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Introduction: integrins, dynamic cell receptors

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Abstract. Integrins are a family of adhesive receptors consisting of α- and β-subunits which attach cells together via adhesive protein ligands or bind cells to extracellular matrix. They are found on virtually all cell types and link the external ligand to the cytoskeleton of the cell. Integrins also act as signal transducers both from the outside of the cell to the interior and also inside-out. Their main functions are in recognition and in tight but regulated binding. The series of reviews presented here cover both basic aspects of integrin function, including signal transduction, snake disintegrins and structure and function of I-domains in some integrin α-subunits, as well as the role of integrins in diseases, cancer, inflammation and cardiovascular diseases. The search for suitable inhibitors of integrins for treatment of these diseases and future prospects for their use are also discussed.

Key words. Integrins; inhibitors; signal transduction; disintegrins; I-domain; cancer; inflammation; cardiovascular.

The integrins are a ubiquitous class of adhesion receptors, managing the interactions of cells with adhesive proteins (or receptors on other cells) in their environment and, by internal links and clustering altered by these extracellular interactions, controlling the organization of the cytoskeleton and the cell phenotype. As such they have an essential role in nearly all aspects of cell biology, stretching from the adhesion between sperm and oocyte necessary for fertilization to occur [1], via the cell recognition events which establish the embryo structure and regulate its development, all the way through to neuron-neuron recognition in the organization of the brain involved in memory [2]. Of course, they do not perform these functions completely on their own, being supported by a wide range of other classes of adhesive receptors, but they nevertheless provide the high affinity and strong binding which is indispensible for these cohesions. While there is still a lot to learn about how integrins carry out their functions, and an important research effort has focussed on this problem, the importance of integrins in physiology and in pathology has attracted the attention of the pharmaceutical industry, and already inhibitors are being applied clinically and have reduced suffering and death. In the series of reviews presented here, selected topics of integrin biology have been presented by experts in these fields. There are two broad areas covered; in the first more basic aspects of integrin structure and function are considered, and in the second, the emphasis is on the role of integrins in various aspects of disease. Celia Longhurst and Lisa Jennings deal with signalling via integrins and the way in which integrins allow cells to communicate in both directions between their environment and their interior. This is an extremely complicated four-dimensional jigsaw puzzle where the arrangement of the pieces changes with time; it is complicated even further by the fact that many of the pieces have not yet been identified, and we do not know how they fit together. Despite these handicaps, the progress of the last decade, starting from virtually zero, has been remarkable, and we are beginning to have an idea about how some parts of this mechanism work. These authors have done a remarkable job of fitting the available data together and making them comprehensible. There is considerable interest in these signal transduction processes not only from a basic scientific viewpoint but also as a source of genetic and environmental health problems. As well, on the positive side, they are a source of targets for a possible alternative therapeutic approach to inhibition of specific cell functions.

Tur-Fu Huang has been a leading pioneer in the art of identification and isolation of snake venom molecules that interact with platelet receptors, in particular, integrins. The determination of the structure of these snake venom integrin inhibitors – now called disintegrins because of their ability to dissociate adhering cells – has played an important role in the development of present-day pharmaceutical inhibitors, and their use as tools has provided much information about how integrins work. In his review he deals with several aspects of these fascinating proteins. Many physiologically important proteins contain an Arg-Gly-Asp (RGD) sequence which is the key to the role of many integrins as well as to the ability of disintegrins to block these functions. The ideas behind the conformations of small cyclic peptides endowing high specificity for a given integrin also came largely from studies of disintegrins. The success of these earlier studies has prompted the search for venom components which interact with other cell receptors, such as the I-domain integrins, including proteins that combine both disintegrin and metalloprotease domains. Huang also deals with snake venom proteins that inhibit platelet function via nonintegrin receptors. These appear to be promising models for a new class of thrombosis inhibitors which act by preventing or reducing platelet activation rather than by blocking its consequences.

Kent Dickeson and Samuel Santoro deal in detail with the distinguishing features of an important subclass of the α-subunits of integrins which is just starting to be understood, those containing I-domains, and their biological function. Seven α-subunits as well as other adhesive proteins like von Willebrand factor and some types of collagen contain this domain structure. Recent crystallographic studies of several different I-domains have revealed a typical structural motif, both a cation-binding site and a ligand-binding site. The ligand binding is dependent on that of the cation as well as on the particular cation bound. The specific function of this class of integrins and its relation to the cytoskeleton compared with 'classic' integrins is an area of active research. Its understanding will help to clarify several aspects of developmental biology ranging from how tissue structure develops to, perhaps, giving a clue to the role of magnesium in cardiovascular disorders.

Cellular adhesion and its dysfunction plays a critical role in cancer, in particular in the propagation and distribution of cancer cells from a primary locus, which is known as metastasis. Philippe Clezardin deals with the involvement of integrins in this process, as well as in the organization of the blood supply to solid tumours by adapting the physiological process of angiogenesis. These are areas where inhibitors of integrins may aid in the battle against tumour growth and distribution and may allow cytotoxic agents to have a much greater efficacy. Changes in expression patterns of integrins as well as in their function are regularly observed in tumours. Integrins are thought to have a role in the regulation of apoptosis and may be involved in its disturbance and dysfunction in tumour cells. The important role of integrins in cell anchorage and in helping to establish tissue recognition may also be critical factors. Integrin inhibitors are now being tested for inhibition of angiogenesis and will provide information about the suitability of this approach.

Carl Gahmberg and his colleagues describe the role of integrins in inflammation. This is again a very important area that touches upon many aspects critical for modern medicine. The response of the body to pathogenic organisms as well as many chronic disorders is dependent on the cellular components of the immune system and how they are regulated. In addition to being essential to an adequate defence, this role in diseases such as asthma and arthritis, as well as in tissue damage in organ transplants and after reestablishment of circulation following stoppages due to thrombosis, suggests that suitable modulation might reduce these consequences of inflammation. Indeed, trials with inhibitors such as specific antibodies to leukocyte integrins support this hypothesis. There is still a lack of suitable high-avidity, small molecular mass inhibitors but much research is directed to the search for such compounds.

Cardiovascular diseases are an area where inhibitors of integrins have already been applied with success but where there is still a great deal to do. With J. M. Clemetson I have surveyed the role of integrins in these disorders and the efforts that have been made and are being made to develop prophylaxis and treatment. The major target so far has been platelets. These often neglected, but nonetheless vital; cellular elements of the blood are deeply involved in the process of atherosclerosis as well as being far from innocent bystanders during surgical intervention. The principal platelet integrin, $\alpha_{IIb}\beta_3$, has an indispensible role in platelet function that was discovered by the existence of natural 'knockout' conditions leading to bleeding problems. This was the inspiration for the development of both specific antibodies as well as inhibitors based on snake venom peptides. Since both of these are effective in reducing cardiovascular problems, a major research effort has been directed at producing orally active peptidomimetics. When these have been confirmed to be effective and safe, a new era in the treatment of these disorders will have opened. However, this is not the end of the line, and both in terms of devising other ways of modifying platelet function as well as investigating the role of other cells in atherosclerosis, much research still remains to be done.

A large number of integrin types are already known, and they are widely distributed over many tissues. In these six reviews the structure and function as well as some medical aspects of integrins are surveyed in detail. Because of limitations of space it is not possible to look at all areas of integrin function which are of interest from a biological and medical standpoint. Some of these, such as functions in fertility and in neurology, are only beginning to be explored. It is certain that here and in many other areas the integrins still have many surprises in store for us.

1 Almeida E. A., Huovila A. P., Sutherland A. E., Stephens L. E., Calarco P. G., Shaw L. M. et al. (1995) Mouse egg integrin alpha6 beta 1 functions as a sperm receptor. Cell **81:** 1095–1104
2 Grotewiel M. S., Beck C. D. O., Wu K. W., Zhu X.-R. and Davis R. L. (1998) Integrin-mediated short-term memory in *Drosophila*. Nature **391:** 455–460