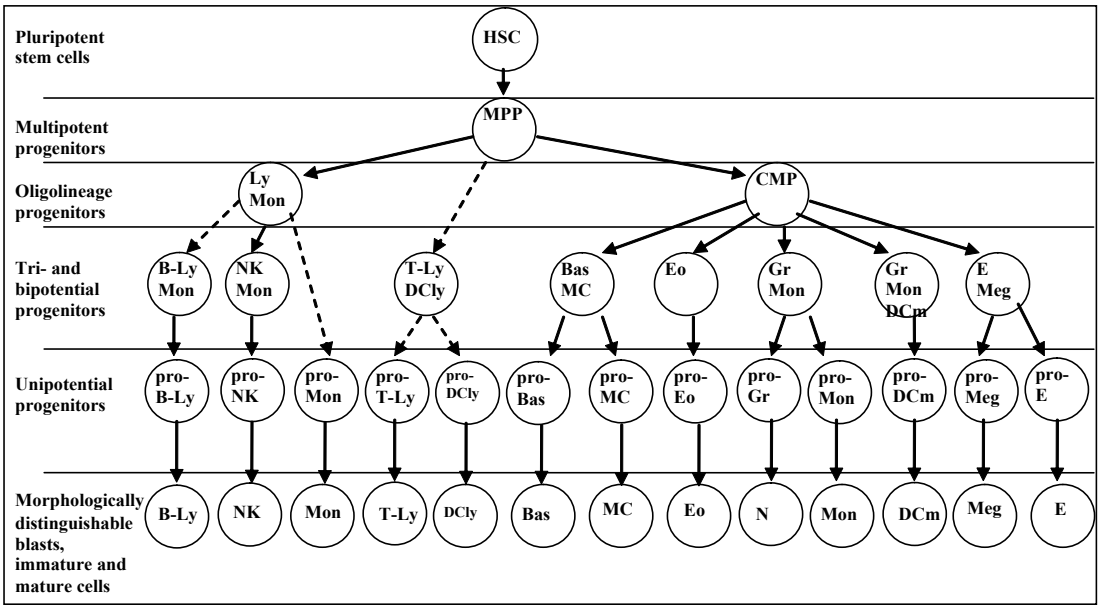

Figure 1: Modern scheme of hematopoiesis with suggested additions.

HSC: Pluripotent Hematopoietic Stem Cell; MPP: Multipotent Progenitor; LyMon: Oligolineage Progenitors Of B Cells/Monocytes; B-LyMon: Progenitor of B Cells/Monocytes; NKMon: Progenitor of NK Cells/Monocytes; pro-B-Ly: progenitor of B cells; pro-NK: progenitor of NK Cells; pro-Mon: progenitor of Monocytes; T-LyDCly: progenitor of T Cells/Dendritic Cells Of Lymphoid Type; pro-T-Ly: progenitor of T Cells; pro-DCly: progenitor of Dendritic Cells Of Lymphoid Type; CMP: Common Myeloid Progenitor; BasMC: Progenitor of Basophiles/Mast Cells; GrMon: Progenitor of Granulocytes/Monocytes; GrMonDCm: Progenitor Of Granulocytes/Monocytes/Dendritic Cells of Myeloid Type; EMeg: Progenitor of Erythrocytes/Megakaryocytes; pro-Bas: Progenitor of Basophiles; pro-MC: Progenitor of Mast Cells; pro-Eo: Progenitor of Eosinophiles; pro-Gr: Progenitor of Neutrophiles; pro-Mon: Progenitor of Monocytes; pro-DCm: Progenitor of Dendritic Cells Of Myeloid Type; pro-Meg: Progenitor of Megakaryocytes; pro-E: Progenitor of Erythrocytes.

Dash line denotes suggested pathways being a subject of discussion (see text).

lymphoid progenitor cells and mature B cell and T cell neoplasms. Due to the same reason, the combination of mature T and NK cell neoplasms into the common group according to WHO classification 2008 [19] also seems rather questionable.

The schematic representation of the differentiation and commitment pathways in hematopoiesis according to the modern modified scheme is given in figure 1 with several suggested pathways (dash line) being a subject of discussion. The existence of the supposed oligolineage progenitor of B cells, NK cells and monocytes is in line with the shared antigen profile of pro-B-ALL and AML M5a as well as recurrent AML M5a cases in children originally diagnosed as pro-B-ALL described above. The bipotential progenitor of T cells/dendritic cells of lymphoid type and finally T cell progenitors seem to be derived from MPP and not CLP since our findings based on studying the phenotypes of leukemic cells as well as the corresponding data of literature call into question the real existence of common lymphoid progenitor (CLP) in human hematopoiesis postulated elsewhere. This question appears to be of high importance not only as theoretical aspects of hematopoietic schemes but also for practical oncohematology and clinical immunology and is worth of further studying. We believe that analysis of characteristic features of leukemic cells in different biological subtypes of hematopoietic malignancies may be useful for elucidating some ambiguous pathways in the conventional schemes of hematopoiesis.

The study of lineage-specific and differentiation antigens of human hematopoietic progenitors is under way in many laboratories [6,9]. Such research advantageous in finding out the novel markers that may be useful also for supplementing the existing panels recommended for the diagnosis of various forms of tumors of hematopoietic and lymphoid tissues.

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