

## **Summaries Ley (ed.): Adhesion Molecules: Function and Inhibition**

### **Summary**

**Rodger P. McEver**

#### **P-selectin glycoprotein ligand-1 (PSGL-1)**

PSGL-1 is a homodimeric, transmembrane mucin on leukocytes that interacts with each of the three selectins. These interactions mediate adhesive contacts among leukocytes, platelets, and endothelial cells during inflammation. Specific posttranslational modifications of PSGL-1 are required for selectin binding. Additional structural properties of PSGL-1 and selectins enable them to support rapid leukocyte tethering to and rolling on vascular surfaces despite the kinetic and mechanical constraints of flowing blood. Dysregulated binding of PSGL-1 to selectins contributes to inflammatory and thrombotic disorders. Newly described interactions of PSGL-1 with chemokines and other molecules may extend its biological functions.

**Keywords:** PSGL-1, selectin, adhesion, rolling, glycosylation, sulfation, inflammation, thrombosis, mucin, leukocyte, platelet, endothelial cell, chemokine, hematopoietic cell

### **Summary**

**Doug Steeber**

#### **L-selectin-mediated leukocyte adhesion and migration**

L-selectin is a cell adhesion molecule that mediates lymphocyte recirculation and leukocyte migration during inflammation. It is expressed constitutively on most leukocytes and binds to complex carbohydrate ligands present on vascular endothelium and leukocytes. Migration of lymphocytes to peripheral as well as some mucosal lymphoid tissues is critically dependent on L-selectin. L-selectin can also act as a signaling molecule via its cytoplasmic tail allowing it to interact synergistically with other adhesion molecules. L-selectin-mediated leukocyte migration plays a role in the development of multiple chronic inflammatory diseases making it an attractive target for therapeutic intervention. This chapter will examine the structure and function of L-selectin and its role in leukocyte recirculation, migration, and the development of disease.

**Keywords:** selectin, adhesion, leukocyte, T cell, B cell, vascular endothelium, high endothelial venules, homing, migration, inflammation, disease, autoimmunity

### **Summary**

**Daniel C. Bullard**

#### **P- and E-selectin**

P- and E-selectin have been intensively studied since their initial discovery during the 1980's. One of the main functions of these proteins is to mediate leukocyte rolling along activated endothelial cells, which facilitates both firm adhesion and emigration, while P-selectin also participates in a number of different platelet responses. However, there is growing evidence suggesting that their functions are not limited simply to rolling, and that these molecules play

key roles in promoting leukocyte and platelet adhesion and signaling events during inflammatory responses, as well as serve regulatory roles in the development of different diseases. In the following sections, I will briefly review the structure and expression characteristics of these molecules, discuss their ligand relationships, highlight a number of studies of P- and E-selectin function in inflammatory model systems, and summarize the current information regarding the roles these adhesion proteins in the development of inflammatory diseases. Finally, I will discuss the results of several recent therapeutic studies that used selectin-based inhibitors for the treatment of patients with different human inflammatory disorders.

## **Summary**

**Scott D. Auerbach, Lin Yang and Francis W. Luscinskas**

### **Endothelial ICAM-1 functions in adhesion and signaling during leukocyte recruitment**

Intercellular adhesion molecule-1 (ICAM-1, CD54) was identified more than 20 years ago as a cytokine-inducible adhesion molecule. Endothelial cell ICAM-1 surface expression is elevated at sites of endothelial cell activation *in vivo* and *in vitro*, and contributes to stable adhesion and transmigration of circulating blood leukocytes through its interaction with leukocyte  $\beta$ 2-integrins. This chapter will briefly review ICAM-1 structure, function and then address the mechanisms through which ICAM-1 dependent adhesion and signaling control leukocyte transmigration.

**Keywords:** endothelium, inflammation, adhesion molecule, integrins, neutrophil, monocyte, lymphocytes, cardiovascular disease, atherosclerosis, chronic inflammation, monoclonal antibody

## **Summary**

**Britta Engelhardt**

### **$\alpha$ 4-integrins: structure, function and secrets**

The integrins  $\alpha$ 4 $\beta$ 1 (VLA-4, CD49d/CD29) and  $\alpha$ 4 $\beta$ 7 are cell surface heterodimers expressed mainly on cells of the innate and adaptive immune system.  $\alpha$ 4 $\beta$ 7-integrin plays a central role in mediating lymphocyte homing to gut associated lymphoid tissue via adherence to mucosal addressin cell adhesion molecule (MAdCAM)-1.  $\alpha$ 4 $\beta$ 1-integrin controls trafficking of immune cells to inflamed tissues by mediating adhesion to vascular cell adhesion molecule (VCAM)-1 present on inflamed vascular endothelium. Therapeutic targeting of  $\alpha$ 4-integrin mediated inflammatory cell recruitment has proven successful for the treatment of multiple sclerosis and Crohn's disease. Despite this rapid development, our knowledge on the unique regulation of  $\alpha$ 4-integrin mediated adhesion or signal transduction is far from complete. This chapter summarizes our current knowledge on the structure, activity regulation and biological functions of  $\alpha$ 4-integrins. A special effort is made in pointing out the unresolved issues of  $\alpha$ 4-integrin biology, which will have to be resolved to fully understand the pathophysiological role of this unique member of the integrin family.

**Keywords:**  $\alpha$ 4 $\beta$ 1-integrin, VLA-4,  $\alpha$ 4 $\beta$ 7-integrin, CD49d, CD29, integrin activation, hematopoiesis, propeller domain, Natalizumab, MIDAS, LIBS

## **Summary**

**Sharon J. Hyduk and Myron I. Cybulsky**

### **VCAM-1 and its functions in development and inflammatory diseases**

VCAM-1 is a type I transmembrane glycoprotein and member of the immunoglobulin gene superfamily of adhesion molecules. VCAM-1 was identified in cytokine activated human-umbilical vein endothelial cells. Expression is low on unactivated endothelium and rapidly upregulated following stimulation with IL-1 or TNF. Endothelial expression of VCAM-1 is induced in many acute and chronic inflammatory conditions and other pathological processes and is regulated by the transcription factor NF- $\kappa$ B. In addition to inducible expression on vascular endothelium, VCAM-1 can be induced on vascular smooth muscle cells and is expressed constitutively on a variety of cell types including bone marrow stroma, myeloid and dendritic leukocytes, skeletal muscle myoblasts and differentiating vascular smooth muscle cells.

The primary ligand for VCAM-1 is the  $\alpha$ 4 $\beta$ 1 integrin, which is expressed on mononuclear leukocytes and on non-hematopoietic cells in a number of embryonic tissues. VCAM-1 and  $\alpha$ 4 integrins have been shown to participate to various degrees in all steps of leukocyte emigration; rolling, arrest, adhesion and migration and thus are important regulators of leukocyte recruitment in inflammatory disease. VCAM-1 and  $\alpha$ 4 integrins are important in the pathogenesis of a variety of inflammatory disorders including multiple sclerosis and rheumatoid arthritis. VCAM-1 also has a critical role in atherogenesis, and mice deficient in VCAM-1 have greatly reduced lesion size. A soluble form of VCAM-1 consisting of the entire extracellular region is found in plasma and other body fluids and can serve as a marker of inflammatory disease activity. VCAM-1 also binds the integrins  $\alpha$ 4 $\beta$ 7,  $\alpha$ 9 $\beta$ 1 and  $\alpha$ D $\beta$ 2 and through these interactions regulates leukocyte adhesion and migration. Recently, SPARC was identified as a non-integrin ligand for VCAM-1 that regulates leukocyte migration, but not adhesion.

The temporal and spatial expression patterns of VCAM-1 and its ligands suggest that these adhesion molecules participate in a variety of physiological and developmental processes. They play a critical role during fusion of the allantois to the chorion and may play roles in myogenesis and pericardial development. They also participate in hematopoiesis and lymphocyte homing.

**Keywords:** VCAM-1,  $\alpha$ 4 integrin, NF- $\kappa$ B signaling, leukocyte emigration, atherogenesis, hematopoiesis, placentation

## **Summary**

**Alan Schenkel and Min Soo Kim**

### **Lymphocyte function-associated antigen-1 (LFA-1) and macrophage antigen-1 (Mac-1): Cooperative partners in leukocyte emigration and function**

Lymphocyte Function-Associated antigen-1 (LFA-1) and Macrophage antigen-1 (Mac-1) are heterodimeric integrins with a common  $\beta$  subunit, common structural features, and common roles in some leukocyte functions. They also have some rather diverse functions and ligands.

Many of the ligands for both LFA-1 and Mac-1 are members of the immunoglobulin-domain super family. By using overlapping members of their respective ligands, both LFA-1 and Mac-1 have vital roles in the extravasation of leukocytes and cell signaling/activation. In a bit of adaptive function, Mac-1, unlike LFA-1, also serves to recognize pathogenic surfaces.

Recent advances in defining the structure of these molecules have demonstrated important molecular mechanisms for integrin activation and ligand binding, and show how the three-dimensional structures of these integrins relate to function. Finally, the roles of each integrin at many different steps in leukocyte function are elucidated, showing that these molecules share some overlapping functions but also play different roles at distinct cellular processes.

**Keywords:** lymphocyte function-associated antigen-1 (LFA-1), macrophage antigen-1 (Mac-1), integrins, adhesion, extravasation, ligands, emigration, activation, signaling, clustering, structure, locomotion, rolling

## Summary

**William A. Muller**

### **PECAM: Regulating the start of diapedesis**

Platelet/endothelial cell adhesion molecule-1 (PECAM-1, CD31) is a transmembrane glycoprotein concentrated at endothelial cell borders and expressed diffusely on platelets and most leukocyte types. Homophilic interaction of leukocyte PECAM with endothelial PECAM is critical for leukocytes to migrate across endothelial cells into sites of inflammation. Despite *in vivo* studies in three animal species demonstrating the utility of PECAM blockade, enthusiasm for PECAM as an anti-inflammatory target waned when PECAM-deficient mice showed little deficiency in inflammation. However, this turns out to be due to the mouse strain (C57Bl/6) into which they were originally bred. PECAM knockout mice in the FVB/n strain show severe inflammatory deficiencies, and C57Bl/6 appear unique among mouse strains in their ability to overcome blockade of PECAM. This underscores the importance of careful comparison of inbred strains when evaluating mouse models. The mechanisms by which PECAM regulates diapedesis are discussed.

**Keywords:** diapedesis, platelet/endothelial cell adhesion molecule-1, CD31, leukocyte, endothelial cell, inflammation, cell adhesion, membrane trafficking, cell signaling, transendothelial migration, animal models

## Summary

**Mathieu-Benoit Voisin and Sussan Nourshargh**

### **Role of $\alpha_6\beta_1$ integrin in leukocyte adhesion and transmigration**

The integrin  $\alpha_6\beta_1$  is a key receptor for the extracellular matrix protein laminin. It is expressed on numerous cell types including leukocytes, epithelial cells and endothelial cells and its functional roles include regulation of cell adhesion, anchorage and motility. Through its ability to act as a receptor for the principal laminin isoforms of the vascular basement membrane, laminins 8 and 10,  $\alpha_6\beta_1$  appears to play a critical role in mediating leukocyte migration through the vessel wall. Indeed there is now significant evidence to suggest that regulated expression of this integrin during the transmigration process facilitates the migration of neutrophils through the venular basement membrane. The growing interest in the role of  $\alpha_6\beta_1$  in regulation of inflammatory events has led to the dedication of this Chapter to its biology. Specifically, the Chapter details the structure, expression profile and ability of  $\alpha_6\beta_1$  to act as a signalling molecule. Furthermore, the role of  $\alpha_6\beta_1$  in mediating leukocyte adhesion to and migration through basement membrane like structures *in vitro* and migration through venular walls *in vivo* will be reviewed.

**Keywords:** leukocyte, adhesion, inflammation, integrin, migration, vessel wall,  $\alpha_6\beta_1$ , basement membrane, laminin

#### **Summary**

**Marko Salmi and Sirpa Jalkanen**

#### **Vascular adhesion protein-1 (VAP-1)**

Vascular adhesion protein-1 (VAP-1) is a cell-surface expressed amine oxidase that is involved in leukocyte traffic. When its function is blocked either by monoclonal antibodies or small molecule enzyme inhibitors, the leukocyte extravasation cascade is altered. Inhibition of VAP-1 ameliorates inflammation in multiple experimental models. Generation of VAP-1 deficient mice has recently confirmed the importance of this oxidase in leukocyte migration. The ecto-enzymatic control of leukocyte extravasation by VAP-1 has opened a new paradigm in understanding leukocyte traffic.

**Keywords:** adhesion molecules, endothelium, enzymes, amine oxidases, inflammation, soluble, leukocyte traffic, gene-deficient, inhibitors, AOC3, SSAO

#### **Summary**

**Dietmar Vestweber and Stefan Butz**

#### **The role of endothelial cell-selective adhesion molecule (ESAM) in neutrophil emigration into inflamed tissues**

Recent studies propose the tight junction-associated endothelial cell-selective adhesion molecule (ESAM) as a new player in the process of leukocyte emigration into inflamed tissues. This functional role of ESAM was established by analysing mice carrying a genetically inactivated ESAM gene in different inflammation models. As a consequence of this gene disruption neutrophil, but not lymphocyte, extravasation at inflammatory sites was reduced. Intravital microscopy analysis revealed that neutrophil emigration was impaired in ESAM<sup>-/-</sup> mice at the level of transmigration. Knocking down ESAM expression in endothelial cells resulted in reduced levels of activated Rho, a GTPase implicated in the destabilization of tight junctions. Indeed, VEGF-triggered increase of vascular permeability was reduced in ESAM<sup>-/-</sup> mice. Collectively, these results suggest that ESAM participates in the migration of neutrophils through the vessel wall, possibly by influencing endothelial cell contacts.

**Keywords:** endothelial cell-selective adhesion molecule, ESAM, neutrophil emigration, leukocyte extravasation, immunoglobulin superfamily, endothelial cell contacts, endothelial tight junctions, CTX-family, transendothelial migration, diapedesis

#### **Summary**

**Eric Severson and Charles A. Parkos**

#### **Structure and function of JAM proteins**

Junctional adhesion molecules (JAMs) are immunoglobulin superfamily (IGSF) members that are variably expressed in a number of cell types, most notably at cell-cell contacts in

endothelial and epithelial cells and in a variety of hematopoietic cells. Three of the best studied members termed JAM-A, B and C contain two extracellular Ig-like domains, a single type I transmembrane segment and a cytoplasmic tail ending in a PSD-95/Discs-Large/ZO-1 (PDZ) type II binding motif at the carboxy terminus. JAM proteins play important roles in diverse cell biological functions including regulation of barrier/permeability, cell adhesion/migration, angiogenesis and development of cell polarity. Furthermore, members of this protein family have been shown to function as receptors for certain viruses. This review will focus on the current understanding of the three most studied members of the JAM protein family, JAM-A, B and C and will highlight structural features, protein interactions and the functional significance of such in vivo.

**Keywords:** homophilic interactions, cis-dimerization, PDZ binding motif, immunoglobulin superfamily (IgSF), cell polarity, cell barrier, cell adhesion, cell migration, leukocyte transmigration, angiogenesis

## **Summary**

**Karyn Yonekawa and John M. Harlan**

### **Promises and limitations of targeting adhesion molecules for therapy**

The identification of the adhesion molecules involved in leukocyte trafficking promised the development of new therapeutics for inflammatory and immune diseases. Antagonists that disrupted one or more steps in the adhesion cascade demonstrated striking efficacy in multiple experimental models. However, as reviewed in this chapter, the early excitement has been tempered by disappointing results with more than twenty unsuccessful clinical trials of various adhesion antagonists in multiple disease indications. Moreover, the report of progressive multifocal leukoencephalopathy, a rare viral infection, in three patients treated with the  $\alpha$ 4-integrin antagonist natalizumab, has highlighted the risks of targeting molecules that are pivotal in host defense and repair as well as disease. Despite these disappointments and challenges, the tremendous potential of anti-adhesion therapy is demonstrated by the approval of two integrin antagonists, efalizumab for the treatment of psoriasis and natalizumab for the treatment of multiple sclerosis.

**Keywords:** enlimomab, CY-1503, efalizumab, natalizumab, alicaforsen, fingolimod, rovelizumab, erlizumab, enlimomab, odulimomab, aselizumab, PML, progressive multifocal leukoencephalopathy, AGI-1067, UK279,276, MLN02

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