Leukocyte Trafficking

Molecular Mechanisms, Therapeutic Targets, and Methods

Edited by Alf Hamann and Britta Engelhardt

WILEY-VCH Verlag GmbH & Co. KGaA

Leukocyte Trafficking

Edited by
Alf Hamann and
Britta Engelhardt

Related Titles

R. A. Meyers (Ed.)
Encyclopedia of Molecular Cell Biology and Molecular Medicine, 2nd Edition
2005
ISBN 3-527-30542-4
http://meyers-emcbmm.de

D. Wedlich (Ed.)
Cell Migration in Development and Disease
2005
ISBN 3-527-30587-4

A. Ridley, M. Peckham, P. Clark (Eds.)
Cell Motility: From Molecules to Organisms
2004
ISBN 0-470-84872-3

A. Steinkasserer, N. Romani, M. Lutz (Eds.)
Handbook of Dendritic Cells – Biology, Diseases and Therapies
2005
ISBN 3-527-31109-2

S. H. E. Kaufmann (Ed.)
Novel Vaccination Strategies
2004
ISBN 3-527-30523-8

H. Kropshofer, A. Vogt (Eds.)
Antigen Processing Cells – From Mechanisms to Drug Development
2005
ISBN 3-527-31108-4

A. Meager (Ed.)
The Interferons – Characterization and Application
2005
ISBN 3-527-31180-7

K. M. Pollard (Ed.)
Autoantibodies and Autoimmunity – From Mechanisms to Treatments
2005
ISBN 3-527-31141-6

Leukocyte Trafficking

Molecular Mechanisms, Therapeutic Targets, and Methods

Edited by Alf Hamann and Britta Engelhardt

WILEY-VCH Verlag GmbH & Co. KGaA

Editors

Prof. Dr. Alf Hamann
Charité University Medicine Berlin
Experimental Rheumatology
Medical Clinic for Rheumatology and
Clinical Immunology
c/o German Rheumatism Research Center
Schumannstr. 21/22
10117 Berlin
Germany

Prof. Dr. Britta Engelhardt
Immunobiology
Theodor Kocher Institute
University of Bern
Freiestrasse 1
3012 Bern
Switzerland

All books published by Wiley-VCH are carefully produced. Nevertheless, authors, editors, and publisher do not warrant the information contained in these books, including this book, to be free of errors. Readers are advised to keep in mind that statements, data, illustrations, procedural details or other items may inadvertently be inaccurate.

Library of Congress Card No.: Applied for
British Library Cataloging-in-Publication Data: A catalogue record for this book is available from the British Library.

Bibliographic information published by Die Deutsche Bibliothek
Die Deutsche Bibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data is available in the Internet at ⟨http://dnb.ddb.de⟩.

© 2005 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

All rights reserved (including those of translation in other languages). No part of this book may be reproduced in any form – nor transmitted or translated into machine language without written permission from the publishers. Registered names, trademarks, etc. used in this book, even when not specifically marked as such, are not to be considered unprotected by law.

Printed in the Federal Republic of Germany.
Printed on acid-free paper.

Composition Asco Typesetters, Hong Kong
Printing betz-druck GmbH, Darmstadt
Bookbinding J. Schäffer GmbH i.G., Grünstadt

ISBN-13 978-3-527-31228-3
ISBN-10 3-527-31228-5

Contents

Preface

A Mobile Society – The Constitutive Role of Cell Trafficking in the Organization of the Immune System

Among other evolutionary achievements of the vertebrates, the immune system stands out not only for its complexity, but also for its unique construction as a system composed of highly cooperative individual cells as basic elements, which are mobile and distributed all over the body. The various subpopulations of leukocytes resemble the members of a complex society, with functional specializations, numerous interactions, order – and chaos. It is a consistently fascinating fact that this society of migrating leukocytes allows the execution of functions as diverse as balancing self-tolerance against defense, systemic response to antigens with generation of effector mechanisms and specific memory, and tailored, local immune reactions. Molecular mechanisms allowing the targeted migration of cell types into distinct compartments are a central organizational feature of this system because they allow the precise topographical and temporal delivery of leukocyte subpopulations.

Directed migration of cellular elements of the immune system begins after development within the primary compartment, predominantly the bone marrow. Some cell types emigrate as precursors and complete their differentiation within another compartment, e.g., pre-T cells, which migrate into the thymus where a highly specialized environment provides the appropriate conditions for their maturation and selection. Also linked to specific differentiation phases is the changing location of B-cells after their maturation within the bone marrow (or, in birds, the bursa of Fabricius), from where they migrate into the spleen or the lymph nodes and, after antigen encounter and differentiation into plasma blasts, back into the bone marrow, into the lamina propria, or into some inflamed tissues (see Chapter 9).

Unidirectional migration is typical for cells of the innate immune system such as neutrophils. Generated within the bone marrow, they stay for a short time (less than a day) idle within the blood stream without extravasating into any tissue until they undergo apoptosis and are cleared away by the liver. Eventually, inflammation recruits them into a peripheral tissue site and calls up their effector mechanisms, as discussed in this book (Chapter 12).

Since the pioneering work of Sir James L. Gowans [1] we have known that

lymphocytes behave differently: naïve lymphocytes, both T cells and B cells, recirculate continuously between blood and lymphoid tissues. This process allows them to percolate for most of their time through lymphoid tissues all over the body, where a few dendritic cells – the critical antigen-presenting cell fraction involved in T cell priming – might have arrived after taking up antigen in the peripheral sites (see Chapter 10). It may be imagined that this continuous cycling greatly enhances the chances that lymphocytes of a given antigen specificity will meet those dendritic cells that present the cognate antigen.

Naïve lymphocytes do not enter peripheral tissues, including inflamed sites; these compartments are reserved for the more mature members of the society, the memory and effector lymphocytes. Thus, the places where an immune response is induced – the lymphoid tissues – and the places where the actual defense reactions take place – the nonlymphoid tissues exposed to microbial attacks – are strictly separated. It only can be speculated that the evolutionary benefit of this organization is to keep cells concentrated in a few relevant places, and to provide separate environments for either priming and maturation of naïve lymphocytes or for activation and execution of effector functions.

Lymph node high endothelial venules provide an armamentarium of traffic signals for the rapid recruitment of naïve lymphocytes from the blood stream. Investigation of lymphocyte traffic across high endothelial venules in lymph nodes and Peyer's patches helped to define the multi-step cascade of lymphocyte–endothelial interaction as a universal scheme for how leukocytes in general can extravasate from the blood stream into any tissue (see Chapter 1). According to this model, adhesion molecules from different families – the selectin family (Chapter 2), the integrin family (Chapter 4), and the Ig supergene family (Chapter 5) – act in synergy with chemokines (Chapter 3) to govern the finely regulated process of leukocyte tethering, adhesion, and transmigration. Within the tissue, molecules of the extracellular matrix modulate the final step of leukocyte migration and entry into the target tissue (Chapter 6), whereas distinct chemokines produced by their respective cell populations help to facilitate the exact positioning of interacting partners.

In addition to recirculation, Gowans and others also detected 40 years ago the capacity of some lymphocyte populations to return selectively to the tissues from which they were isolated (''homing'' in the narrower sense). It later became clear that this topographical memory is a property of activated or memory/effector cells. Memory of the site of priming is induced upon encounter with antigen and subsequent differentiation into effector/memory cells. The current dogma assumes that tissue-specific factors, most likely produced by local dendritic cells, shape the differentiation so as to generate lymphocytes that home back to the tissue of initial antigen encounter (see Chapter 7). The crucial question of how the expression of organ-specific homing receptors is regulated, what factors are involved, and whether permanent imprinting occurs, is a matter of recent research.

Tissue-specific homing has been interpreted as a means of focusing memory cells on the sites of initial priming, where the likelihood of later recurrence of the same infectious agent is highest. However, even after 40 years of research, it is

unclear whether this concept applies to more compartments than the gastrointestinal tract together with its associated lymphoid structures, with perhaps the skin as another defined target. Lymphocytes are recruited to a variety of other tissues by more or less universal sets of receptors, or by inflammation-related migration pathways.

The mobile cell of the immune system needs anchor points to perceive the topographical information required for tailored, site-specific activities. Two cell populations have well-described functions in this context. First, the dendritic cell provides signals that shape the quality and direction of an immune response, in addition to presenting antigen. Although dendritic cells originate from bone marrow and arrive only in their final phase from different tissue in lymphoid organs, they seem to acquire a local flavor upon settling, with an ability to shape the homing behavior of T-cells upon interaction. Secondly, endothelial cells act as gatekeepers and selective catchers, guiding distinct cell populations into various compartments of the body. They provide the range of traffic signs recognized by the mobile leukocyte within the blood stream. In addition, the great variability in the composition of extracellular matrix and the multitude of chemokines produced by resident tissue cells or cells of the immune system constitute further road signs to guide traveling cells.

While the tissue-related determinants allow the assignment of specific subpopulations to site-specific duties, inflammation is a condition where adhesion molecules and chemokines become transiently upregulated and for a certain time window define a new target for leukocyte – especially effector cell – trafficking. Indeed, rapid infiltration of leukocytes into the affected tissue is a classical hallmark of inflammation. This feature allows the immune system to store large numbers of reactive cells in the circulation or in central depots such as spleen or lymph nodes from where they can be rapidly mobilized and redirected to the sites of immune reactions taking place at any place of the body.

A few adhesion molecules, notably the endothelial selectins (Chapter 11) and a series of chemokines and their receptors (Chapter 13), are exclusively induced under inflammatory conditions; other receptors might be upregulated in their expression levels. The functioning of endothelium is crucial in this process; its activation (Chapter 14) by inflammatory mediators such as cytokines produced within the tissue provides the key signals that attract different populations of leukocytes or lymphocyte differentiation stages out of the circulation into the inflamed area.

The inflammation-triggered accumulation of leukocytes at the site of an immune reaction represents a powerful adaptive response of the system. Not only does it allow the quantitative number of effector cells to be rapidly increased, but it also enables the character of the response to be shaped qualitatively. Increasing data suggest that the large number of toll-like and other innate receptors for pathogen-associated determinants affects the specific pattern of chemokines, cytokines, and adhesion molecules induced depending on the nature of the pathogen, so that customized reactions result.

Rapid inflammation-triggered recruitment into affected tissue sites is observed for cells of the innate immune system such as neutrophils (Chapter 12) in the

same way as for the memory/effector stage of lymphocytes (Chapter 8), suggesting that trafficking and transmigration mechanisms evolved early in evolution and differentiated to allow finely tuned regulation of leukocyte positioning.

The relevance of these mechanisms for understanding the pathophysiology of acute and chronic inflammatory diseases and for the development of novel therapeutic options is obvious; accordingly, the field has attracted much attention in the last years. Indeed, some approaches to target either adhesion molecules (Chapter 15) or, to a lesser extent, chemokines (Chapter 16) for an anti-inflammatory treatment have yield promising results already being tested in initial clinical trials.

The chapters in this book, written by experts in their respective fields, cover many important aspects of the basic mechanisms, molecular pathways, cellular features, and possible therapeutic modulation of leukocyte trafficking mentioned above. Such a book can never be either complete or as up to date as a journal article. We hope, nevertheless, that it will help the reader to understand the central features of migration of cellular elements of the immune system. We hope that it will both serve as an introduction to novices in the field and provide the experienced researcher with some new insights that will complement his or her own work.

Last but not least, the series of chapters describing the armamentarium of available methods for studying leukocyte trafficking (Chapters 17–23) aims to help an understanding of how major findings were achieved in the field and to advise readers in the design of their own experiments or laboratory classes for immunology students.

Acknowledgements

Experimental work by A.H. was supported by the German Research Foundation (DFG; SFB366, SFB421, and SFB633); work by B.E. was supported by the Max Planck Society, the DFG (individual grants and program grants SFB293, SFB297, and SFB629), Astra Zeneca, Sweden, and GlaxoSmithKline, UK.

We thank the members of our research groups for their past and present scientific contributions to our research and their valuable help in editing this book.

Reference

Gowans, J.L., and E.J. Knight. 1964. The route of recirculation of lymphocytes in the rat. *Proc. Roy. Soc. Lond. B* 159:257–282.

List of Authors

Ronen Alon
The Weizmann Institute of Science
Department of Immunology
Rehovot 76100
Israel

Carrie N. Arnold
Stanford University School of Medicine and Veterans Affairs–Palo Alto Health Care System
Department of Microbiology & Immunology
3801 Miranda Avenue
Palo Alto, CA 94304
USA

Claudine S. Bonder
University of Calgary
Immunology Research Group
Department of Physiology and Biophysics
Institute of Infection, Immunity and Inflammation
3330 Hospital Drive N.W.
Calgary, Alberta, T2N 4N1
Canada

Michael J. Briskin
Director of Immunology
Merrimack Pharmaceuticals, Inc.
101 Binney St.
Cambridge, MA 02142
USA

Eugene C. Butcher
Stanford University School of Medicine
Laboratory of Immunology and Vascular Biology
Department of Pathology, L235
Stanford, CA 94305-5324
USA

Daniel J. Campbell
Benaroya Research Institute
1201 9th Ave.
Seattle, WA 98101
USA

Guy Cinamon
University of California San Francisco
Howard Hughes Medical Institute
Department of Microbiology
San Francisco, CA 94143–0414
USA

Matthias Clauss
Indiana University School of Medicine
Cellular and Integrative Physiology
975 W. Walnut Str. IB 433
Indianapolis, IN 46202
USA

Gabriela Constantin
University of Verona
Department of Pathology
Division of General Pathology
Strada Le Grazie 8
37134 Verona
Italy

Gudrun F. Debes
Stanford University School of Medicine and Veterans Affairs–Palo Alto Health Care System
Department of Pathology
3801 Miranda Avenue
Palo Alto, CA 94304
USA

Britta Engelhardt
University of Bern
Theodor Kocher Institute
Freiestrasse 1
3012 Bern
Switzerland

Stefan Floess
Charité University Medicine Berlin
Experimental Rheumatology
Medical Clinic for Rheumatology and Clinical Immunology
c/o German Rheumatism Research Center
Schumannstr. 21/22
10117 Berlin
Germany

Alexander Flügel
Max Planck Institute of Neurobiology
Department of Neuroimmunology
Am Klopferspitz 18
82152 Martinsried
Germany

Reinhold Förster
Hanover Medical School
Institute of Immunology
Feodor-Lynen-Str. 21
30625 Hannover
Germany

Rupert Hallmann
University of Münster
Institute for Physiological Chemistry and Pathobiochemistry
Waldeyerstr. 15
48149 Münster
Germany

Alf Hamann
Charité University Medicine Berlin
Experimental Rheumatology
Medical Clinic for Rheumatology and Clinical Immunology
c/o German Rheumatism Research Center
Schumannstr. 21/22
10117 Berlin
Germany

Markus Hammel
Lund University
Department of Experimental Pathology
Soelvegatan 25
22362 Lund
Sweden

Sandra Holzmann
Innsbruck Medical University
Department of Dermatology and Venereology
Anichstrasse 35
6020 Innsbruck
Austria

Richard Horuk
Berlex Biosciences
Department of Immunology
2600 Hilltop Drive
Richmond, CA 94806
USA

Silke Jennrich
Charité University Medicine Berlin
Experimental Rheumatology
Medical Clinic for Rheumatology and Clinical Immunology
c/o German Rheumatism Research Center
Schumannstr. 21/22
10117 Berlin
Germany

Naoto Kawakami
Max Planck Institute of Neurobiology
Department of Neuroimmunology
Am Klopferspitz 18
82152 Martinsried
Germany

Paul Kubes
University of Calgary
Immunology Research Group
Department of Physiology and Biophysics
Institute of Infection, Immunity and Inflammation
3330 Hospital Drive N.W.
Calgary, Alberta, T2N 4N1
Canada

Carlo Laudanna
University of Verona
Department of Pathology
Division of General Pathology
Strada Le Grazie 8
37134 Verona
Italy

F.W. Luscinskas
Harvard Medical School
Brigham and Women's Hospital
Department of Pathology
77 Ave Louis Pasteur
Boston, MA 02115
USA

Ruth Lyck
University of Bern
Theodor Kocher Institute
Freiestrasse 1
3012 Bern
Switzerland

Rudolf A. Manz
German Rheumatism Research Center
DRFZ
Schumannstrasse 21/22
10117 Berlin
Germany

Federica Marelli-Berg
Imperial College London
Faculty of Medicine
Hammersmith Hospital Campus
Du Cane Road
London W12 ONN
UK

Rodger P. McEver
Cardiovascular Biology Research Program
Oklahoma Medical Research Foundation
825 N.E. 13th Street
Oklahoma City, OK 73104
USA

Sussan Nourshargh
Imperial College London
Faculty of Medicine
Hammersmith Hospital Campus
Du Cane Road
London W12 ONN
UK

Martin Oppermann
Georg-August-University Göttingen
Department of Immunology
Kreuzbergring 57
37075 Göttingen
Germany

Carolyn E. Patterson
Indiana University School of Medicine
Roudebush VA Medical Center
1481 W. 10th St. VA111 P
Indianapolis, IN 46202
USA

Sofia Ribeiro
Berlex Biosciences
Department of Immunology
2600 Hilltop Drive
Richmond, CA 94806
USA

Nikolaus Romani
Innsbruck Medical University
Department of Dermatology and Venereology
Anichstrasse 35
6020 Innsbruck
Austria

Antal Rot
Novartis Institutes for Biomedical Research
Brunner Str. 59
1235 Vienna
Austria

Kerstin Siegmund
Charité University Medicine Berlin
Experimental Rheumatology
Medical Clinic for Rheumatology and Clinical Immunology
c/o German Rheumatism Research Center
Schumannstr. 21/22
10117 Berlin
Germany

Michael Sixt
Max-Planck-Institute for Biochemistry
Department of Molecular Medicine
Am Klopferspitz 18
82152 Martinsried
Germany

Lydia M. Sorokin
University of Münster
Institute for Physiological
Chemistry and Pathobiochemistry
Waldeyerstr. 15
48149 Münster
Germany

Markus Sperandio
University of Heidelberg
Children's Hospital, Neonatal Unit
Im Neuenheimer Feld 150
69120 Heidelberg
Germany

Jens V. Stein
University of Bern
Theodor Kocher Institute
Freiestrasse 1
3012 Bern
Switzerland

Patrizia Stoitzner
Department of Dermatology and Venereology
Innsbruck Medical University
Anichstrasse 35
6020 Innsbruck
Austria

Christoph Tripp
Innsbruck Medical University
Department of Dermatology and Venereology
Anichstrasse 35
6020 Innsbruck
Austria

Barbara Walzog
Ludwig-Maximilians-University
Department of Physiology
Schillerstr. 44
80336 Munich
Germany

Olaf Zilles
Lund University
Department of Experimental Pathology
Soelvegatan 25
22362 Lund
Sweden

[Text not available in this electronic edition.]

[Text not available in this electronic edition.]

Color Plates

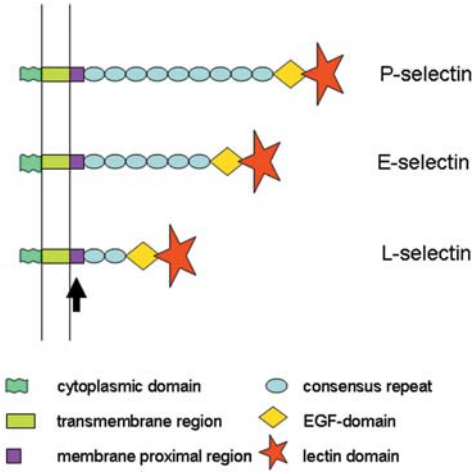

Fig. 2.1. Structural organization of selectins. The N-terminal domain of each selectin is homologous to C-type lectins and binds to carbohydrate groups on their respective ligands. Following this is an epidermal growth factor-like domain and then a variable number of short consensus repeats homologous to complement regulatory proteins. The arrow indicates the cleavage site of L-selectin. (This figure also appears on page 15.)

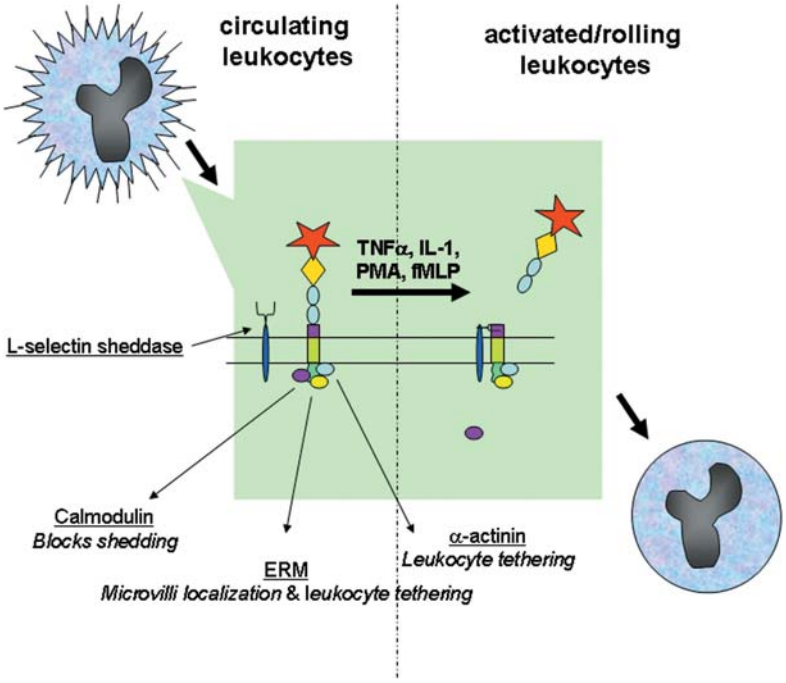

Fig. 2.2. Shedding of L-selectin by leukocytes. In resting leukocytes, calmodulin, α-actinin, and ERM proteins are associated with the cytoplasmic tail of L-selectin as well as actin filaments. Upon cell activation by TNFα, IL-1, PMA, etc., calmodulin is released and L-selectin sheddase cleaves the 69-kDa extracellular domain whilst α-actinin and ERM proteins retain their contact and are involved in microvilli localization as well as leukocyte tethering. (This figure also appears on page 18.)

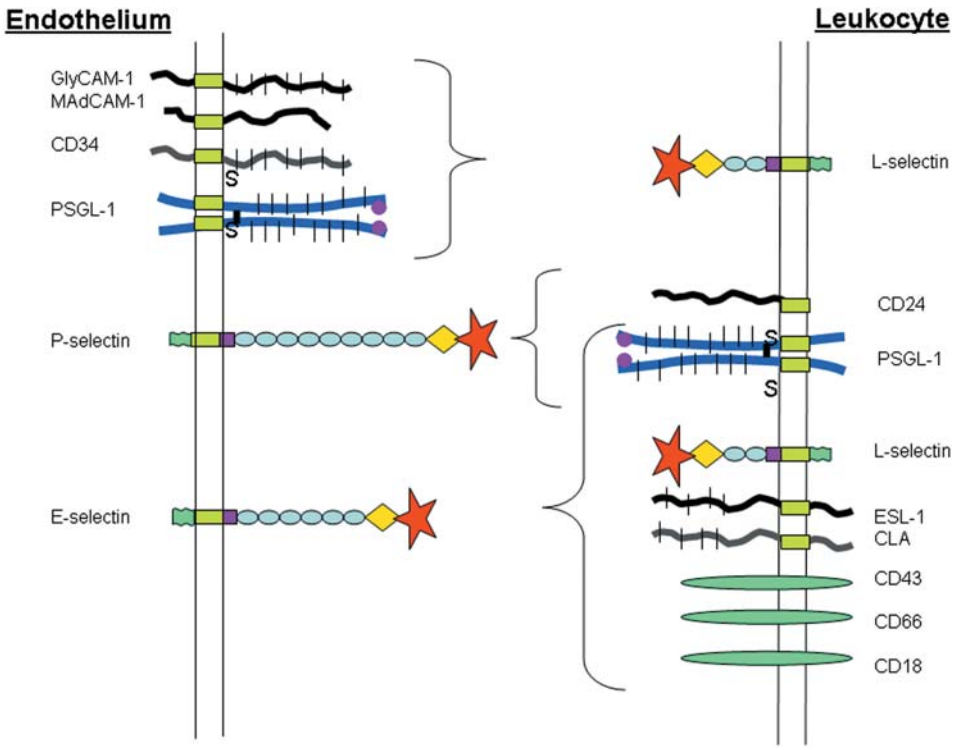

Fig. 2.3. Multiple ligands for L-, P-, and E-selectin have been detected on endothelial cells and leukocytes. (This figure also appears on page 23.)

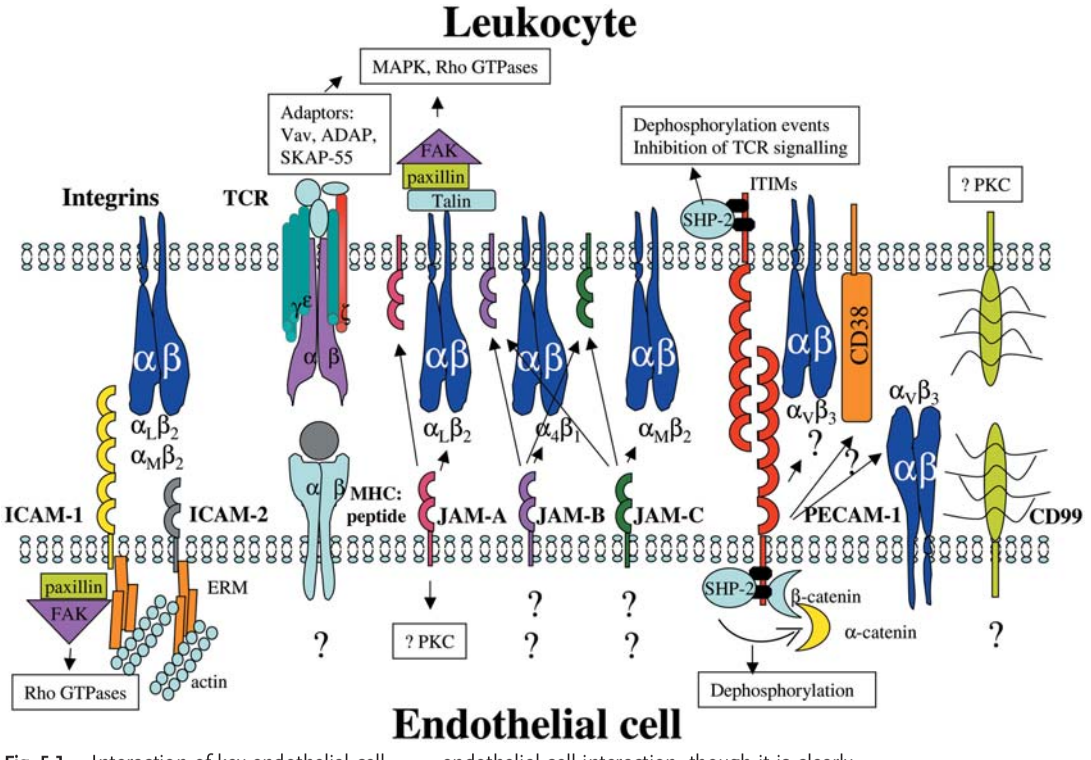

Fig. 5.1. Interaction of key endothelial cell molecules implicated in the process of transendothelial cell migration with their respective leukocyte ligands. Key signaling pathways implicated with specific molecules/molecular interactions are also shown. It should be noted that with respect to the JAM molecules, although homophilic interactions have been shown in other systems (e.g., in endothelial cell–endothelial cell interactions; see text for details), this has not always been demonstrated in the context of leukocyte/endothelial cell interaction, though it is clearly a possibility. FAK, focal adhesion kinase; T cell receptor (TCR); ERM, ezrin–radixin–moesin; PKC, protein kinase C; ADAP, adhesion and degranulation promoting adaptor protein; SKAP-55, src kinase-associated phosphoprotein of 55 kDa; MAPK, mitogen-activated protein kinase; SHP-2, Src homology domain protein-2; ITIM, immunoreceptor tyrosine-based inhibitory motif; MHC, major histocompatibility complex. (This figure also appears on page 85.)