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Spontaneous Rosetting of T Lymphocytes to Reed-Sternberg Cells Is Mediated by the CD2/LFA-3 and LFA-1/ICAM-1 Pathways of Antigen-Independent Adhesion

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Reed-Sternberg cells (RS) are a malignant cell type of uncertain origin that are found in diseased lymphoid tissues of patients with Hodgkin's disease. A well-described characteristic of RS is that they spontaneously form rosettes with autologous or allogeneic T lymphocytes without subsequent RS lysis.[1] The mechanism and pathophysiologic significance of this rosetting phenomenon have remained unclear. Recent studies from our laboratories have identified two pathways of antigen-independent adhesion used by T lymphocytes. T-cell CD2 is a receptor for target-cell LFA-3, and T-cell LFA-1 is a receptor for ICAM-1 and probably other ligands.[2,3]

We investigated the possible involvement of these previously described adhesion pathways in the phenomenon of RS/T-cell rosetting using the RS line L428.[4] This line was derived from a pleural effusion from a patient with Hodgkin's disease, and has morphologic and cell-surface marker patterns identical to freshly isolated RS.[5] L428 expresses high amounts of cell-surface LFA-3 and ICAM-1, and does not express CD2 or LFA-1, whereas peripheral blood T lymphocytes express high amounts of LFA-1 and CD2, but express very modest amounts of LFA-3 or ICAM-1. Monoclonal antibody (mAb) blocking studies showed that mAb to either CD2 or LFA-3 profoundly inhibited L428/T-cell rosettes (TABLE 1 and FIG. 1). Monoclonal antibody to LFA-1 inhibited moderately, and the combination of mAb to LFA-1 and LFA-3 completely inhibited rosettes. Monoclonal antibody to HLA class I or CD3 inhibited only marginally.

Conjugate formation of L428 with a T-cell clone that was noncytolytic for L428 showed a similar pattern of mAb blocking. CD2 or LFA-3 mAb blocked conjugates by greater than 50%, whereas mAb to LFA-1 or ICAM-1 blocked to a lesser degree. The combination of mAb to LFA-3 plus LFA-1 completely inhib-

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TABLE 1. Monoclonal Antibody Inhibition of L428/T-Cell Adhesion[a]

Monoclonal Antibody	Percent Inhibition	
	Rosettes	Conjugates
HLA class I	15	0
CD3	4	3
CD2	85	57
LFA-3	96	77
LFA-1	51	30
LFA-1 + LFA-3	100	100
ICAM-1	ND	10
ICAM-1 + LFA-3	ND	93

[a] Monoclonal-antibody inhibition of T-cell rosettes or conjugates with the RS line L428. Percent inhibition is calculated relative to rosettes or conjugates formed with media alone. ND indicates conditions not done.

ited conjugates, whereas the combination of mAb to LFA-3 plus ICAM-1 inhibited by 93% (TABLE 1). Monoclonal antibody to HLA class I or CD3 did not significantly inhibit conjugates.

These results indicate that RS/T-cell rosetting is a manifestation of exaggerated antigen-independent adhesion mediated predominantly by CD2/LFA-3, and to a lesser extent by LFA-1/ICAM-1 interactions. Such adhesion, in a lesser degree, is characteristic of normal T lymphocytes binding with a variety of targets. The exaggeration of normal antigen-independent adhesion seen in RS/T-cell rosetting may reflect alterations in RS surface–adhesion proteins associated with malignant transformation of RS. Our data indicate that RS/T-cell rosetting is not a manifestation of antigen-specific cell-mediated antitumor immunity, because it is not blocked by CD3 mAb and because it occurs with unprimed allogeneic T cells.

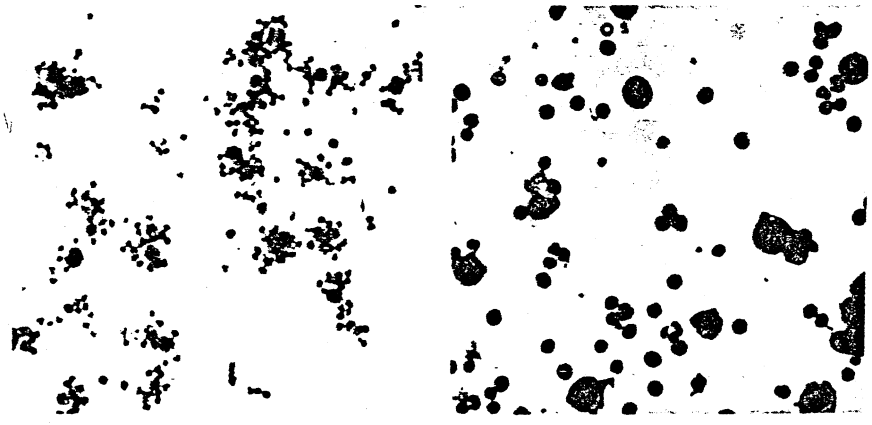

FIGURE 1. Spontaneous rosettes of peripheral blood T cells with L428 (left panel) and partial inhibition of rosettes with anti-LFA-3 (right panel).

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