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Short Communication

CD79α Expression in Acute Myeloid Leukemia

High Frequency of Expression in Acute Promyelocytic Leukemia

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CD79α is a subunit of an intracytoplasmic protein reported to be specific for B lymphocytes, including immature B lineage cells. To evaluate expression of the CD79α antigen in acute myeloid leukemia (AML), we studied forty-eight cases of AML by paraffin section immunohistochemistry. The cases included four M0, nine M1, nine M2, ten M3, ten M4, and six M5 AMLs using criteria of the French-American-British cooperative group. Eleven cases demonstrated cytoplasmic staining for the CD79α antigen, including one M1, nine M3, and one M5 AML. These CD79α-positive cases represented 5% of all non-promyelocytic AMLs and 90% of all acute promyelocytic leukemias studied. All acute promyelocytic leukemias had the characteristic t(15;17)(q24;q21), including two cases of the microgranular variant (M3v). No other B-lineage-associated antigens were found in the CD79α-positive cases, with the exception of a subpopulation of CD19-positive leukemic cells in one patient. The two non-promyelocytic leukemias that expressed CD79α had no evidence of t(15;17) and did not express any additional B-lineage-associated antigens that might suggest a mixed lineage proliferation. This study demonstrates that CD79α expression in acute leukemia is not restricted to B-lineage acute lymphoblastic leukemias and that CD79α expression is frequently associated with t(15;17) acute myeloid leukemia. (Am J Pathol 1996, 149:1105–1110)

The CD79 molecule is a dimeric, intracytoplasmic protein that initiates intracellular signaling in B lymphocytes after antigen binding to immunoglobulin.[1–6] It is expressed on B lymphocytes from the immature stages to the plasma cell level of differentiation[4] and has been described as the B cell equivalent of the CD3 molecule in T lymphocytes.[7] The antigen is composed of two polypeptides that are encoded by the *mb-1* and *B29* genes, and the two component chains are respectively referred to as CD79α (mb-1) and CD79β (B29). The CD79α antigen has been studied in a variety of tissues and cell lines by several different immunophenotyping methods, including paraffin section immunohistochemistry.[7–11] These previous studies have found CD79α expression to be restricted to B cell neoplasms, including the immature B cells of acute lymphoblastic leukemia. All T cell neoplasms and most acute myeloid leukemias (AMLs) are reported to be CD79α negative, and the majority of non-B-lineage cell lines have been CD79α negative.

Because of the reported B-lineage specificity of this antigen, CD79α antibodies have great potential utility in diagnostic pathology.[7,11] The presence of this antigen on immature lymphocytes would also suggest that it is a reliable marker of precursor B cell lymphoblastic malignancies. To evaluate the utility of CD79α antibodies in the paraffin section analysis of acute leukemias, we studied 48 cases of AML that included 10 cases of acute promyelocytic leukemia (FAB-M3). CD79α expression was correlated with

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Table 1. *Classification, Clinical Data, and Immunophenotype of CD79α-Positive Acute Myeloid Leukemias*

Case	FAB	Age/sex	CD45	CD2	CD7	CD10	CD19	CD20	TdT	CD14	CD13	CD15	CD33	MPO	HLA-DR	CD34
1	M1	38/M	+	–	+	–	–	–	–	–	+	+	+	+	+	+
2	M3v	47/F	+	+	–	–	+ (25%)	–	–	ND	+	–	+	+	+ (26%)	+
3	M3v	27/F	+	–	–	–	–	–	U	–	+	+	+	+	–	+
4	M3	54/F	+	ND	–	–	–	–	–	–	+	–	+	+	–	–
5	M3	45/F	ND	ND	ND	ND	ND	–	–	ND	ND	ND	ND	+	–	–
6	M3	53/F	ND	ND	ND	ND	ND	ND	–	ND	+	+	+	+	–	–
7	M3	38/F	+	–	–	–	–	–	–	–	+	+	+	+	–	+
8	M3	58/F	+	–	–	–	–	–	–	–	+	–	+	+	–	–
9	M3	53/F	+	–	–	–	–	–	–	–	+	+	+	+	–	+
10	M3	26/F	+	+	–	–	–	–	–	–	+	–	+	+	–	–
11	M5	55/F	+	–	–	–	–	–	–	–	+	+	+	+	+	–

M, male; F, female; MPO, myeloperoxidase; ND, antigen not studied; U, uninterpretable. A + score is defined as 20% or more of the blast cell population expressing the antigen. A – score is defined as less than 20% of the blast cell population expressing the antigen.

cytochemical, immunophenotypic, and cytogenetic findings in all positive cases.

Materials and Methods

Archival material was studied from specimens from 48 patients with AML diagnosed at the City of Hope National Medical Center. All cases were classified according to the criteria of the French-American-British cooperative group (FAB),[12,13] and included 4 FAB M0, 9 FAB M1, 9 FAB M2, 10 FAB M3, 10 FAB M4, and 6 FAB M5 leukemias.

Paraffin section immunohistochemical studies were performed using the avidin-biotin complex method as previously described[14] with heat-induced epitope retrieval.[15] All available paraffin-embedded tissue was studied, including clot sections and bone marrow trephine biopsy sections. A variety of antibodies were used, which included CD79α (mb-1, clone HM57; Dako, Carpinteria, CA), myeloperoxidase (Dako), CD3 (Dako), CD20 (L26; Dako), HLA-DR (Dako), and TdT (Supertechs, Bethesda, MD). The CD79α antibody was used at a 1:25 dilution after steaming in citrate buffer for 8 minutes.[15] Immunohistochemical studies were performed on the Techmate 1000 automated stainer with reagents provided by the manufacturer (Biotek Solutions, Santa Barbara, CA).

Prior cytochemical and flow cytometric immunophenotyping results were reviewed. The immunophenotyping studies were performed with antibodies directed against the following antigens: CD45, CD2, CD7, CD10, CD19, CD20, CD13, CD14, CD15, CD33, CD34, and HLA-DR (Coulter, Hialeah, FL, and Becton Dickinson, San Jose, CA). Antibodies were considered positive by both flow cytometry and immunohistochemistry when 20% or more of the neoplastic cells expressed the antigen.

Formalin-fixed, paraffin-embedded cell buttons from the leukemic cell lines HL-60, KG-1, and U-937 (American Tissue Culture Collection, Rockville, MD) were also studied for CD79α expression. Cultured cells were centrifuged three times for 10 minutes at 1500 rpm, with the cells resuspended in Hanks solution (Irvine Scientific, Irvine, CA) each time. The final cell pellet was then fixed in 10% neutral buffered formalin for 2 hours and paraffin embedded using standard procedures. Immunohistochemical studies for CD79α were performed on paraffin sections of the cell pellet using the procedure described above.

Cytogenetic analyses were performed according to the standard method using 50 μg/ml Colcemid for 45 minutes before cell harvesting. GTG banding was used to identify the individual chromosomes, and the chromosomes were classified according to the 1995 International System for Human Cytogenetic Nomenclature.[16] Fluorescence *in situ* hybridization (FISH) studies were performed to rule out the possibility of a masked or aberrant *PML/RARα* fusion gene in a patient characterized by a normal karyotype at presentation of AML but contained a clone with a 15q24 breakpoint at relapse. FISH was performed according to the manufacturer's instructions using a t(15; 17) translocation DNA probe (Oncor, Gaithersburg, MD). Slides were examined on a Nikon Labophot II microscope equipped with epifluorescence and multiple band pass filters.

Results

Eleven of forty-eight AMLs were CD79α positive, including one of nine M1 AMLs, nine of ten M3 AMLs, and one of six M5 AMLs (Table 1; Figure 1). These patients included ten females and one male with a median age of 45 years (mean, 44.9 years). CD79α expression was clearly demonstrated in immature

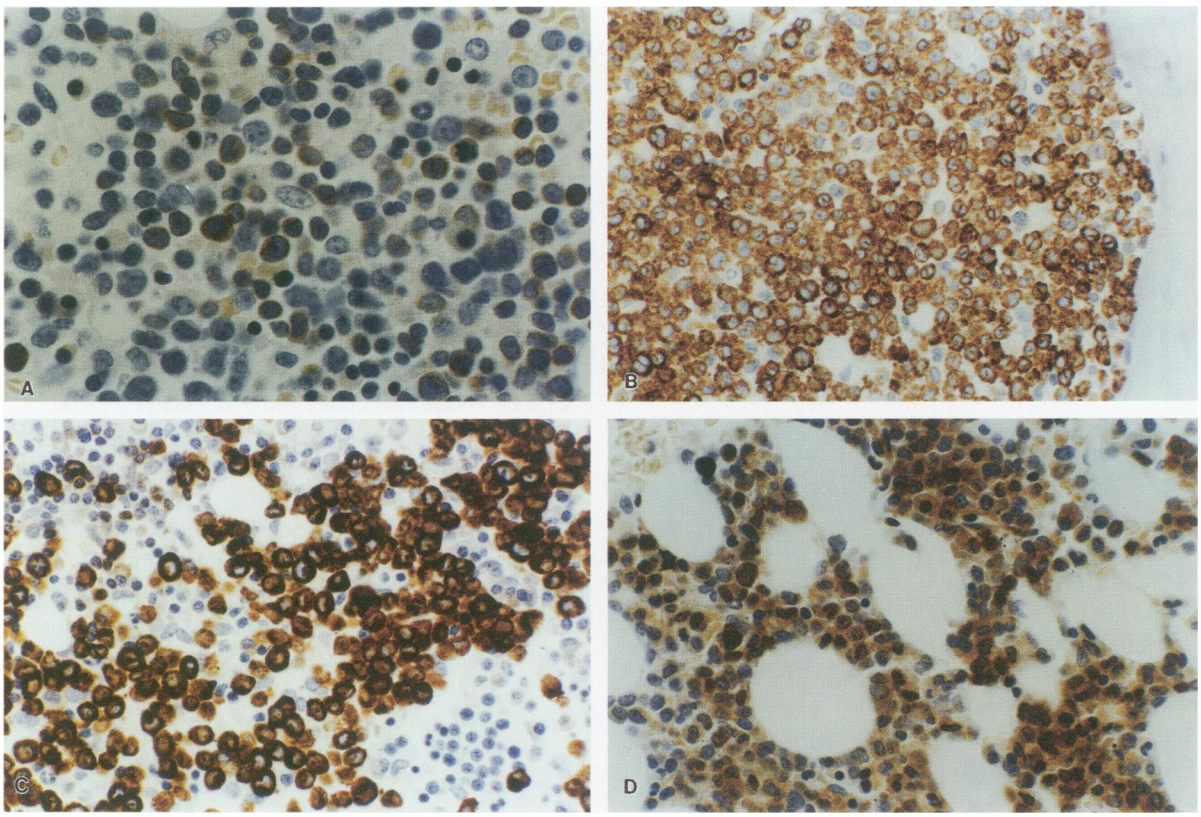

Figure 1. A: *Weak CD79α expression in the cytoplasm of leukemic cells in a case of M1 AML (case 1). Clot section; hematoxylin counterstain; magnification, ×600.* B: *Strong cytoplasmic staining for CD79α in the leukemic cells of a case of M3 AML (case 2). Biopsy section; hematoxylin counterstain; magnification, ×400.* C: *Strong cytoplasmic staining for CD79α in another case of M3 AML (case 5). Clot section; hematoxylin counterstain; magnification, ×400.* D: *Cytoplasmic staining for CD79α in a case of M5 AML (case 11). Clot section; hematoxylin counterstain; magnification, ×400.*

cells in all cases. The positive cells were myeloperoxidase positive and CD20 negative, excluding the possibility of interspersed non-neoplastic B lymphocytes. In general, CD79α expression was demonstrated by strong cytoplasmic staining of the majority of leukemic cells. In two cases, only weak cytoplasmic staining was detected in the neoplastic cells. This included the one M1 AML (case 1) and one case of M3 AML (case 4). In general, the CD79α expression was detected more strongly in clot sections that had not been decalcified than in bone marrow trephine biopsy specimens. All cases were myeloperoxidase positive by cytochemical and immunohistochemical study. None of the patient specimens expressed the B-lineage antigen CD20, and only one of the nine specimens studied was CD19 positive (case 2). This specimen, an M3 leukemia, demonstrated 25% of the blast cells to be CD19 positive compared with 1% CD20, 90% CD13, 5% CD15, and 93% CD33. Interestingly, this was the only case of M3 AML to express HLA-DR (present on 26% of blast cells). Two of eight cases studied, both M3 AMLs, were CD2 positive. One of nine cases studied, the M1 AML, was CD7 positive. TdT was negative in all ten CD79α-positive AML cases that had interpretable results. One M3 AML case was uninterpretable for TdT due to repeatedly high background staining.

Nine of ten cases of acute promyelocytic leukemia studied were CD79α positive, and all demonstrated the t(15;17)(q24;q21) characteristic of this disease (Table 2). One patient had additional karyotypic abnormalities (case 8). Seven of the CD79α-positive acute promyelocytic leukemia cases had characteristic morphological features with immature, occasionally folded nuclei, dark-staining cytoplasmic granules, and scattered cells with numerous Auer rods. Two cases (2 and 3) had few dark-staining granules and Auer rods were not prominent, features of the microgranular variant (M3v) of acute promyelocytic leukemia. The one case of M1 AML expressing CD79α was characterized by normal cytogenetics. This patient, however, had a cytogenetically abnormal subpopulation of cells in a morphologically uninvolved specimen submitted after bone marrow transplantation, with 2 of 20 cells having a translo-

Table 2. *Results of Karyotypic Analysis of CD79α-Positive Acute Myeloid Leukemias*

Case	Cytogenetics Data
1	46,XY [20]*
2	46,XX,t(15;17)(q24;q21) [20]
3	46,XX,t(15;17)(q24;q21) [20]
4	46,XX,t(15;17)(q24;q21) [17]/ 46,XX [3]
5	46,XX,t(15;17)(q24;q21) [18]/ 46,XX [2]
6	46,XX,t(15;17)(q24;q21) [20]
7	46,XX,t(15;17)(q24;q21) [18]/ 46,XX [2]
8	46,XX,del(12)(q13q24.1), t(15;17)(q24;q21), add(19)(q13.3) [14]/ 46,XX [6]
9	46,XX,t(15;17)(q24;q21) [16]/ 46,XX [4]
10	46,XX,t(15;17)(q24;q21) [17]/ 46,XX [5]
11	47,XX,+i(11)(q10) [2]/ 46,XX [18]

*Cytogenetic study of a morphologically uninvolved specimen on the same patient after bone marrow transplantation demonstrated 46,XY,t(?4;15)(p12;q24) [2]/46,XY [18]. FISH analysis of the original, leukemic specimen failed to identify a masked t(15;17).

cation involving 15q24. FISH analysis was therefore performed on the remaining cells from the original leukemic specimen to exclude a masked translocation. FISH analysis using the t(15;17) probe failed to detect evidence of this translocation in the M1 AML. The single case of M5 leukemia expressing CD79α demonstrated the gain of an isochromosome for the long arm of chromosome 11 [+i[11](q10)] by karyotypic analysis. Additional material was not available for FISH analysis on this case.

Immunohistochemical study of the HL-60, KG-1, and U-937 cell lines failed to identify CD79α expression in any of the cultured cells.

Discussion

CD79α is a 47-kd glycoprotein that is coupled with the 37-kd protein CD79β in B lymphocytes to form an intracytoplasmic signaling molecule. CD79α is expressed by B lymphocytes at all stages of maturation, including precursor B cells.[4] The antigen has a similar pattern of expression to CD19 and CD22 but is felt to be more B-lineage specific.[10] This conclusion is drawn from multiple studies of *mb-1* gene expression and CD79α antigen expression on a variety of tissues and cell lines. Before the current study, CD79α expression has been reported to be almost exclusive to B cell proliferations or mixed-lineage leukemias. We describe eleven cases of AML expressing CD79α, with nine of ten acute promyelocytic leukemias being positive. None of the cases demonstrated any other evidence of B-lymphoid antigen expression, with the exception of one case that had a subpopulation of CD19-positive blast cells. Two cases were CD2 positive, an antigen previously reported to be expressed in some cases of acute promyelocytic leukemia,[17–19] and one other case was CD7 positive, a nonspecific antigen expressed in 19 to 26% of AMLs.[20,21]

Mason et al[7] demonstrated that 97% of B cell malignancies were CD79α positive by paraffin section immunohistochemistry whereas none of 28 AMLs expressed this antigen. The types of AML studied were not identified. Buccheri et al[11] reported five cases of AML that expressed mb-1 protein. All five cases were TdT positive, and four expressed two additional lymphoid antigens (CD10, CD19, or CD22). These four cases were reclassified as biphenotypic leukemias. The fifth CD79α-positive AML in that study was considered a typical case of AML (one of sixty-six cases studied), but further cytogenetic or FAB classification information was not reported. Other studies have failed to identify mb-1 protein expression in multiple myeloid cell lines[8,10]; however, *mb-1* gene expression has been reported in the myeloid cell line HL-T.[10] We were unable to demonstrate CD79α expression in the HL-60, KG-1, and U-937 cell lines.

Our results demonstrate that CD79α expression can occur in AMLs and is particularly frequent in cases of acute promyelocytic leukemia. The overall frequency of expression of CD79α in AML is probably artifactually high in the present series, as a high percentage of FAB M3 leukemias were studied. Only 5% of non-promyelocytic AMLs were CD79α positive in this series compared with 90% of acute promyelocytic leukemias. CD79α expression, therefore, may be coupled with other previously reported findings characteristic of acute promyelocytic leukemia such as CD2 expression and the lack of HLA-DR.[18,22] Previously, CD2 expression has been reported to correlate with t(15;17); however, cases of AML with inv(16)(p13q22) have also been reported with this immunophenotype.[23,24] CD2 was present in two of the nine CD79α cases, all FAB M3 leukemia. The CD79α-positive/HLA-DR-negative phenotype was found exclusively in specimens with t(15;17); however, two cases with t(15;17) did not have this combined phenotype (including the one CD79α-negative/HLA-DR-negative M3 leukemia not shown in Table 1 and case 2, a CD79α-positive M3 AML with a subpopulation of HLA-DR-positive blast cells).

The function and significance of CD79α expression in M3 AML is not clear. The CD79α antibody (clone HM57) used in the current study actually detects an intracellular epitope, and the designation CD79αcy has been suggested by the Fifth Workshop on Leukocyte Typing for these antibodies.[25] The detection of cytoplasmic CD79α in cases of AML,

therefore, is not proof of a functionally active protein transported to the cell surface. Study of CD79β expression in these cases would be of interest, but we have not been able to demonstrate such expression in paraffin-embedded tissues (data not shown).

The finding of CD79α expression in cases of acute promyelocytic leukemia may be analogous to the high frequency of another B-lineage antigen, CD19, in a subgroup of M2 AMLs.[19,26] Similar to the t(8;21) AML that commonly expresses CD19, acute promyelocytic leukemia does not usually demonstrate other evidence of B-lineage antigen expression. The mechanism of this antigen expression, therefore, deserves additional study. The 15;17 translocation involves the *PML* gene of chromosome 15q24 and the *RARα* gene of chromosome 17q21,[27] and this translocation may not be detectable in all cases by classical cytogenetics.[28,29] The resultant fusion protein of this translocation shows some variations due to differences in breakpoints on chromosome 15.[30,31] The high frequency of CD79α expression in the randomly selected M3 AML cases in the current study would suggest that expression of this antigen is unrelated to these molecular variations. Fresh or frozen material, however, was not available for molecular evaluation of specific breakpoint sites in these cases, and such study may be warranted in future cases.

This study suggests that CD79α expression is not restricted to normal and neoplastic cells of B lineage. The paraffin section detection of CD79α, however, may prove to be valuable in the subclassification of AMLs, as the identification of some cases of M3 AML can be difficult without cytogenetic confirmation. Because the therapeutic approach to these leukemias differs from other forms of AML, early recognition and classification of such cases are essential.

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