Ann. N.Y. Acad. Sci. 532: 427-428

Intercellular Adhesion Molecule-1 (ICAM-1) Monoclonal Antibody Inhibits Cytotoxic T Lymphocyte Recognition

M. W. MAKGOBA, M. E. SANDERS, G. E. GINTHER LUCE, E. A. GUGEL, M. L. DUSTIN,[a] T. A. SPRINGER,[a] AND S. SHAW

National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20892
and
[a]Dana Farber Cancer Institute
Boston, Massachusetts 02115

Recent studies have shown that cytotoxic T lymphocytes form conjugates with antigen-negative targets.[1] These studies have further demonstrated that this process of antigen-independent conjugate formation (AIC) is mediated by way of two adhesion pathways: one involving the T cell–CD2 receptor binding to the ligand LFA-3[2] on the target, and the other involving the T cell–LFA-1 receptor interacting with ICAM-1 and probably other ligands[3] on the target. While the roles of CD2, LFA-1, and LFA-3 in CTL-mediated lysis (CML) have been demonstrated abundantly,[4] very little is known about the role of ICAM-1 in such lysis. ICAM-1 was initially proposed as a ligand for LFA-1, based upon monoclonal antibody (mAb) inhibition of LFA-1–dependent T-cell adhesion to fibroblasts and the finding that inhibition occurred with pretreatment of the fibroblasts and not the T cell.[5,6] These findings have been extended to and confirmed in AIC using CTL clones.[3]

We initially investigated the role of ICAM-1 by mAb-inhibition studies of AIC formation, and showed that its utilization in LFA-1–dependent conjugates varied significantly between targets,[3] irrespective of the ICAM-1 level expressed on the target. To analyze its role in CML, targets that predominantly used ICAM-1 in AIC were selected. One such target is U937 (a promonocytic line).[3] The ability of the ICAM-1 mAb to inhibit antigen-independent, phorbol myristic acetate (PMA)/ionophore–triggered lysis of U937 by a CTL clone was studied. The results in FIGURE 1A showed that ICAM-1 mAb inhibits lysis by 70%; lysis is also inhibited well by the LFA-1 mAb (80%), and to a limited extent by CD2 (27%) and LFA-3 (38%) mAb. Following this result, a bulk population of allospecific T cells were prepared by two cycles of *in vitro* stimulation of peripheral blood mononuclear leukocytes with irradiated U937 as stimulator cells. The bulk population was tested in a standard CML assay. The result in FIGURE 1B showed 75% inhibition by the ICAM-1 mAb, compared with 95%, 20%, and 15% inhibition by LFA-1, CD2, and LFA-3 mAb, respectively. These results showed that ICAM-1 is critical for antigen-specific CTL recognition in this effector/target combination. Studies with various effector/target combinations revealed differing utilization and requirements for ICAM-1 in CTL recognition.[3] The results are consistent with the interpretation that ICAM-1 can serve as one ligand for LFA-1 in CTL recognition. The role of ICAM-1 in CTL recognition correlates closely with its ability to inhibit

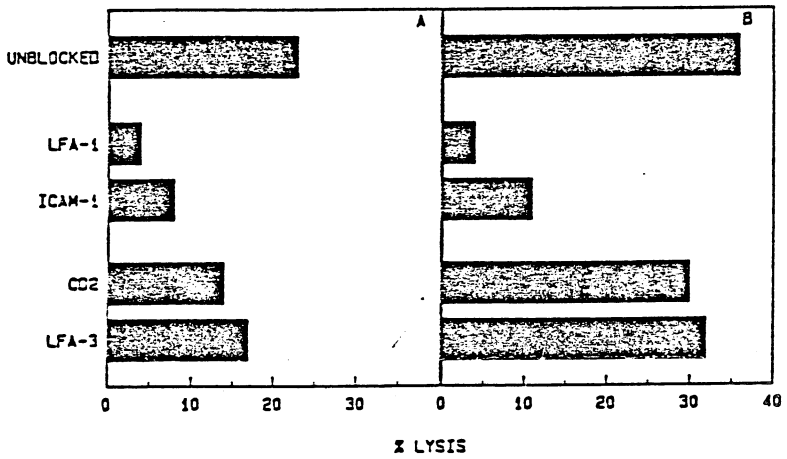

FIGURE 1. Monoclonal antibody inhibition of CML. Effector/target combinations tested include a DPw2-specific CTL clone 8.2, rendered antigen-nonspecific by PMA/ionophore, tested on U937 (A), and an allospecific bulk T-cell population sensitized against and tested on U937 (B). Both were tested at 10 : 1 E : T ratio in a 4 hr ^{51}Cr-release assay in the continuous presence of the indicated mAb.

AIC formation. The variable utilization of ICAM-1 in LFA-1–dependent interactions in both AIC and cell-mediated lysis strongly indicates the existence of alternative ligands for LFA-1. This variable requirement may explain why the ICAM-1 mAb would not be identified by screening for inhibition of CML in many effector/target combinations.

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