It has been approximately 20 years since the discovery of the integrin family of cell adhesion receptors. The identification of this class of proteins answered a long-standing question regarding how cells interact with the extracellular matrix. Integrins clearly play a key structural role in cell–matrix interactions by bridging across the plasma membrane and linking the fibrillar proteins of the matrix to the actin cytoskeleton. Over the years we have learned that this structural role is actually quite complicated, with a variety of adaptor proteins involved in the formation of multiprotein complexes that link integrins to the cytoskeleton. Further, these complexes are dynamic rather than static, thus contributing to the ability of cells to change their shape, extend protrusions, and move.

More than a decade ago the integrin field entered a new stage when it was realized that integrins play a role in signaling as well as in cytoskeletal architecture. Indeed it is increasingly clear that these two functions of integrins are closely intertwined, and that it is primarily the ability of integrins to organize the actin cytoskeleton that underlies integrin contributions to signaling. Although ligation and clustering of integrins can directly initiate signaling events, perhaps the most interesting aspect of integrin signaling is the ability of cells to change their shape, extend protrusions, and move.

Much of the early work on integrin-cytoskeletal interactions and integrin signaling was done by a small number of laboratories, many of which had been interested in cell–matrix interactions for a long time. However, the complexity and inherent biological significance of integrins and integrin signaling soon recruited a whole new cohort of talented investigators to this research arena. These new entrants have provided much of the dynamism of the field for the last few years. Thus, this Special Issue of Biochimica et Biophysica Acta is devoted to the contributions of this newer cohort of investigators, who are in the ascendant phases of their careers. The topics addressed in this issue range broadly over the integrin/cell adhesion/signaling field including integrin activation, formation of specialized integrin-cytoskeletal complexes, control of cell migration, and effects of integrins on programmed cell death. A theme that pervades this Issue is the complex interplay between integrins, the actin cytoskeleton, and signaling proteins, as they impact on cell motility.

In the first article, Scott Blystone probes the relationship between integrin activation and the nucleation of actin filaments at sites of cell adhesion. Most current models suggest that actin filament formation takes place in the cytosol, with the filaments then projecting toward the membrane and eventually linking to specialized adaptor proteins at adhesion sites. Blystone takes an opposing view and posits that actin filament assembly can be triggered at adhesion sites and then project into the cytosol. This novel hypothesis will surely elicit a great deal of interest and will be put to the test using powerful new tools to study the kinetics and directionality of actin filament assembly.

In the second article, Cary Wu presents the PINCH–ILK–Parvin complex as a key regulator of cell shape, cell motility, and the deposition of extracellular matrix material at the cell surface. Further, this complex may also contribute to control of proliferation and cell death. This article focuses on the assembly and regulation of the PINCH–ILK–Parvin complex. Since Integrin-Linked Kinase (ILK) can bind directly to integrin β-subunit cytoplasmic domains, while Parvins bind to actin and paxillin, the complex can clearly contribute to membrane–cytoskeletal linkages, thus playing a structural role. However, in addition, the complex can exert signaling effects through the kinase activity of ILK and through the association of signaling proteins with PINCH and Parvins. Both cell biological and genetic evidence have supported an important role for the PINCH–ILK–Parvin complex in cell morphology and function. Thus, this review provides a timely examination of a multi-protein complex whose significance is becoming increasingly appreciated.

Next, David Chodniewicz and Richard Klemke discuss another key cytoskeletal complex comprised of p130Cas and Crk (or more precisely members of the Cas and Crk families). Both of these proteins are adaptor molecules with the ability to bind many other structural and signaling proteins. The functions of the Cas/Crk complex are en-
hanced by integrin-stimulated tyrosine phosphorylation most likely mediated through FAK and Src-family kinases, while the Abl tyrosine kinase exerts a negative regulatory effect. The overall phosphorylation, assembly and function of the complex are modulated spatially and temporally consequent to integrin engagement. While many signaling molecules can associate with the Cas/Crk complex, its biological role is thought to be focused primarily on the regulation of cell motility through recruitment of DOCK180 and activation of Rac. However, recent evidence has also implicated the Cas/Crk complex in the control of apoptosis. Both of these aspects are fully discussed in the review.

Ever since its discovery, Focal Adhesion Kinase (FAK) has elicited a great deal of attention as a key player in cell adhesion and signaling. In the next review, David Schlaepfer and colleagues provide a thorough and wide-ranging discussion of the biochemical and biological aspects of FAK structure and function. Thus, the roles of the FAK FERM and kinase domains are considered in terms of kinase activity regulation and interactions with other proteins. Another particular strength of this review is an insightful analysis of the role of FAK in early development in mammals and lower organisms. FAK has long been recognized as a key mediator of focal adhesion turnover and cell migration. FAK also plays a role in the invasive and metastatic behavior of tumor cells. However, recent observations suggest that FAK’s role in tumor invasion is not solely due to its effects on cell motility. This fascinating set of observations is fully discussed in the review.

In the following article, Patricia Keely and colleagues provide an overview of the assembly and function of the focal adhesion complex. The functions of FAK, Src-kinases and structural proteins such as paxillin, p130Cas and talin are discussed in this context. This article also examines the role of small GTPases such as R-Ras in activating integrins and enhancing focal adhesion formation. Going further, the authors discuss the dynamics of focal adhesions and the role of external force and of intracellular contractility in this process. Finally, they compare and contrast adhesive structures observed in three-dimensional as opposed to two-dimensional cell culture environments. Thus, this review integrates some of the themes of the previous reviews and helps to place them in a biological context.

The role of Src and other non-receptor tyrosine kinases in cytoskeletal regulation and cell motility is addressed by Margaret Frame and colleagues. This article first discusses the relationship between integrins and the Arp2/3 complex (and associated proteins such as SCAR/WASP) in regulating actin branching and membrane protrusions. It then explores the role of activated Src in regulating integrins and actin function. This has many facets including direct phosphorylation of integrin cytoplasmic tails, actions on small GTPases and their regulators including GAPs and exchange factors, and actions on structural proteins such as talin, cortactin and mDia. This review also deals with the complex interplay between FAK and Src in regulating focal adhesion formation and cell migration. A section of the review introduces the c-Abl tyrosine kinase and its role in actin assembly. Finally, the article goes on to consider the role of Src and other tyrosine kinases in the cadherin adhesion network and the formation of adherens junctions. Interestingly, it points out potentially parallel roles for FAK at focal contacts and p120catenin at adherens junctions as key regulators of actin remodeling and junctional turnover.

Taking up another theme, Alan Howe addresses the role of protein kinase A in cell migration. He first deals with general aspects of PKA structure and function, and with the multiple effects of PKA on motility in different cell systems. He then seeks to place these diverse observations in a mechanistic context by addressing two important issues. The first issue relates to the regulation of PKA activity and subcellular localization during cell adhesion and migration. The second deals with the many targets of PKA that may be involved in migration. The list of PKA targets is extensive, ranging from actinomycin-associated proteins, such as VASP and myosin light chain, to signaling proteins including Rho GTPases, PAK kinases, and tyrosine phosphatases. Thus, this review nicely delineates the complexities of PKA signaling in the context of cell migration.

The last review in the issue deals with a very different theme. Kristiina Vuori and Stuart Martin address the role of Bcl-2 proteins in anoikis and amorphosis, which is cell death triggered by loss of integrin-mediated anchorage or by loss of cytoskeletal architecture. The article first deals with the impact of Bcl-2 family proteins on mitochondrial function. It then goes on to explore the mechanisms of regulation of Bcl-2 proteins by cell anchorage. It then goes on to discuss the concept of amorphosis and the evidence supporting this concept. Thus, this review provides a stimulating and timely account of the interplay between cell adhesion and cell survival.

In summary, in this Special Issue a talented cohort of younger investigators have provided timely and comprehensive reviews of some of the key themes of the integrin signaling area. Hopefully these reviews will be of value both to experts in the field and to scientists in other fields interested in learning more about this dynamic area of research.