Leukocyte Adhesion Deficiency as a Model for the Study of the Functional Role of LFA-1

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Introduction

In the past years, a new inherited immunodeficiency has been identified and been named the leukocyte adhesion deficiency (LAD) (1). Leukocyte adhesion deficiency is characterized by a defective expression of three related leukocyte adhesion molecules, i.e., LFA-1, Mac-1, and p150,95 which are heterodimers, the α chain being specific and the β chain common to the three molecules.

The basic defect has been shown to reside in the β subunit synthesis leading to either no β chain synthesis or the synthesis of an abnormal subunit (2–5). The main functional consequences of LAD are related to a defective in vivo adhesion of phagocytic cells to endothelial cells and to the extracellular matrix leading to uncontrolled bacterial infections (6).

In this chapter, we review some new data dealing with the heterogeneity of the structural defect, with the dysfunctions of LFA-1 T lymphocytes and with the therapy of LAD.

Heterogeneity of the Structural Defect Underlying Leukocyte Adhesion Deficiency

Anderson et al. (1) and Kishimoto et al. (7) have shown that there are two types of the LAD, one known as the severe phenotype characterized by a complete lack of α-β dimer expression and the second known as the moderate phenotype characterized by low but detectable α-β expression.

Further heterogeneity of LAD has been found by biosynthetic studies of LFA-1 and α and β chains and β chain RNA expression in PHA-induced blasts and in EBV-transformed B cells from LAD patients (8). We found in the patients we have studied three different phenotypes:
1. No β chain mRNA, no β chain precursor.
2. Low amounts of β chain mRNA with no detectable β chain precursor.
3. Normal β subunit mRNA level of normal size associated with detectable β precursor synthesis and extremely low α-β complex membrane expression (8).

The β chain precursor detected in the cell lysates from patient type 3 was not glycosylated and was no longer detected after chase indicating rapid degradation. Interestingly, β chain-specific mRNA transcription could be enhanced in this case by reagents such as PMA or γ interferon, but this was not associated with increase in membrane α-β complex expression.

These data point to the degree of heterogeneity of the disease. Further studies of sequencing of abnormal β chain gene may give new insights into the functional sites of the β chain.

T Cell Dysfunction in Leukocyte Adhesion Deficiency

A variety of T cell anomalies have been reported to occur in association with the severe phenotype of LAD (1, 9,-11). Defective T cell cytotoxicity is the most frequently encountered anomaly. In some cases, a T helper cell defect for antibody production has also been reported (12).

We have further studied the activation, helper function and adhesion of LFA-1- T cells (13). In coculture experiments of LFA-1- T cells with HLA identical LFA-1+ monocytes, it appears that antigen-specific T cell activation does occur, an observation that has also been made in the presence of LFA-1- monocytes. In contrast, the mixture of either LFA-1- T lymphocytes or monocytes with HLA identical LFA-1+ B lymphocytes gives rise to suboptimal in vitro specific antibody production to influenza virus. LFA-1- B lymphocytes appear nonfunctional but such a result could be the consequence of defective in vivo priming as well.

Similar poor functions of monocytes and T lymphocytes in antibody production assay could be reproduced by preincubating purified LFA-1+ cells with saturating concentrations of anti-LFA-1 antibodies (25/3 or TS1/22) (12, 13). B cell function is not directly inhibited by these antibodies. In a mirror image, anti-ICAM-1 antibody 87H10 is able to block in vitro antibody production to influenza virus at the monocyte and B cell levels.

The adhesion of LFA-1- T lymphocytes to B lymphocytes is impaired as judged by measurements of cell conjugate formation (11). This impairment is not due to a delay in attachment as shown by kinetic studies of conjugate formation. In contrast, there is no difference in binding of LFA-1- or LFA-1+ B lymphocytes to T lymphocytes.

This is in correlation with the apparent unidirectional functional interaction between LFA-1 on T lymphocytes and ICAM-1 (+ x) on B