Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Cell Biology

Signal transduction via integrin adhesion complexes

Jonathan D Humphries[1], Megan R Chastney[1], Janet A Askari[1] and Martin J Humphries

Integrin adhesion complexes (IACs) have evolved over millions of years to integrate metazoan cells physically with their microenvironment. It is presumed that the simultaneous interaction of thousands of integrin receptors to binding sites in anisotropic extracellular matrix (ECM) networks enables cells to assemble a topological description of the chemical and mechanical properties of their surroundings. This information is then converted into intracellular signals that influence cell positioning, differentiation and growth, but may also influence other fundamental processes, such as protein synthesis and energy regulation. In this way, changes in the microenvironment can influence all aspects of cell phenotype. Current concepts envisage cell fate decisions being controlled by the integrated signalling output of myriad receptor clusters, but the mechanisms are not understood. Analyses of the adhesome, the complement of proteins attracted to the vicinity of IACs, are now providing insights into some of the primordial links connecting these processes. This article reviews recent advances in our understanding of the composition of IACs, the mechanisms used to transduce signals through these junctions, and the links between IACs and cell phenotype.

Address
Wellcome Trust Centre for Cell-Matrix Research, Faculty of Biology, Medicine & Health, Manchester Academic Health Science Centre, University of Manchester, Manchester M13 9PT, UK

Corresponding author:
Humphries, Martin J (martin.humphries@manchester.ac.uk)
[1] These authors contributed equally.

Current Opinion in Chemical Biology 2019, **56**:14–21

This review comes from a themed issue on **Cell architecture**

Edited by **Johanna Ivaska** and **Manuel Théry**

https://doi.org/10.1016/j.ceb.2018.08.004

IAC components

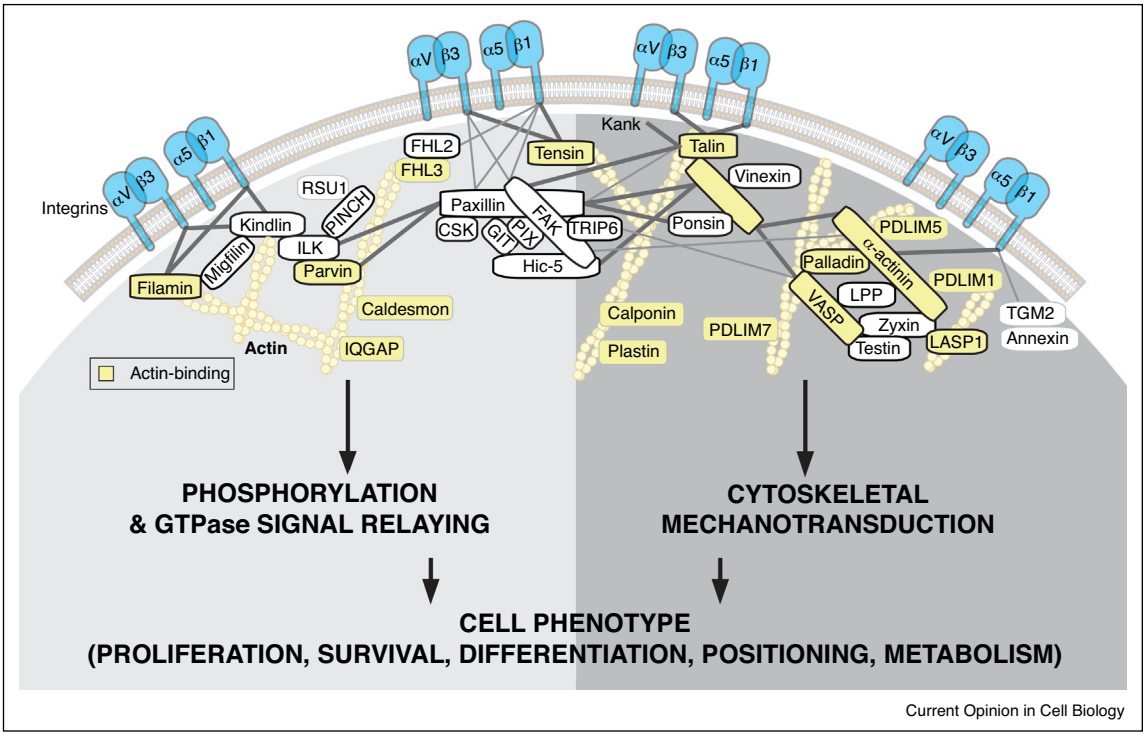
Cells adherent to ECM proteins assemble a range of IACs that are focally distributed [1,2]. Detailed functional and morphological analyses have defined several major forms of IAC, including focal complexes, focal adhesions and fibrillar adhesions [2]. Each type of IAC is formed sequentially and disrupted as cells migrate and, based on immunofluorescence analyses, each has a distinct composition. Most recently, a new class of adhesion, which contains high levels of integrin β5, clathrin and endocytic adaptors, has been identified by a range of laboratories and variously termed flat clathrin lattices, clathrin plaques or reticular adhesions [3–6]. The extent to which these reports describe the same type of adhesion complex is currently unclear. All IACs are connected to the actomyosin cytoskeleton via adaptor proteins such as talin and vinculin (except reticular adhesions [6]), but they also serve as hubs that link integrin-containing plasma membrane regions to the cytoplasmic signalling network.

IACs are located at the membranous junction between ECM-bound, plasma membrane-intercalated integrins and intracellular, actin-based cytoskeletal filaments. Isolation of such a structure away from all adjacent cellular material is currently not possible, but in the last decade techniques have been developed to purify ventral IACs from cells in 2D culture, together with material that is found in close apposition to the junction [7–9]. Since the function of IACs is to convert spatiotemporal information about the extracellular environment into signals with wide-ranging consequences, the composition of these purified IACs, and their associated material, is highly relevant.

Although a range of cell types has been investigated, most IAC preparations have been isolated from cells attached a fibronectin substrate. Compilation of seven of these datasets led to the definition of a fibronectin-induced 'meta adhesome' of over 2400 proteins, which was further refined to 60 core proteins most frequently identified in IACs, termed the 'consensus adhesome' [10••]. The consensus adhesome is likely to represent the core cell adhesion machinery, centred round potential axes that link integrins to actin (e.g. ILK-PINCH-parvin-kindlin, FAK-paxillin, talin-vinculin and α-actinin-zyxin-VASP; Figure 1). This core connection network has recently been integrated with a 'literature-curated adhesome', generated *in silico* by Geiger and colleagues [11,12], and has proven valuable for filtering large datasets and identifying potential candidates for follow-up experimentation [13–19,20•,21•]. A recent meta analysis suggests nearly 20% of the human kinome is found in the adhesome, supporting the view tha t this region of the cell is a general signalling hub [22].

Since publication of the meta adhesome, IAC preparations have been generated from other cell types, such as

Figure 1



Signal relaying via the consensus adhesome. A schematic representation of proteins most commonly found in IACs [10••]. The diagram shows the interactions between adhesome proteins. Interactions with the highest confidence, based on the literature, have greater thickness. Proteins with a thick black node border are members of the literature-curated adhesome protein. Recent evidence suggests the left half of the network transduces signals that regulate phosphorylation and small GTPases [21•,28], while the right half is primarily responsible for mechanosensitive connections to actin filaments [45]. Together, these outputs are integrated to influence many aspects of cell phenotype.

endothelial cells [23], but in the future proteomic analysis of IACs isolated from a wider range of cell types in various cellular contexts (e.g. different ligands, in 3D culture, or *in vivo*) will undoubtedly broaden our understanding of adhesome composition and regulation. Similarly, current IAC preparations are isolated from thousands of cells, and therefore comprise a range of different types of IAC, found in different subcellular locations. Future improvements in mass spectrometric sensitivity will enable more focused analyses of the composition of IACs in space and time. In recent years, new techniques for IAC analysis have been developed, including the use of mass spectrometry in conjunction with the proximity-dependent biotinylation technique, BioID [20•]. By using this method with paxillin and kindlin baits, a number of well-established adhesome components were identified, but in addition several new associations were revealed, including Kank2 (for paxillin) and liprin-β1 for kindlin). In parallel studies, another Kank family member, Kank1, was localised to the periphery of mature IACs through its ability to bind talin. At these sites, Kank1 coordinated the formation of cortical microtubule stabilisation complexes (containing ELKS, liprins, KIF21A, LL5β and CLASPs), which in turn led to the destabilisation of IACs [24••,25]. Thus, although marginally failing to meet the criteria for inclusion in the original consensus network [10••], Kank proteins now appear central to integrin regulation and should be considered core adhesome components. Additional key functional interactions within the consensus adhesome that have been elucidated recently include a role for kindlin-2 dimerisation in integrin activation and clustering [26], direct kindlin-actin binding [27], and a role for the kindlin-paxillin axis in activation of Rac1 and recruitment of Arp2/3 to early IACs [28].

The coordinated assembly and disassembly of IACs must be tightly regulated for effective cell adhesion and migration. A highly multiplexed, high resolution imaging approach revealed that as IACs were assembled, molecular noise was reduced, suggesting that despite the large number, and extensive binding capabilities, of adhesome components, IAC assembly is tightly regulated [29]. Further studies have identified novel roles for well-known adhesome components in the maintenance of integrin activation during integrin endocytic recycling before IAC assembly. FAK, talin, and PIPKIγ2 were shown to associate with endocytosed integrins,