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COMMENT

ADHESION MOLECULES IN ACUTE MYELOID LEUKEMIA*

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Abstract—That adhesion molecules play a major role in the regulation of normal hematopoiesis is suggested by the abundance of these molecules present on early bone marrow progenitor cells and their differential pattern of expression at discrete stages of differentiation along the various cell lineages. In particular, precursor cell matrix/endothelial interactions determine retainment or release of hematopoietic cells from the bone marrow microenvironment. Consequently, changes in the affinity or quantitative expression of adhesion molecules on either the bone marrow stroma or the blood cell precursor component — during normal development or due to activation or a malignant process — will affect cell attachment. Adhesion molecules, therefore, are modulator molecules which alter the biological behavior of normal or leukemic hematopoietic cells, primarily in terms of migration and localization properties, although they also participate in many other cell functions such as cytotoxicity, antigen presentation and binding of viruses or cancer cells. Several membrane-bound adhesion molecules and, in some instances, their soluble counterparts which may be biologically active, have been described in acute myeloid leukemia. The potential diagnostic or physiological significance of leukocyte antigens with adhesive properties will be addressed in this comment.

Key words: Adhesion molecules, acute myeloid leukemia.

Our knowledge of adhesion molecules expressed by hematopoietic or endothelial cells is constantly expanding, partly because of increasing reports that identify established leukocyte antigens as adhesion molecules or their interacting ligands. The most recent examples are the characterization of the stem cell antigen CD34 as a sialomucin that promotes cell adhesiveness via its O-linked carbohydrate moiety and may function as a ligand for L-selectin (reviewed in [1]), of CD43, another cell-associated mucin (leukosialin), as a counter-receptor for the intercellular adhesion molecule ICAM-1 (CD54) (reviewed in [2]), and of CD33, the pan-myeloid antigen, as a member of the sialoadhesin family, together with the B-cell antigen CD22 [3]. Following from that is that although few studies published address the expression and/or potential biological or clinical significance of adhesion molecules in acute leukemia *per se*, e.g. the study of Kawada *et al.* [4], many such studies already exist on those antigens that have only recently been recognized for their cellular interacting properties.

New leukemia syndromes are emerging, predominantly among the acute myeloid leukemias (AML), based on biological properties that may be related to the presence of adhesion molecules which discern a particular subtype from otherwise morphologically, often immunophenotypically and sometimes even cytogenetically, identical leukemias. The molecule CD56, the neural-cell adhesion molecule (N-CAM), is implicated in the propensity of M2-AML cells containing the t(8;21) translocation to localize in extramedullary sites [1, 5], and in conjunction with CD106 the vascular cell adhesion molecule (VCAM-1) correlates with dermal infiltrates of leukemic cells in poorly differentiated (FAB-M1) and monocytic leukemias (FAB-M5) [6]. Molecule VCAM-1, as well as the expression of CD62E [E (endothelial)-selectin] on human endothelium on the

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other side, permit a productive interaction with their respective ligands on AML blast cells, namely CD49d (very late activation antigen-4, integrin α4 or VLA-4) and $CD15_s$ (sialylated Lewis x antigen), respectively, possibly contributing to trans-endothelial migration of leukemic cells and the establishment of extravascular disease [7]. Also, CD56 characterizes a novel AML subtype termed myeloid/natural killer (NK) cell acute leukemia which by cytology resembles FAB-M3v but lacks the t(15;17). Immunophenotypically, myeloid/NK blasts lack HLA-DR and CD34, as do acute promyelocytic leukemia (APL) cells, but they express CD56 (in the absence of CD16, another natural killer cell antigen) and CD11a [8, 9], a β_2-integrin typically absent from APL cells [1]. *In vitro* resistance to all-*trans* retinoic acid [8, 9] and an aggressive clinical course that parallels the level of NK-cell mediated cytotoxic function of the blasts cells related to the CD56/CD11a expression [8] further segregate myeloid/NK acute leukemia from APL.

Negativity for CD11a (lymphocyte function-associated antigen-1 or LFA-1) is a characteristic feature of APL, as this adhesion molecule is expressed by the majority of non-APL AMLs ([10]; E. Paietta, unpublished) reflecting an early feature of hematopoietic precursor cells that accompanies all stages of normal myeloid differentiation [1, 10]. Interestingly, whereas neutrophils and monocytes express CD11a and its β_2 chain CD18 [11], induction of differentiation of APL cells by all-*trans* retinoic acid into maturing myeloid cells, while consistently increasing expression of CD11b, another β_2-integrin, failed to promote CD11a up-regulation [12]. This deficit in the differentiative response of APL cells appears to be a direct consequence of the expression of the PML-RARα hybrid gene [13].

Of potential clinical value in the management of APL patients may be CD13, in that this membrane-bound aminopeptidase N, which serves as a receptor for coronaviruses [14] and has been linked to invasive properties of tumor cells [15, 16], has been correlated with the development of the life-threatening retinoic acid syndrome and the extent of hyperleukocytosis with all-*trans* retinoic acid therapy [17]. Presence of the pan-T cell antigen CD2, a member of the immunoglobulin gene superfamily of cellular adhesive proteins and the counter-structure for CD58 (LFA-3), another member of that family [2, 11], has been suggested to be associated with the short form of the PML/RARα transcript, a proposed molecular marker for impaired response duration and survival in APL (reviewed in [1]).

On the other hand, expression of CD2 characterizes the immunophenotype of patients with favorable AML associated with the inv(16) (p13q22) karyotype [18, 19]. The CD2 expression in AML in general was found to correlate significantly with the expression of the myelomonocytic antigen CD11b and the prototype monocytic antigen CD14 [19]. Although not an adhesion molecule itself, CD14 on the surface of monocytes mediates the adherence of CD11b to its ligand CD54 (ICAM-1) on endothelial cells [20], suggesting differential adhesive properties at early ($CD11b^+$, $CD14^-$) vs late ($CD11b^+$, $CD14^+$) stages of monocytic development. In a large study from the Eastern Cooperative Oncology Group, immature acute monocytic leukemia (AMOL), characterized by CD11b positivity in the absence of CD14, has recently been demonstrated to have a significantly inferior prognosis in terms of remission achievement than $CD14^+$ mature AMOL [21].

Maturation-dependent modulation of intercellular adhesion molecules can affect their potential to mediate cellular interactions. This has been reported for the sialic acid dependent adhesion via CD33 [3] and it applies to the lectin–carbohydrate recognition between selectins and their ligands [22–24] in that glycosyltransferases are developmentally regulated, thereby controlling the pattern of carbohydrate residues on myeloid cell structures at various stages of differentiation [25, 26]. Thus, while the binding of antibodies used to recognize the presence of selected adhesion molecules may not be affected by subtle differences in the glycosylation of their respective antigens, the efficiency in adhesion mediated by these antigens may be entirely different, depending upon their oligosaccharide structure. On the other hand, variable antibody reactivity patterns of CD15 and CD15s antibodies, the latter recognizing the sialylated epitope, have been used in the differential diagnosis of APL [27]. Yet unexplored in terms of its diagnostic or biological significance is the glycosylation-dependent distribution of CD34 epitopes. Differences in CD34 antibody reactivities seen among AMLs as well as between leukemic and normal precursor cells [2] suggest that the activities of glycosyltransferases that affect this heavily glycosylated cell surface sialomucin are regulated by the maturation/differentiation stage of hematopoietic cells. That the cytoadhesive properties of CD34 positive cells vary with the O-glycosylation state of CD34 epitopes [28] supports its proposed role as a ligand for CD62L [11]. Given the known sensitivity of CD34 antibodies (or others with analogous properties) to epitope carbohydrate composition, proposals on a predictive role for CD34 in AML must be viewed in the context of antibody source which may explain the discrepancy of data reported in the literature.

That expression profiles of adhesive antigens may contribute to a novel, functional classification system for AML is an intriguing concept, as it may lead to subtype-specific therapy. Few other antigens known to date have offered a similar opportunity, noteworthy here would be P-glycoprotein, the multidrug resistance mediator, in

that P-glycoprotein modulators have already found their way into the clinic. For P-glycoprotein, its clinicobiological relevance in AML has been found to correlate with CD34 expression and specific cytogenetic abnormalities [1, 29], as well as with the type of therapeutic regimen employed [30]. Similar associations are beginning to be disclosed for adhesion molecules in AML. Based on that experience, studies on the clinical value of cytoadhesive antigens in AML, rather than considering those antigens as independent biological entities [4], need to incorporate prognostically implicated immunophenotypic as well as karyotypic features in carefully controlled patient populations with comparable treatment in order to be informative.

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