Application of Basic Science to Hematopoiesis and Treatment of Disease, edited by E. Donnall Thomas.
Raven Press, Ltd., New York © 1993.

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Adhesion Receptors in Inflammation

A Précis

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This is an illustrated précis for the nonspecialist desiring a molecular overview of the structure of adhesion receptors and their function in inflammation. Literature citations and detail may be found in ample reviews and selected articles (Springer *et al.*, 1987; Springer, 1990, 1991; Lawrence and Springer, 1991; Hemler, 1990; Ruoslahti, 1991; Picker and Butcher, 1992; Mackay, 1991; Harlan *et al.*, 1991; Huber *et al.*, 1991; Oppenheim *et al.*, 1991).

Adhesion molecules regulate the interactions of lymphocytes with antigen-bearing cells, as well as the other kinds of interactions of lymphocytes, monocytes, and granulocytes involved in immune interactions and emigration from blood and migration within tissues. Adhesion molecules not only can regulate interactions with other cells and cell migration but also can sense the extracellular environment and convey information to the cell that can regulate proliferation and differentiation; thus they should be called adhesion receptors. Almost all adhesion receptors fall into three families of related proteins. The proteins in each family are related in amino acid sequence and must have evolved from a common ancestral gene, but often have quite different binding specificities. However, the way in which proteins within a family function in adhesion is conserved, particularly for the integrin and selectin families discussed below.

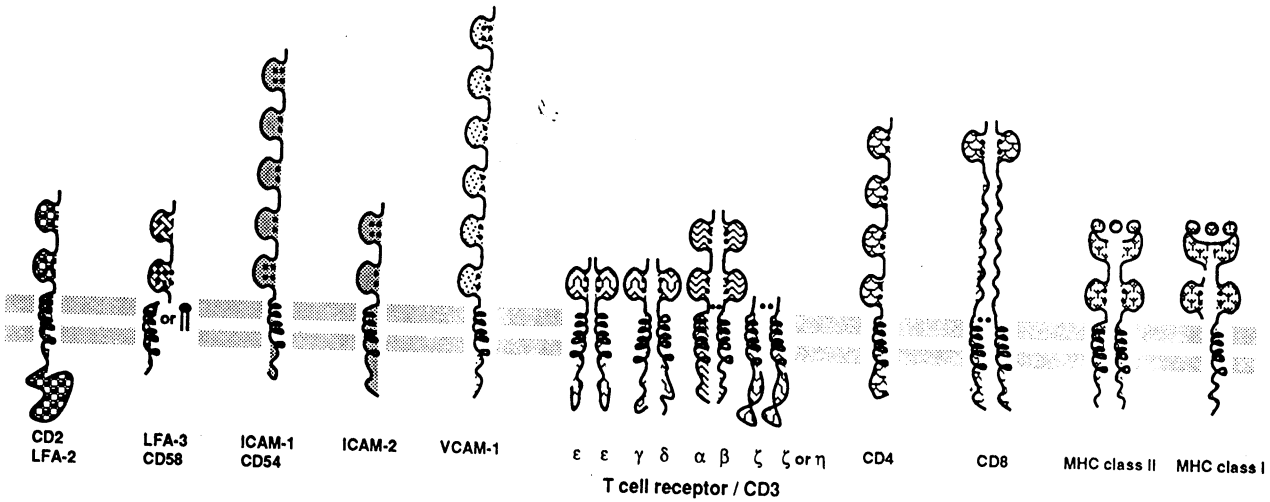

FIG. 1. Immunoglobulin superfamily members important in immune cell interactions.

The immunoglobulin (Ig) superfamily has the Ig domain as the common structural unit, but with the exception of the B and T cell antigen receptors does not undergo gene rearrangement or somatic mutation to generate variability. A recognition function in adhesion predates specialization for antigen recognition, as demonstrated by Ig superfamily members in insects that act as nervous system adhesion molecules. Ig family members function widely in adhesive interactions in the immune system (Fig. 1). Increased cell surface density of these receptors, e.g., ICAM-1 and VCAM-1 on endothelium, can regulate adhesion in inflammation. Other members important in interactions in the immune system include ICAM-2, CD2, LFA-3, CD4, and CD8.

The integrin family is also an ancient adhesion molecule family, as it is present in insects. Integrins have distinct and large (1,000 and 760 amino acid) α- and β-subunits. The α-subunit has divalent cation-binding sites, and ligand binding depends on Ca^{2+} or Mg^{2+} (Fig. 2). All cells but erythrocytes have integrins; they function in adhesion to both extracellular matrix components and cell surface glycoproteins. One subfamily of integrins sharing a common β-subunit (CD18) that includes LFA-1 and Mac-1 is found only on leukocytes and is thus called the leukocyte integrins. This subfamily is missing in patients with inherited leukocyte adhesion deficiency, in which the β-subunit is mutated, resulting in a lack of neutrophil emigration and lack of pus formation. Patients die of infections unless they receive a bone marrow transplant, showing the importance of these molecules in vivo. The extracellular domains of integrins can be rapidly conformationally altered by signals from within the cell, allowing rapid regulation of lymphocyte binding to antigen-bearing cells, leukocyte binding to endothelium at inflammatory sites, and regulation of migration, without any change in integrin surface density. Site-directed mutagenesis has shown that the CD18 β-subunit cytoplasmic domain is required for avidity regulation.

The selectins regulate leukocyte interactions with platelets and endothelial cells and are found on all three of these cell types (Fig. 3). They are named because of a lectin-like (carbohydrate binding) N-terminal domain. Stimulation of endothelial cells with, for example, thrombin causes upregulation of the P-selectin (CD62) from Weibel-Palade bodies in minutes; activation of endothelial cells

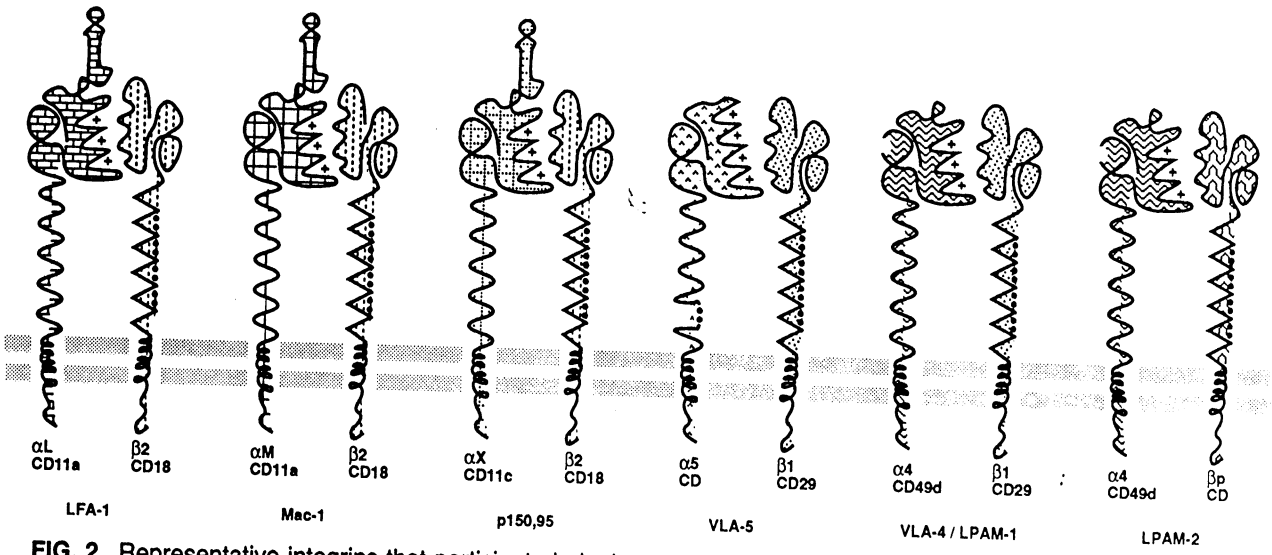

FIG. 2. Representative integrins that participate in leukocyte interactions with other cells and extracellular matrix.

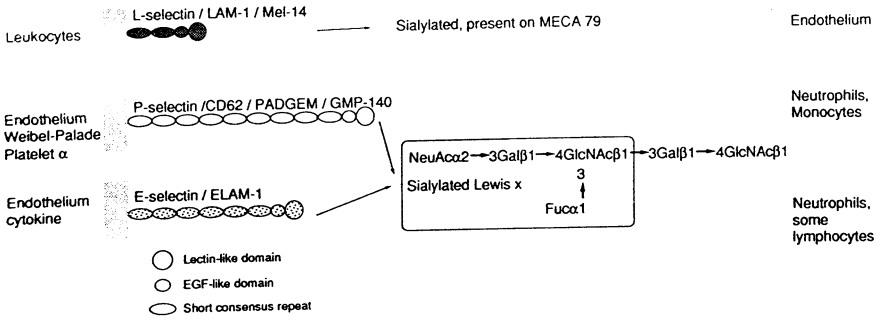

FIG. 3. Selectins and their carbohydrate ligands. Although both P-selectin and E-selectin can recognize sialylated Lewis^x, there are differences between the ligands they recognize on neutrophils with high affinity.

with cytokines causes mRNA and protein synthesis of the E-selectin ELAM-1 over hours. The L-selectin is expressed on all leukocytes, including lymphocytes.

Selectins mediate the initial step of leukocyte localization at an inflammatory site—the attachment of cells in shear flow to the vessel wall—and mediate rolling of marginated cells along the vessel wall (Fig. 4). Furthermore, the L-selectin also functions as a receptor for lymphocyte binding to high endothelial venules during migration into lymph nodes. The structure of selectins seems well suited to efficient attachment of flowing cells. The lectin domain is located atop a stalk of modular consensus repeats that is predicted to have considerable segmental flexibility. This together with the predicted segmental flexibility of carbohydrate structures, the location of the recognition site at the terminus of the carbohydrate structure, and the small size of the tetrasaccharide recognition structure, should enhance the diffusiveness of these structures above the cell surface and also, once the ligand and receptor have "bumped into" each other, the rapidity of orientation so that a complementary receptor-ligand binding complex is formed, leading to rapid kinetics of ligand binding by selectins.

The second step in leukocyte localization, arrest of rolling, development of firm adhesion to the vascular wall, and transendothelial migration (diapedesis), is mediated by leukocyte integrin interaction with ICAMs. Rolling of neutrophils along the vessel wall slows

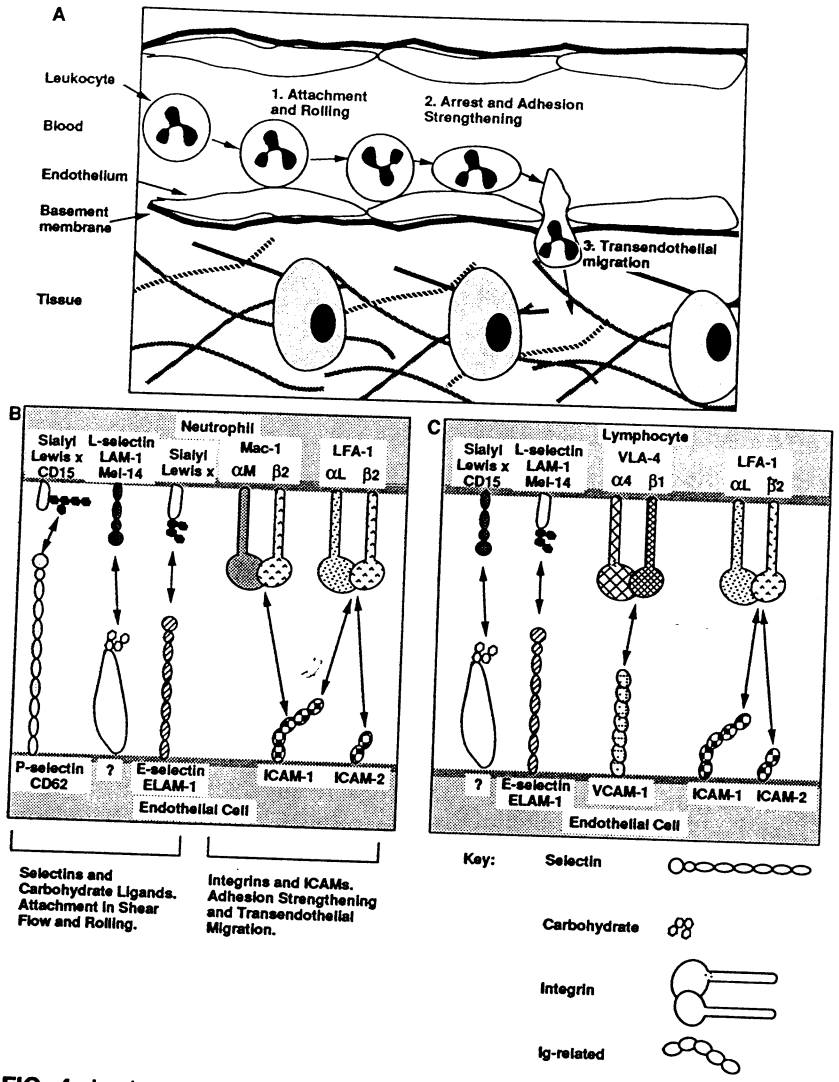

FIG. 4. Leukocyte and lymphocyte interactions with endothelium. **A**: The major steps in leukocyte and monocyte localization at inflammatory steps. **B, C**: Molecules that participate in interaction with endothelium of neutrophils and lymphocytes, respectively.

their transit through postcapillary venules up to 100-fold and brings them into close contact with the endothelial surface, where they are exposed to chemoattractants secreted by endothelial cells (IL-8), present on the endothelial surface (PAF), released from activated platelets, or diffusing from tissue (LTB4, C5a, formylated bacterial peptides). These chemoattractants bind to specific receptors on the surface of neutrophils and generate intracellular signals. In turn, this activates over a time scale of seconds to minutes the adhesiveness of integrins, probably due to a change in the conformation of the ligand binding site that is transduced from inside the cell. This is well documented for the interaction of the leukocyte integrins LFA-1 and Mac-1 with ICAMs. Expression of the integrin VLA-4 on lymphocytes and eosinophils that binds to the Ig family member VCAM-1 is suggested to be responsible for the ability of these cells to extravasate in patients that are deficient in the leukocyte integrins; however, the physiologic mechanisms that regulate VLA-4 adhesiveness have not yet been defined.

Chemoattractants and cytokines act in concert with adhesion molecules to regulate cell migration and localization in inflammation. Cytokines and LPS can increase gene expression for the adhesion molecules ICAM-1, VCAM-1, and ELAM-1, leading to increased surface expression. Furthermore, cytokines can stimulate gene expression and secretion of chemoattractants such as IL-8 and MCP-1 by endothelial and other tissue cells. The adhesion molecules on endothelium and tissue and the components of extracellular matrix to which leukocytes bind can be thought of as paving; the adhesion molecules on leukocytes can be thought of as wheels. The wheels must gain traction on the pavement to allow leukocyte migration. Both acceleration and steering appears to be regulated by chemoattractants. Chemoattractants act at two levels. After initial binding of leukocytes to endothelium through selectins, chemoattractants first activate adhesiveness through integrins. Second, they provide a directional signal that attracts leukocytes into tissues, because leukocytes can sense a concentration gradient of chemoattractant and move up it. Many chemoattractants are highly cell-type specific, based on highly specific expression of their receptors. There are chemoattractants specific for neutrophils (IL-8) and for monocytes (MCP-1). The type of chemoattractant produced at an inflammatory

site and the adhesion molecules that are induced by cytokines are likely to be the key factors that determine the type of infiltrating cells and their localization.

Adhesion molecules, cytokines, and chemoattractants are attractive targets for therapeutics. Antibodies to integrins, ICAM-1, and selectins have been shown to block leukocyte infiltration in vivo and in a surprisingly diverse range of animal models of disease. These include neutrophil-mediated injury after ischemia and reperfusion in models of myocardial ischemia, hypovolemic shock, limb reimplantation, and frostbite; and monocyte and T lymphocyte–mediated injury in organ allograft rejection and delayed-type hypersensitivity. Support for the requisite participation of selectins and integrins in sequential steps in neutrophil localization at inflammatory sites comes from observations that monoclonal antibodies to either integrins (CD18) or selectins (L-selectin) can equivalently and almost completely block emigration in vivo.

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RAVEN PRESS NEW YORK

Springer, T. A., and Lasky, L. A. (1991). Sticky sugars for selectins. *Nature* **349**, 196.

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Raven Press Ltd., 1185 Avenue of the Americas, New York, New York 10036

Made in the United States of America

Library of Congress Cataloging-in-Publication Data

Application of basic science to hematopoiesis and treatment of disease / edited by E. Donnall Thomas.

p. cm. — (Bristol-Myers Squibb cancer symposia ; 15)
Includes bibliographical references and index.
ISBN 0-88167-999-2
1. Hematopoiesis. 2. Hematopoietic growth factors.
3. Hematopoietic system—Cancer. I. Thomas, E. Donnall. II. Series.
[DNLM: 1. Gene Expression Regulation—physiology. 2. Hematologic Diseases—therapy. 3. Hematopoiesis—physiology. 4. Hematopoietic Cell Growth Factors—physiology. 5. Hematopoietic Stem Cells—physiology.
W1 BR324 v. 15 / WH 140 A652]
QP92.A77 1993
616.1'5—dc20
DNLM/DLC
for Library of Congress

92-48858
CIP

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