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Invited review

Hematogones: An overview

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ABSTRACT

Hematogones were initially described as mysterious cells in bone marrow smears more than 70 years ago. These cells are normal bone marrow B-lymphocyte precursors with properties that overlap those of lymphoblasts. Their morphological and immunological features are described here with an update on the knowledge of hematogones in hematological and non-hematological disorders.

Contents

1. History of hematogones

Hematogones (B-lymphocyte precursors) were first described in 1937 by Peter Vogel as "lymphoid-appearing cells" in bone marrow aspirates from children [1]. The term hematogones comes from the Latin term "hematogonia" meaning "blood-maker" and describes cells of uncertain significance.

For several decades their origin and function were unknown. Several terms have been used to describe these immature, lymphoid-appearing bone marrow cells, including marrow precursor cells [2], post-therapeutic stem cells [3], lymphocytes [1,4], [2,5], blasts [3,6], [7], terminal deoxynucleotidyl transferase (TdT)-positive cells [8,9] and common-ALL antigen (CALLA)-positive cells [10–18]. The many terms used reflect the difficulty in determining the nature of these cells as immune-reactive or neoplastic cells. In the 1960s and early 1970s, several physicians described bone marrow lymphocytosis after the end of chemotherapy for acute lymphoblastic leukemia (ALL) and discussed weather this lymphocytosis represented early relapse or immune recovery [5,19–22].

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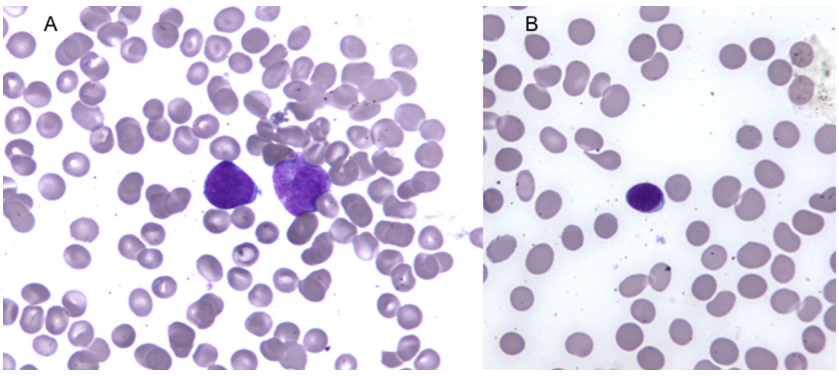

Fig. 1. Morphologic immature (A) and mature (B) HGs.

Confusion has also arisen because the morphologic and immunological phenotypes studied by several groups only partially overlapped. These immature B-cells do not have a unique phenotype. In the 1970s, indirect immunofluorescence and flow cytometry analysis showed that, under particular conditions, immature cells with an immunophenotype similar to previously described B-lineage acute lymphoblastic leukemia (B-ALL) could be found in non-leukemic bone marrow. A number of investigators have characterized immature bone marrow lymphoid cells using a variety of cell surface flow cytometry assays [13,15–18].

Several markers have been studied, including TdT [8,9,23], human leukocyte antigen DR-1 (HLA-DR) [23,24], CD34 [25], [26], CD10 [27], [28] and CD19 [29]. These immature bone marrow cells were considered to be normal marrow lymphoblasts. From the 1980s, advances in immunology led to the recognition of these cells as physiological precursor B-cells. First, immunological studies demonstrated that these bone marrow lymphoid cells were pre-B cells or more mature B-cells; later studies demonstrated that TdT and/or CALLA expression was present in a subset of these cells [3,7–9,11,12,22,27,30]. Because the enrichment of lymphoid B precursors in the bone marrow occurred without extrinsic antigenic stimulation and was followed by an increased number of IgG-bearing and IgM-expressing peripheral blood lymphocytes, researchers attributed the high pre-B cell count in these patients to chemotherapy-induced dysfunction in lymphopoiesis and the immune response [5,19]. Other investigators assumed that these cells are not linked to chemotherapy but were present in any regenerating bone marrow [3,8].

2. Morphologic features

Hematogones (HGs) are lymphoid-appearing cells. A bone marrow trephine biopsy study of HGs-rich specimens showed that the most immature cells were diffusely dispersed within the bone marrow without significant clustering [31].

Examination of bone marrow smears allowed a better appreciation of their cytological characteristics [32]. Although the diameter varied from 10 to 20 μ, these morphologically distinct cells characteristically exhibit highly condensed, uniform nuclear chromatin and scant cytoplasm.

The most immature HGs have common cytological features with lymphoblasts and are in some cases indistinguishable from neoplastic lymphoblasts in ALL. Stage 1 HGs often have round nuclei with indentations, scant cytoplasm, and homogeneous nuclear chromatin with indistinct or at times variably prominent nucleoli (Fig. 1A). When present, the cytoplasm is moderately to deeply basophilic and lacks inclusions, granules or vacuoles. The presence of 1 or more nucleoli reflects cell immaturity [33]. Thus, the distinction between HGs and neoplastic B lymphoblasts may be problematic, particularly during the bone marrow regeneration stage following chemotherapy for ALL. The most mature HGs resemble mature B-lymphocytes with condensed homogeneous nuclear chromatin. The nucleoli are absent or indistinct (Fig. 1B). The HGs are usually not present in a peripheral blood smear, except for samples from neonates [28] or umbilical cord blood [1,34]. However, flow cytometry or immunofluorescence microscopy on concentrated smears of blood leukocytes has identified a small number of HGs in the blood of most children and adults [2,28,35–39]. The HGs in adult blood sample are exclusively mature stage and positively correlate with the number of mature B-cells in the blood [3,39]. An immature fraction of HGs expressing TdT has been reported in fetal lymph nodes from mid-term fetuses and in reactive lymph nodes from children [4,40,41]. Benign TdT-positive cells were located mostly adjacent to lymph node sinuses or small vessels, in the medulla and occasionally in the cortex but they were never located in the follicles. These cells did not form clusters larger than 4–5 cells [5,41].

3. Immunophenotypic features

With the arrival of multi-parametric FC and peroxidase staining, HGs were identified as bone marrow B-cells precursors. HGs are non reactive with Sudan black B, myeloperoxidase and non-specific esterase stains [6,8]. Flow cytometry has become the most useful tools for characterizing HGs [7,17,29]. Several studies have described the different stage of HG development [8,9,42]. Fig. 2 depicts the phenotypic characteristics of the three stages of HGs.

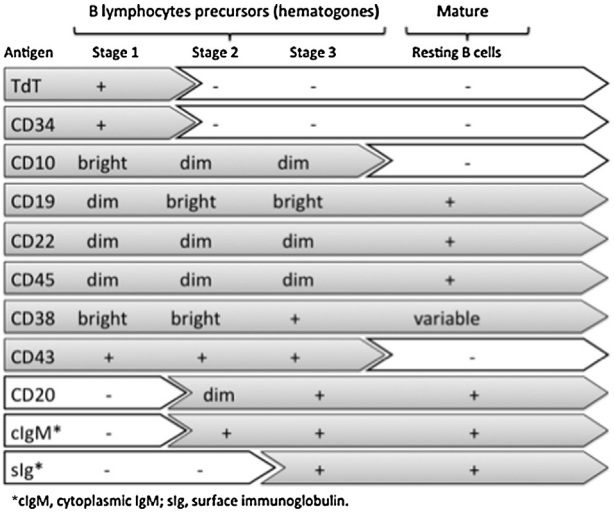

Fig. 2. Antigen expression during B-lymphocytes precursors maturation.