



Cell-to-cell contact and extracellular matrix

Editorial overview: Cell-cell and cell-matrix interactions – running, jumping, standing still

Eric Brown and Elisabetta Dejana

Current Opinion in Cell Biology 2003, **15**:505–508

This review comes from a themed issue on
Cell-to-cell contact and extracellular matrix
Edited by Eric Brown and Elisabetta Dejana

0955-0674/\$ – see front matter
© 2003 Elsevier Ltd. All rights reserved.

DOI 10.1016/S0955-0674(03)00108-X

Eric Brown

Program in Microbial Pathogenesis and Host Defense, University of California, San Francisco, Campus Box 2140, 600 16th Street, San Francisco, CA 94143-2140, USA

Eric Brown is a professor at the University of California, San Francisco, where his laboratory works on integrins and associated molecules in host defense, inflammation and immune responses.

Elisabetta Dejana

Department of Biomolecular and Biotechnological Sciences, Faculty of Sciences, University of Milan, Mario Negri Institute and Institute of Molecular Oncology of the Italian Foundation for Cancer Research, Via Adamello 16, 20139 Milan, Italy

Elisabetta Dejana is the director of the Laboratory of Vascular Biology at IFOM. Her group has a lasting interest in the molecular organization of endothelial cell-cell junctions, with a particular focus on cadherins and tight junction adhesion molecules such as the members of the JAM family.

Although many cell biologists often study cells in isolation, in metazoan organisms cells exist in a complex environment of other cells and proteins organized into an extracellular matrix. Most environmental cues are interpreted in the context of this complex milieu, and it is increasingly clear that the effects of even classical soluble signals such as hormones, growth factors and cytokines are highly dependent on these surrounding elements. Thus, for any cell, its interactions with other cells and the extracellular matrix underlie all its responses. It is therefore unsurprising that adhesion molecule functions have a central place in virtually all major phenomena of multicellular organisms from embryo development, organization of organs and their substructures, through diverse functions of the mature organism, including angiogenesis, wound repair, and defense against infection. Given this broad array of functions underlain by adhesion events, it is no wonder that this field is rapidly diversifying. For every biological phenomenon, investigation makes the complexity underlying the function of adhesion molecules more apparent. It is quite a daunting task to survey this very broad area of cell biology once a year in a single issue of *Current Opinion in Cell Biology*, or even to summarize the new concepts that have emerged recently.

One general theme becoming increasingly clear is that, while once thought of as cellular ‘glue’, adhesion molecules are not simply velcro or passive links connecting the cytoskeleton to the adhesive surface. Instead, adhesion molecules actively communicate with a surprising variety of signal transduction cascades, and the molecular events in this communication are being elucidated in a variety of contexts. Adhesion molecule influence on signal transduction can be manifest in a variety of ways, such as direct activation of signaling pathways, interaction with growth factor receptors and other signaling partners, or binding to transcription factors to limit their nuclear translocation.

An implication of the now well-accepted idea that adhesion molecules act as signal transduction receptors is that input through these receptors must be regulated dynamically in order to vary inputs to the signaling pathways; this is indeed the case even in apparently static adhesions, such as those between epithelial cells or endothelial cells. An emerging concept in this field is the remarkably dynamic nature of all cell adhesions. Many adhesion molecules are members of four structural superfamilies: the integrins, the immunoglobulin superfamily, lectins, and cadherins, and it is now clear that

members of each of these families have important roles in signaling, even in apparently 'static' junctions at epithelial and endothelial barriers. Indeed, what may appear as a 'resting' condition in these cells requires a continuous readjustment of adhesive proteins and their signaling machineries at cell–cell or cell–matrix junctions. This is a prerequisite to maintain homeostatic conditions, limit cell growth and apoptosis, and to control interaction with other cells in the immediate environment or circulating in the bloodstream.

The significance of signaling by cadherins in epithelia is reviewed by Wheelock and Johnson, who discuss the emergence of understanding the quite diverse roles for this family of proteins. An important question in this field is how classic cadherins, which have highly homologous cytoplasmic tails and identical intracellular partners, can transduce different signals. It is possible that interaction with still undefined effectors or the membrane micro-environment in which the cadherin is found modulates the specificity of response. In general, the cellular context can greatly influence the adhesive and signaling properties of a given molecule. The same cadherin behaves differently in different cell types; and the same is true for integrins and other adhesive proteins. It is assumed that the presence of cell-specific cofactors, other adhesive proteins or cell–cell interactions could strongly influence the final signaling outcome. Ilan and Madri review the emerging panoply of functions for PECAM-1 (CD31), long known to participate in formation of the endothelial permeability barrier, and recently shown to regulate a variety of signaling events important in development and in endothelial responses in the adult. The junctional adhesion molecules (JAMs) are another, recently discovered, set of immunoglobulin superfamily members present at intercellular junctions of epithelial and endothelial cells. The recent discovery that these proteins can act as receptors for leukocyte integrins assures that these, too, will be involved in dynamic regulation of the endothelial barrier. Current understanding of this intriguing group of adhesion molecules is reviewed by Bazzoni.

Nowhere is the dynamic nature of adhesions clearer than in cell migration. Migration requires the coordinate regulation of both adhesion and de-adhesion. In cells moving over extracellular matrix, the regulation is confined largely to the migrating cell, but in cells migrating over or through other cell layers, it is clear that regulation must occur on both sides, even though only one cell is moving. Leukocyte migration, both through matrix and across endothelial barriers, has been an area of investigation for many years in the adhesion community. The paradigm that leukocyte interactions with endothelium involve rolling interactions followed by firm adhesion and ultimately transendothelial migration, each mediated by a distinct set of receptors and modulated by distinct signals, is now supported by a large amount of data. The initial

rolling interactions, dependent on shear stress from blood flow for their creation, are mediated by selectins, a family of molecules constitutively expressed on leukocytes but selectively upregulated on endothelium overlying sites of inflammation. Lowe reviews selectin biology, with a particular emphasis on the nature, biosynthesis and regulation of the carbohydrate structures that constitute an essential part of the selectin ligands. Cambi and Figdor take a broader perspective and review the whole family of C-type lectins, of which the selectins represent a single branch. Besides its function in leukocyte adhesion and migration, the C-type lectin family has additional important roles in host defense, including antigen uptake and direct recognition of bacteria and viruses, which can sometimes be exploited by pathogens, including *Mycobacterium tuberculosis* and HIV, to their own advantage.

The second step in successful transmigration requires integrin-mediated adhesion of leukocytes to the endothelium. Leukocyte integrins are not constitutively active, but must be induced to an adhesion-competent state by molecules present at sites of inflammation. This second signal requirement is probably a central mechanism to prevent spontaneous and undesirable inflammatory and immune responses. Remarkable strides have been made over the past few years in understanding the mechanism of this critical regulation of integrin avidity. Mechanisms involving both integrin conformational change to higher affinity and integrin clustering to increase valency have been demonstrated. Carman and Springer review these data and, in an opinion, propose a comprehensive model to understand the disparate observations.

A third step in leukocyte recruitment is their passage through endothelial and epithelial barriers. PECAM-1 and JAMs have been implicated in the regulation of leukocyte transmigration through endothelial and epithelial junctions (see the reviews of Zen and Parkos, and Bazzoni). Their mechanisms of action are still largely unknown, but there is evidence that these junctional proteins might form a ring-like structure around the leukocytes that is able to transport these cells through junctions. The expression of both proteins on the surface of leukocytes suggest that homophilic interactions of these molecules between leukocytes and endothelial cells might be important in this process. In addition, JAM–JAM or PECAM–PECAM adhesion could constitute a transient seal around migrating cells for maintenance of barrier properties. To what extent do leukocyte–epithelial interactions mimic the much better studied transendothelial migration of leukocytes? Most of the adhesion proteins implicated are the same in the two systems. However, Zen and Parkos, who review the work in this area, suggest that there might be many differences from the model generated from studies of migration of leukocytes from the blood. Shear stress, a critical component of the initiation of leukocyte–endothelial interactions, is missing once

leukocytes have extravasated. Moreover, the direction of leukocyte migration is opposite in the two situations: from basal to apical surface in the epithelium and from apical to basal for the endothelium. In addition, the overall organization of cell–cell junctions and in particular of tight junctions is much more complex in epithelial than in endothelial cells, implying different types of adhesive interactions.

The study of the specific signaling cascades that interact with adhesion molecules is an area that has undergone explosive growth in the past few years. Virtually all aspects of adhesion molecule function are subject to bidirectional regulation with signaling cascades. Among the best studied are the interactions of adhesion molecules with tyrosine kinase cascades. From the time that it was recognized that the mitogenic response to growth factors requires cell adhesion, the interaction of adhesion molecules, especially integrins, with growth-factor-stimulated mitogenic pathways has been under analysis. Besides integrins, cadherins and members of the immunoglobulin family also might interact with growth factor receptors and modulate their signaling and internalization in positive and negative ways. The association between growth factor receptors and adhesion molecules can be quite intimate, and considerable unraveling of the molecular mechanisms for their cooperation has occurred in recent years. The molecular mechanisms for their reciprocal regulation are reviewed by Comoglio *et al.*, who conclude that the adhesion receptors and growth factor receptors have distinct and complementary functions in generation of the mitogenic signal.

Another critical aspect of integrin signaling involves communication with the cytoskeleton. Initially, attention focused primarily on the ability of many adhesion molecules to couple physically to actin-containing microfilaments and to intermediate filaments. The model was that a ligated adhesion molecule could exert traction on the cytoskeleton; the cytoskeleton could, in turn, help organize adhesion molecules on the plasma membrane. It is now clear that the crosstalk between adhesion molecules and cytoskeleton is immensely more complex and can involve multiple families of protein and lipid kinases and phosphatases. The state of understanding of this critically important and very complicated area is reviewed for a single family of adhesion molecules, the integrins, by DeMali, Wennerberg and Burridge. Within this complexity, it is clear that cytosolic GTPases, especially those of the Rho family, are central players in adhesion molecule regulation of the cytoskeleton. Rap1, a member of the Ras family, also has an important place in inside–out signaling to integrins. The Rho family is the subject of two reviews in this issue, which take different perspectives on the role of these enzymes in adhesion receptor function. Malliri and Collard review the evidence that activation of Rho-family proteins by adhesion is important in cell cycle

progression in tumorigenesis, through collaboration with other mitogenic signaling cascades. Fukata, Nakagawa and Kaibuchi review the roles of these same GTPases in establishing cell polarity, amplifying external gradients of chemoattractants, and mediating directional cell motility. The juxtaposition of these reviews reminds us that these signaling molecules, and probably all signaling cascades, affect quite diverse cell functions, and conclusions are very dependent on perspective.

Another area of adhesion molecule biology that has received increasing attention is regulation by other plasma membrane molecules. Some of this regulation occurs because of the formation of supramolecular complexes involving adhesion molecules and their regulators at the cell surface. Multiple examples of such regulation exist, for example, between integrins and tetraspanins, CD47, or the urokinase receptor uPAR. However, in most cases the mechanisms of regulation remain obscure. Perhaps the best understood regulators of adhesion molecule function are the ADAMs family, reviewed by White. These adhesive molecules with protease activity modulate many aspects of the biology of cell–cell and cell–matrix interactions. They may regulate — by causing shedding from the cell surface — the availability of adhesion proteins, growth factor receptors or substrates. Moreover, ADAMs can modulate cell–matrix interactions both because they can disengage matrix receptors from substrates through their disintegrin domain and because they can induce matrix remodeling through direct cleavage of matrix proteins via their metalloprotease activity.

Of course, progress in understanding the complexities of adhesion molecule biology will require new experimental approaches that take advantage of the revolutions in genetics, proteomics, bioinformatics, and so on, that are underway. In this issue, there are reviews of two examples of new approaches. *Drosophila* has three major integrin genes — two alpha chains and a single beta chain — so the receptor complexity present in mammals is greatly reduced. Combined with the ability to do genetic screens and use tools such as RNA interference, this simplicity has proved a potent tool for dissecting both integrin-dependent signaling pathways and multimolecular adhesion structures. In general, the use of genetically tractable model organisms such as *Drosophila*, *Caenorhabditis elegans* and zebrafish for screens to identify proteins important in cell signaling, tissue organization and organogenesis is more and more attractive in the field, because of the simplicity of the systems and the rapidity with which definitive information can be obtained. Brower reviews recent progress in this area using *Drosophila*. Webb *et al.* review a very different approach to understanding adhesion and migration, based on advances in the ability to visualize directly the assembly and disassembly of adhesion structures. These microscopic methods allow direct

visualization of kinetic processes that would be hopelessly complex to describe by traditional, static methods, and which therefore promise new insights because of an entirely new perspective.

Ultimately, the enhanced understanding that comes from studying the cell biology of adhesion molecules has to be incorporated into the much more complex functions of organs and whole organisms. Yamagata *et al.* review progress in addressing this increased complexity at neuronal synapses, and discuss roles for adhesion molecules in formation, stability, differentiation and regulation of the synapse. It is clear that very much more needs to be done to understand how the many functions of adhesion molecules are integrated at a multicellular level. Boyle and Finlay review a completely different aspect of integrative biology: the interaction of metazoan organisms with the prokaryotic world in which they live. In each of us, there are about 100 times as many bacteria (living at epithelial surfaces in the gut, in the respiratory tree, and on the skin) as eukaryotic cells, so the interface between the two worlds needs to receive a lot of attention from metazoan hosts. At the same time, there are many opportunities for the more rapidly dividing prokaryotes to find ways to take advantage of normal host cell biological processes for their own survival and proliferation. In their review, Boyle and Finlay survey the mechanisms by which bacterial pathogens exploit host-cell adhesion molecules to establish, maintain or spread infection. Interestingly, all four families of adhesion molecules — cadherins, integrins, immunoglobulins and selectins — have been found to interact with specific counter-receptors on pathogens. These insights, fascinating from

a scientific point of view, might also offer new perspectives for modulating adhesive interactions, for developing new inhibitory agents, and for treating infectious diseases.

Finally, it is important to be able to turn increased understanding of basic cell biological processes into improvements in human health. The central roles for adhesion molecules in many pathological processes make them attractive targets for therapeutic agents or preventative measures in a wide variety of diseases. However, these targets may be a double-edged sword, since these same molecules are involved in so many normal and necessary physiological events. Increased understanding of the molecular events that occur subsequent to adhesion during specific diseases holds out the hope that therapies can be designed that have minimal side effects on normal functions. With these concerns in mind, 'magic bullet' targeted therapies are being generated; Houshmand and Zlotick review a variety of approaches currently in use or under investigation to treat cancer.

Adhesion-molecule research now encompasses studies ranging from issues of structure at atomic resolution, through many levels of study of molecular interactions and biology of increasing complexity within a single cell, to multicellular structures, and to treatment of a variety of diseases. Such breadth brings a multiplicity of new problems into focus, and the reviews in this issue suggest research areas likely to bring rapid increases in our knowledge in the future. A major challenge for several years will be to integrate the information obtained at all levels of investigation to obtain a complete picture of the roles for cell–cell and cell–matrix adhesion in organismal biology.