The integrin adhesome: from genes and proteins to human disease

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Abstract | The adhesive interactions of cells with their environment through the integrin family of transmembrane receptors have key roles in regulating multiple aspects of cellular physiology, including cell proliferation, viability, differentiation and migration. Consequently, failure to establish functional cell adhesions, and thus the assembly of associated cytoplasmic scaffolding and signalling networks, can have severe pathological effects. The roles of specific constituents of integrin-mediated adhesions, which are collectively known as the 'integrin adhesome', in diverse pathological states are becoming clear. Indeed, the prominence of mutations in specific adhesome molecules in various human diseases is now appreciated, and experimental as well as *in silico* approaches provide insights into the molecular mechanisms underlying these pathological conditions.

Integrins
A family of cell adhesion receptors that mediate either cell–cell interactions or cell–extracellular matrix interactions. Integrins are heterodimers with two distinct subunits, the α-subunit and the β-subunit.

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Adhesions that are mediated by integrins comprise a diverse family of cellular contacts that have key roles in the assembly of individual cells into functional tissues and organs[1]. They derive their name from the heterodimeric integrin receptors that directly mediate the adhesive interactions with the extracellular matrix (ECM) or with counter receptors on the membrane of neighbouring cells[2] (FIG. 1a). A common form of such adhesions are focal adhesions, which have been extensively characterized in cultured cells in which they mediate the interaction of cells with matrix proteins such as fibronectin, vitronectin and collagen (FIG. 1b,c). In intact tissues, integrins mediate cellular adhesion to the basement membrane and to other cells (FIG. 1d,e). Structural and molecular studies have indicated that integrin adhesions are associated with the actin cytoskeleton through an elaborate network of proteins that is collectively known as the 'integrin adhesome'[3–5] (BOX 1). The interactions between the various adhesome components are believed to be responsible for two major functions of the adhesion sites: first, their role as a 'scaffold' in supporting the physical integration of the ECM-bound cell and the cytoskeleton, which leads to the assembly of tissues with a particular structure and mechanical properties; second, their 'signalling' activity, which enables cells to sense the chemical and mechanical properties of the external environment and to respond by activating signalling networks that regulate cell structure, dynamics, behaviour and fate[6,7].

How this rather general 'design principle' enables specific scaffolding and signalling components of the adhesome to integrate into a chemo- and mechano-responsive adhesion site, which, in turn, drives the assembly of complex multicellular systems, is still poorly understood. The main challenges that have been encountered in studying the molecular functionality of the adhesome include the molecular heterogeneity of integrin adhesions within and between different cellular systems, the large number of adhesome components, the presence of multiple 'functional switches' that can turn adhesome components 'on' or 'off' and the overall dynamic nature and plasticity of the adhesion system as a whole.

Recent attempts to explore the molecular mechanisms of adhesome functions at a systems level were based, to a large extent, on a combination of bioinformatic surveys[3,4], immunocytochemistry[8], proteomic analysis[7,9–12] and studies that specifically perturbed adhesome components[7,13]. These studies confirmed that the integrin adhesome currently consists of 232 molecules, including integrins, various actin regulators, adaptor proteins that link cytoskeletal structures to the cytoplasmic tails of integrins and multiple signalling molecules[3,4] (BOX 1; Supplementary information S1 (table)).

Direct attempts to assign specific cellular functions to individual adhesome molecules were primarily based on experiments in which adhesome molecules were pharmacologically or genetically disturbed using

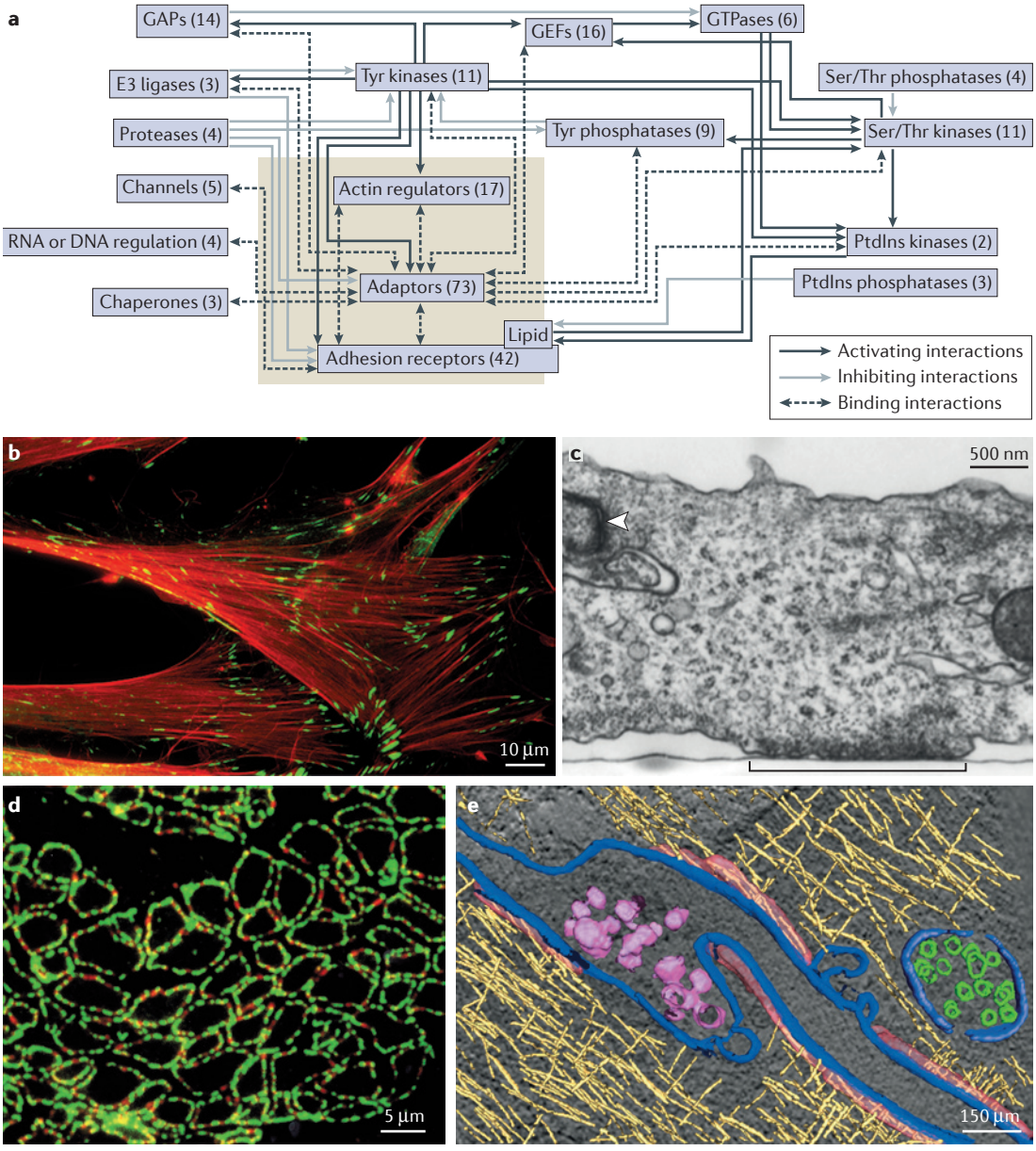

Figure 1 | **Representative scheme of the adhesome and images of focal adhesions.** **a** | Schematic representation of the adhesome. The functional categories of the different adhesome components are shown, with the number of family members in the adhesome given in parenthesis. In addition, the dominant interactions between adhesome component families are depicted, as highlighted in the key. The light brown shading includes all the adhesome components that perform scaffolding function, and they are surrounded by the regulatory (signalling) adhesome components. **b** | WI-38 fibroblasts in which the focal adhesion-associated adaptor protein paxillin (shown in green) and actin (shown in red) were immunofluorescently labelled and detected by fluorescence microscopy. The green patches are focal adhesions located at each end of the red actin fibres. **c** | A side view of a cultured chicken lens cell, which includes part of a cell–cell adherens junction in the upper left corner (arrow head) and an interaction of a focal adhesion with the substrate (indicated by the square bracket), viewed by transmission electron microscopy. **d** | A transverse semi-thin (~1 µm thick) immunofluorescently labelled section of Guinea pig smooth muscle, in which vinculin (shown in green) and dystrophin (shown in red) were visualized by fluorescence microscopy. The image demonstrates a clear separation between the vinculin-rich adhesion sites and the actin and dystrophin-rich cytoskeleton. **e** | Three-dimensional view of a chicken smooth muscle membrane-associated dense plaque. A tomographic slice, 9 nm in thickness, from a reconstructed volume of chicken gizzard smooth muscle tissue was overlaid with the surface-rendered view of the adhesions to the matrix. The different structural subcellular compartments are shown in the following colours: membrane in blue; focal adhesion-related dense plaques in transparent red; actin in yellow; collagen in light pink; multi-vesicular compartment in purple; vesicles inside the multi- vesicular compartment in green. GAP, GTPase-activating proteins; GEF, guanine nucleotide exchange factor; PtdIns, phosphatidylinositol. Image in part **a** is modified, with permission, from REF. 3 © (2007) Macmillan Publishers Limited. Image in part **c** is reproduced, with permission, from REF. 181 © (2010) Elsevier. Image in part **d** is reproduced, with permission, from REF. 182 © (1993) The Rockefeller University Press. Image in part **e** is reproduced, with permission, from REF. 183 © (2012) Elsevier.

Box 1 | **The integrin adhesome**

When integrins bind to the extracellular matrix, scaffold, cytoskeletal and signalling proteins are recruited to the nascent adhesion. The micrometre-scale adhesion sites that form can develop into diverse classes of integrin adhesions, such as focal complexes, **focal adhesions**, fibrillar adhesions, podosomes and invadopodia. All these integrin adhesions have diverse roles in tissue formation, adhesion-mediated signalling, matrix remodelling, cell migration and invasion. The underlying molecular network associated with integrin adhesions is commonly known as the 'integrin adhesome' (FIG. 1a; Supplementary information S1 (table)), which consists of over 232 components that are divided into 148 intrinsic components (that is, those that reside mainly in the adhesion site) and 84 components that transiently associate with the adhesion. Some of the adhesome molecules are involved in the 'scaffolding function' of the adhesome (the physical linking of integrins to the actin cytoskeleton (for example, actin, actin-associated proteins, adaptor proteins and integrin receptors)), whereas others are involved in adhesion-mediated signalling, which affects the adhesion itself as well as multiple cellular downstream targets (for example, kinases, phosphatases and G protein regulators). Analysis of the adhesome network points to a very high connectivity between the different constituents[3] but suggests that these interactions can be modulated by various post-translational modifications[4]. Cryo-electron tomography[173] and three-dimensional super-resolution microscopy revealed specific particles at the cytoskeleton–membrane interface of integrin adhesions and a 'laminated organization', whereby the different components are located at different distances from the membrane[174]. Further functional proteomic mapping of the adhesome requires the systematic knockdown of adhesome molecules and the analysis of the resulting phenotype together with the characterization of mutations in adhesome genes that are associated with diverse pathologies.

various integrin inhibitors[14], specific inhibitors of adhesion-associated enzymes and systematic RNAi-mediated knockdown of genes encoding adhesome components[13,15]. These experiments provided valuable information on the precise molecular interplay that occurs within the adhesome network; however, the contribution of this interplay to the overall role of specific adhesome components in tissue homeostasis and in intact organisms, or to the possible involvement of the adhesome in various pathological states, remains unclear. To address the function of adhesome components at the tissue or organism level, different approaches are used. These include the introduction of disease-related gene mutations to these components or the misexpression of adhesome molecules, and specific perturbation experiments (knockout or knock-in) in experimental animal models[16].

In this Analysis, we aim to provide a clearer picture of the involvement of adhesome components in disease and to understand which molecular functions of the adhesome are impaired in different diseases. This information could provide new insight into the molecular basis of diseases and highlight molecules that could be therapeutically targeted.

From genes to animal models and disease

With the growing interest in personally tailored medical treatment, the need for new genomic and proteomic tools to identify disease-associated genes has become increasingly apparent (BOX 2). Once specific candidate genes are identified, experimental validation is necessary to confirm that the identified mutation or dysregulated activity does cause the disease. Additional experiments are then required to understand the changes that have occurred to cause the disease with the ultimate aim of developing therapies to restore health. Culture-based disease models may be established using RNAi technology or by expressing mutated genes to mimic the disease *ex vivo*[17].

Although such approaches are useful to determine the molecular mechanisms that lead to disease, it is necessary to establish animal models to study the consequences of genetic or functional dysregulation at the whole organism level. Indeed, some animal models mimic the intended human genetic disorder well (see below), but often the models are not very informative. This might be explained by the fact that most human genetic diseases arise from point mutations, insertions, small deletions or gene truncations, whereas most mouse models involve the deletion of an entire gene. Therefore, the severity and course of the disorder may differ considerably in the animal model. Moreover, non-functional or truncated gene products expressed in human patients may behave in a dominant-negative manner and influence cellular function in ways that are not considered in the animal model. It would thus be advantageous, when designing animal models for a particular disease, to introduce specific gene mutations that have been identified in patients to recreate a relevant disorder. Beyond these technical limitations, there are also other considerable differences between humans and mice (for example, the mode and timing of organ development) that might complicate the establishment of useful animal models[18].

Focal adhesions
Stable integrin-mediated, cell–substrate adhesion structures that anchor the termini of actin filaments (stress fibres) and mediate strong attachments to substrates. They also function as integrin signalling platforms.

Focal complexes
Small dot-like adhesions (~1 μm in width) that are mainly found in lamellipodia. They are transient adhesion sites during cell migration and can mature into more stable focal adhesions.

Fibrillar adhesion
A form of integrin-mediated adhesion, which is typically associated with fibronectin fibres and has high levels of tensin and low levels of phosphorylated Tyr residues. These adhesions are less mechanosensitive than focal adhesions.

Podosomes
Adhesive, ring-like, actin-rich structures that are formed on the ventral surface of cells, such as monocytes, osteoclasts and smooth muscle cells.

Box 2 | **Methods for identifying disease-associated genes**

There are multiple approaches for the identification of disease-associated genes. The traditional procedure is based on cytogenetic linkage analysis, in which small chromosomal alterations in pathological specimens are identified, and the genes residing in the altered locus are mapped[175]. In recent years, multiple technologies were developed that enable high-throughput and high-content searches for disease-related genes and potential therapeutic targets. Among these are quantitative transcriptomic analysis tools[176], whole genome and whole exome sequencing technologies[177], and sensitive proteomics that enable the quantification of protein levels and post-translational modifications[178,179]. Combined with powerful bioinformatics analyses[180] these advanced (and rapidly improving) techniques provide rich databases of potential disease-causing candidates. Genes can be associated with two forms of disease; monogenic diseases, which display a typical Mendelian inheritance (for example, sickle cell anaemia, Huntington's disease, phenylketonuria and cystic fibrosis); and polygenic diseases, which are caused by the combined effects of mutations in more than one gene (for example, diabetes, hypertension and many forms of cancer). Naturally, diseases of the first type are easier to define and diagnose, and potential therapeutic targets are more easily identified; addressing polygenic diseases necessitates a mechanistic understanding of the hierarchical relationships between the associated genes, which is far more challenging.

Table 1 | **Adhesome genes and the involvement of their encoded proteins in OMIM disease**

Functional category*	Adhesome genes‡	Disease when adhesome gene mutated
Actin	*ACTB*	Musculoskeletal
Actin regulators	*ACTN1*, *CFL1*, *CORO1B*, *CTTN*, *KEAP1*, *LASP1*, *ENAH*, *NEXN*, *SVIL*, *VASP*, *CORO2A*, *MACF1*§, *ARPC2*§, *MARCKS*§ and *PFN1*§	No disease
	FLNA	Cardiovascular and developmental
	MYH9§	Renal, haematological and other
Adaptors	*JUB*, *SORBS2*, *BCAR1*, *SMPX*, *SH3KBP1*, *CRK*, *CRKL*, *EZR*, *FHL2*, *GAB1*, *GRB2*, *GRB7*, *NEDD9*, *CASS4*, *TGFB1I1*, *ITGB1BP1*, *FERMT2*, *LPXN*, *PPFIA1*, *FBLIM1*, *MSN*, *NCK2*, *PARVA*, *PARVB*, *PXN*, *LIMS1*, *LIMS2*, *GNB2L1*, *RDX*, *OSTF1*, *NUDT16L1*, *SYNM*, *SDCBP*, *TLN1*, *TNS1*, *TES*, *TRIP6*, *SORBS3*, *ZYX*, *NDEL1*, *SH2B1*, *TENC1*, *ZFYVE21*, *ABI2*§, *ABI3*§, *ANKRD28*§, *CSRP1*§, *MAPK8IP3*§, *SORBS1*§, *SHC1*§, *MYOM1*§, *TSPAN1*§, *TUBA1B*§, *VIM*§, *SHARPIN*§, *FABP3*§, *NISCH*§, *CIB1*§ and *SRCN1*§	No disease
	CAV1 and *CIB2*§	Developmental
	HAX1 and *FERMT3*	Immunological
	FERMT1	Dermatological
	LPP	Cancer (and neoplasia) and other
	NF2, *PALLD* and *ABI1*§	Cancer (and neoplasia)
	LDB3 and *VCL*	Cardiovascular
	IRS1§	Metabolic and cardiovascular
	PLEC§	Gastrointestinal, musculoskeletal and dermatological
Adhesion receptors	*SLC3A2*, *KTN1*, *LRP1*, *PVR*, *SDC4*, *ITGA1*, *ITGA3*, *ITGA4*, *ITGA5*, *ITGA8*, *ITGA9*, *ITGA10*, *ITGA11*, *ITGAD*, *ITGAE*, *ITGAL*, *ITGAM*, *ITGAV*, *ITGAW*, *ITGAX*, *ITGB1*, *ITGB5*, *ITGB6*, *ITGB7*, *ITGB8*, *NRP1*, *NRP2*, *ADAM12*§, *CEACAM1*§, *CD47*§, *LAYN*§, *SIRPA*§, *THY1*§ and *PLAUR*§	No disease
	ITGA2 and *ITGB3*	Haematological
	ITGA6 and *ITGB4*	Dermatological and gastrointestinal
	ITGA7	Musculoskeletal and developmental
	ITGB2	Immunological
	CD151	Haematological, renal and dermatological
	ENG§	Cardiovascular
	INSR§	Metabolic, developmental and musculoskeletal
Channel proteins	*SLC16A3*§ and *SLC9A1*§	No disease
	PKD1	Renal
	TRPM7	Musculoskeletal and neurological
	KCNH2§	Cardiovascular
Chaperones	*CALR* and *HSPA2*§	No disease
	HSPB1§	Musculoskeletal and neurological
E3 ligases	*CBL*, *RNF5* and *RNF185*	No disease

Invadopodia
Extracellular matrix (ECM) contacts that are different from focal complexes and focal adhesions but similar to podosomes, which are associated with the invasion of cells into the ECM. Invadopodia can extend up to several micrometres, associate with ECM-degrading enzymes and are seen in transformed fibroblasts or malignant cells.

The integrin adhesome and disease genes

To identify candidate adhesome components that are implicated in disease, which might help to develop more appropriate disease models, we have conducted a literature-based bioinformatics survey of mutations that occur in the known cohort of adhesome genes (Supplementary information S1 (table)) and their association with human disease. We used two main sources: the Online Mendelian Inheritance in Man (OMIM®) database to search for single adhesome components that are involved in Mendelian genetic disorders (Supplementary information S2 (table)); and the Genetic Association Database (GAD)[19] to identify multigenic diseases that show an association with adhesome components (Supplementary information S3 (table)). The information retrieved from both databases is discussed below.

Adhesome components involved in inherited diseases. From the 232 adhesome genes queried within the OMIM database, 52 (22%) were reported to cause specific genetic diseases (Supplementary information S2 (table)). This represents an enrichment of disease-causing genes

Table 1 Cont.) | **Adhesome genes and the involvement of their encoded proteins in OMIM disease**

Functional category*	Adhesome genes‡	Disease when adhesome gene mutated
GAPs	*DDEF1*, *ASAP3*, *GIT1*, *GIT2 GRLF1*, *ASAP2*, *ARHGAP24*, *AGAP2*, *STARD13*, *ARHGAP5*§ and *ARHGAP32*§	No disease
	ARHGAP26 and *DLC1*	Cancer (and neoplasia)
	RASA1	Cancer (and neoplasia) and developmental
GEFs	*DEF6*, *DOCK1*, *ELMO1*, *ARHGEF7*, *BCAR3*§, *RAPGEF1*§, *TIAM1*§, *TRIO*§, *VAV1*§, *VAV2*§, *VAV3*§, *ARHGEF2* §and *CYTH2*§	No disease
	ARHGEF6	Developmental
	SOS1	Cardiovascular and dermatological
	ARHGEF12	Cancer (and neoplasia)
GTPases	*RHOU*, *ARF1*§, *RAC1*§ and *RHOA*§	No disease
	DNM2	Musculoskeletal and neurological
	HRAS§	Cardiovasular, cancer (and neoplasia) and developmental
Others	*PLD1* and *PLCG1*	No disease
	PRNP and *SPTLC1*	Neurological
	PDE4D	Musculoskeletal
Proteases	*CAPN1*, *CAPN2* and *MMP14*§	No disease
	CASP8	Cancer (and neoplasia) and immunological
PtdIns kinases	*PIK3CA*	Cancer (and neoplasia)
	PIP5K1C	Musculoskeletal and developmental
PtdIns phosphatases	*INPP5D* and *INPPL1*	No disease
	PTEN§	Developmental and cancer (and neoplasia)
RNA or DNA regulation	*ITGB3BP*, *RAVER1* and *PABPC1*§	No disease
	STAT3	Immunological
Ser/Thr kinases	*ILK*, *PAK1*, *PDPK1*, *MAPK1*§, *MAPK8*§, *LIMK1*§, *PRKACA*§ and *ROCK1*§	No disease
	PRKCA and *AKT1*§	Cancer (and neoplasia)
Ser/Thr phosphatases	*PPM1M*, *PPM1F*, *PPP2CA*, *ILKAP*§ and *SSH1*§	No disease
Tyr kinases	*ABL1*, *CSK*, *PTK2*, *PTK2B*, *PEAK1*, *FYN*§, *LYN*§, *SYK*§ and *TESK1*§	No disease
	SRC	Cancer (and neoplasia)
Tyr phosphatases	*PTPRF*, *PTPRA*, *PTPN6*, *PTPN1*§, *PTPRO*§, *PTPRH*§ and *PTPN2*§	No disease
	PTPN12	Cancer (and neoplasia)
	PTPN11	Musculoskeletal, cardiovascular, cancer (and neoplasia), dermatological and developmental

GAP, GTPase-activating protein; GEF, guanine nucleotide exchange factor; OMIM, Online Mendelian Inheritance in Man; PtdIns, phosphatidylinositol.
*The assignment of the different molecules to particular categories is based on the adhesome (FIG. 1a; Supplementary information S1 (table)).
‡Gene names are grouped based on the kind of disease they produce when mutated (for further information and links to OMIM reference see Supplementary information S2 (table)). Most genes mainly reside in the adhesion site (intrinsic genes). §Genes that transiently associate with the adhesion site (associated genes) are indicated.

Mendelian genetic disorders
Inherited genetic diseases that are caused by mutations in one gene.

Multigenic diseases
Diseases that are caused by mutations or alterations in more than one gene.

in the adhesome compared with the genomic population, of which only 11% were found to cause disease. This value was calculated by dividing the number of genes found in the OMIM database that have been described to cause disease (around 2,900 at the time of this Analysis) by the estimated number of genes in the genome (about 25,000). The 52 adhesome genes reported to cause specific genetic diseases were then sorted according to the type of disease they produce (Supplementary information S2 (table)). The assignment of a gene to a specific disease group is based on the nature of the disease, the affected organs and the main symptoms the mutation of the gene causes. Genes involved in cancer and neoplasia were assigned to a group of this name irrespective of the organ they affect. Genes were assigned to all disease types they cause.

TABLE 1 shows all of the adhesome genes — grouped by their functional categories and divided into groups on the basis of type of disease they cause when mutated.

Examination of the adhesome OMIM list indicates that the most abundant Mendelian genetic disease in the adhesome is cancer (17 genes) (FIG. 2a; Supplementary information S2 (table)). Cancer is mainly caused by

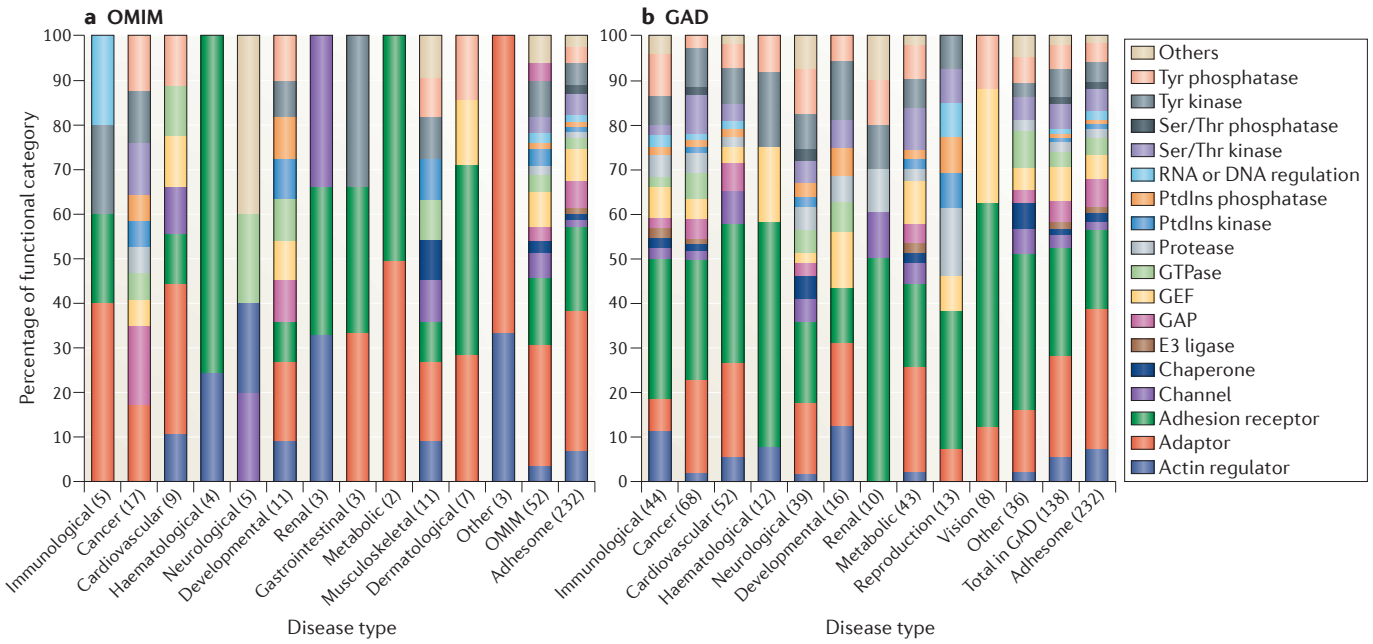

Figure 2 | **Percentage of genes belonging to the adhesome functional categories that lead to each disease type.** **a** | Diseases caused by mutations in adhesome genes, according to the Online Mendelian Inheritance in Man (OMIM) database. **b** | Adhesome genes that are associated with disease, according to the Genetic Association Database (GAD). The graphs show the percentage of genes in each disease type that belongs to the specific adhesome functional category, as highlighted in the key. The number in parentheses shows the total number of adhesome genes related to the particular disease. The percentages of the functional categories in the adhesome as well as in the OMIM database (part **a**) or GAD (part **b**) are shown for comparison. GAP, GTPase-activating protein; GEF, guanine nucleotide exchange factor, PtdIns, phosphatidylinositol.

mutations in genes encoding adhesome signalling proteins, including GTPase-activating proteins (GAPs), guanine nucleotide exchange factors (GEFs), kinases and phosphatases, that are also known to be involved in signalling through growth factor receptors (FIG. 2). Many of the adhesome protein kinases and three GAPs (namely deleted in liver cancer 1 (DLC1), RHOGAP26 (encoded by the gene *ARHGAP26*) and RASA1 (also known as RASGAP)) are involved in cancer, whereas the involvement of GEFs in hereditary diseases is broader and also includes cardiovascular and developmental diseases (FIG. 2a). Interestingly, gene mutations in adhesion receptors are not implicated in cancer (FIG. 2a), despite the fact that changes in integrin expression and activity are believed to have a role in processes commonly associated with malignant transformation and metastasis (for example, invasion and migration).

Two other classes of genetic disease that are enriched in adhesome gene mutations are musculoskeletal (11 genes) and cardiovascular (nine genes) disorders. This reflects the importance of the adhesome in mediating force transduction in these tissues (that is, skeletal and cardiac muscle, bones and the vasculature), by which substantial mechanical load is generated and applied.

Within the different disease types, when focussing specifically on the genes that have a role in blood cell disorders, the haematopoietic system is highly affected by mutations in adhesome components. Twelve adhesome genes are directly involved in haematopoietic diseases (five of these are immunological, four are haematological and three are types of leukaemia; see below). Intriguingly, the genes causing these diseases consist mainly of structural (scaffolding) adhesome components (for example, adaptors, actin regulators and adhesion receptors; Supplementary information S4 (figure)). These findings emphasize the important role of adhesome structure and cytoskeletal maintenance in the development and function of blood cells.

Finally, dermatological diseases are caused by mutations in seven adhesome genes, which illustrates a clear need for cell adhesion in maintaining a barrier against invading microorganisms.

Interestingly, only two genes encoding adhesome-associated actin regulators (filamin A (FLNA) and myosin heavy chain 9 (MYH9)) are listed in the adhesome genes from the OMIM database. Mutations in these genes lead to diseases that affect multiple organs. This low prevalence may be attributed to compensatory action by redundant gene products or to early embryonic lethality when actin regulators are mutated, as the phenotype of knockout mice reveals a very mild defect in some cases (for example, for the gene encoding vasodilator-stimulated phosphoprotein (VASP))[20] and a lethal phenotype in others (for example, for the gene encoding cofilin 1 (REF. 21)).

Interestingly, only two lipid kinases in the adhesome lead to diseases when mutated; the mutation of the gene *PIP5K1C*, which encodes PtdIns(4)P-5-kinase 1γ (phosphatidylinositol 4-phosphate 5-kinase type-1γ), contributes to the lethal congenital contracture

syndrome, and the mutation of *PIK3CA*, which encodes PtdIns(4,5)P2-3-kinase 1α (PtdIns(4,5)-bisphosphate 3-kinase, catalytic subunit-α), has been implicated in the development of cancer. This is in line with the known role of the phosphoinositide pathway in regulating cytoskeletal assembly and function. In general, scaffolding gene mutations (that is, mutations in genes encoding adaptors, adhesion receptors and channel proteins) were prominently found to be associated with haematological and dermatological diseases (Supplementary information S4 (figure)), whereas cancer, neurological, developmental and musculoskeletal diseases are mainly caused by gene mutations in adhesome signalling proteins.

Adhesome genes genetically associated with disease. Searching the GAD[19] revealed the involvement of 138 adhesome components (59.5% of all adhesome genes), the alteration of which has a role in multiple polygenic diseases. Given that about 40% of the genes in the genome are genetically associated with disease[22], it seems that the adhesome is enriched with genes involved in complex human diseases. The most abundant adhesome-associated diseases are cancers (68 genes), followed by cardiovascular diseases (52 genes) and immunological (44 genes), metabolic (43 genes) and neurological conditions (39 genes). Other diseases present in lower abundance are listed in FIGURE 2b and Supplementary information S3 (table). It is worth noting that 63% of the disease-related genes are associated with haematopoietic disorders, including 20 genes involved in leukaemias or lymphomas, 44 genes in immunological diseases and 12 genes in haematopoiesis.

When the adhesome molecules that are associated with disease are genetically classified, we find that genes encoding regulators and adaptor proteins are slightly underrepresented, whereas genes encoding Tyr kinases and phosphatases are enriched (FIG. 2b). In contrast to the OMIM list, adhesion receptors are enriched in the GAD, but no enrichment in channel proteins was observed. Furthermore, in both OMIM and GAD lists, GAPs are less abundant and GTPases are enriched. All the protein classes found in the adhesome are also present in the GAD.

When comparing the involvement of the functional classes of adhesome proteins in the various diseases, we made some remarkable findings. Although adhesion receptors were not indicated in the OMIM database as molecules leading to cancer, in the GAD, they account for 24% of the genes associated with cancer (Supplementary information S4 (figure)). This suggests that dysregulations in genes encoding adhesion receptors frequently combine with other gene malfunctions to cause cancer. Actin regulators are underrepresented in both databases and only have roles in immunological, cardiovascular, haematological and developmental diseases. Adaptors are widely associated with all types of disease (apart from haematological and renal ailments), whereas genes encoding channel proteins are highly abundant in the OMIM database (FIG. 2; Supplementary information S4 (figure)). Our results also confirm the known involvement of Tyr kinases in cancer, as these genes are enriched in our analysis.

One should keep in mind that although our disease survey is focused on adhesome genes, these genes may have other functions outside adhesion sites, which, when impaired, could lead to disease. Our analysis, however, provides a generic understanding of the kind of adhesome molecules that, when mutated, could cause specific diseases.

From OMIM and GAD to disease models

Disease models are valuable tools that enable us to understand the mechanisms underlying disease and to test possible therapeutic modalities. This approach is particularly powerful in cases in which gene mutations found in humans lead to a similar disease in mice, as discussed in this section.

Models of haematological disorders. Mutations in *ITGA2B* and *ITGB3*, which encode the two subunits of platelet integrin αIIbβ3, lead to the bleeding disorder Glanzmann's thrombasthenia[23]. Platelets containing this integrin mutation are unable to bind fibrinogen and therefore cannot aggregate. Gene mutations have been identified throughout the entire length of either integrin subunit, all of which lead to a non-functional protein[24,25] or, more commonly, an absence of or reduction in integrin cell surface expression due to mRNA instability or aberrant trafficking through the secretory pathway[26–28]. In addition to Glanzmann's thrombasthenia, a mutation in the gene encoding β3 integrin in humans has been associated with a range of cardiac and vascular disorders, atherosclerosis, autism, an increased risk of fracture and several cancers (Supplementary information S3 (table)). Mice deficient in β3 integrin show multiple defects reflecting the human disorders, including a bleeding disorder that is similar to Glanzmann's thrombasthenia[29], enhanced tumour angiogenesis[30,31], cardiac hypertrophy and atherosclerosis[32,33], cardiovascular defects[34], age-dependent osteosclerosis[35,36], increased re-epithelialization[37] and behavioural disorders[38]. The direct involvement of β3 integrin in vascular disorders is complicated by the compensatory upregulation of vascular endothelial growth factor (VEGF) receptor in its absence, which increases the sensitivity of cells to VEGF[30]. Certain mutations in the gene encoding β3 integrin may abolish its ability to bind kindlin 3 (also known as FERMT3), which causes leukocyte adhesion deficiency type III (LAD-III)[24] (see below).

Gene mutations in *ITGB2* (encodes β2 integrin), which is restricted to the haematopoietic system, result in leukocyte adhesion deficiency type I (LAD-I)[39–41]. A non-functional integrin or a reduction or absence of its surface expression can be caused by gene mutations. Despite marked neutrophilia, patients with LAD-I suffer from recurrent infections and impaired wound healing, due to the loss of function of all four leukocyte integrins — αLβ2 integrin (also known as LFA1 or CD11A/CD18), αMβ2 integrin (also known as MAC-1 or CD11B), αXβ2 integrin (also known as CD11C) and αDβ2 integrin (also known as CD11D). Mice expressing a hypomorphic allele of β2 integrin have a reduced inflammatory response to chemically induced peritonitis

Glanzmann's thrombasthenia
A bleeding disorder that arises from mutations in genes either encoding αIIb integrin or β3 integrin, which together form the fibrinogen receptor on platelets.

Leukocyte adhesion deficiency type III
(LAD-III). An autosomal recessive immunodeficiency disorder that is caused by mutations in the gene encoding kindlin 3, which reduces the activation of most integrins.

Leukocyte adhesion deficiency type I
(LAD-I). An autosomal recessive immunodeficiency disorder resulting from mutations in the gene encoding β2 integrin, which is expressed on several cells of the immune system.

and persistent skin inflammation but no evidence of chronic infection[42,43], whereas mice carrying a complete deletion of β2 integrin mimic LAD-I more accurately[44].

In addition to a deficiency in neutrophil rolling, which is also seen in mice expressing the hypomorphic allele of β2 integrin, animals that carry a complete deletion of β2 integrin have deficiencies in T cell activation[44,45] or extravasation[46], and also display aberrant B cell differentiation that results from an increase in interleukin-6 (IL-6) production[47]. The source and reason for an increase in IL-6 expression in β2 integrin-null mice has not been determined. Reduced apoptosis in β2 integrin-null neutrophils in combination with its increased accumulation in the blood, due to a defect in extravasation, probably explains the neutrophilia observed in patients[48]. Furthermore, the delayed wound healing detected in patients with LAD-I may be due to the impaired differentiation of myofibroblasts, which are required for wound closure. Myofibroblast differentiation is dependent on transforming growth factor-β (TGFβ)[49], which is secreted from macrophages as they ingest neutrophils at the wound site[50]. In the absence of β2 integrin, not only are there fewer neutrophils present in the wound, but macrophages can no longer engulf cells or secrete TGFβ[51]. This defective signalling cascade, which leads to prolonged healing times, illustrates that mutating components of the adhesome can have consequences beyond cell autonomous adhesion and signalling defects.

Owing to the restricted expression of kindlin 3 in the haematopoietic system and endothelium[52,53], mutations in the *FERMT3* gene that encodes this protein manifest as haematopoietic disorders. *FERMT3* mutations lead to the immune disorder LAD-III (REF. 54), which is characterized by excessive bleeding and frequent infections[55–57]. Moreover, some patients exhibit osteopetrosis[56,58]. Kindlin 3 is involved in the activation of β1, β2 and β3 integrins, the activity of which is impaired in this disease[56,59–61]. Deficiency of kindlin 3 in mice causes a considerable bleeding defect, impaired leukocyte adhesion and osteopetrosis owing to defective osteoclast function[59,60,62]. Erythrocytes from kindlin 3-null mice display cytoskeletal defects that lead to irregularly shaped cells, which to date have not been described in patients[63].

Models of muscular dystrophies. Although most instances of muscular dystrophies arise from gene mutations in ECM molecules or non-adhesome laminin receptors[64], a mutation of the gene encoding α7 integrin, which is highly expressed in cardiac and skeletal muscle, has been implicated in a muscular dystrophy in humans[65]. Likewise, deletion of α7 integrin in mice leads to a muscular dystrophy phenotype[66,67], in addition to vascular smooth muscle defects that have not been reported in humans[68], possibly because the alterations found in humans are not as severe as those caused by the absence of the protein. As with other muscular dystrophies, deletion of α7 integrin causes muscle degeneration that is characterized by centrally located nuclei and variable fibre size[66]. Detachment from the myotendinous junction is also apparent, due to the inability to resist the force of muscle contraction. Interestingly, in mice that lack α7 integrin, the expression of α5 integrin, which is normally only expressed in embryonic muscle, persists into adulthood[67]. Although α7 integrin is also expressed in the heart, no defects in heart structure or function have been reported in knockout mice or humans with mutations in the gene encoding α7 integrin. However, owing to their positioning between the ECM and actin cytoskeleton, changes in other adhesome components contribute to defects in heart function (see below). Talin 2, which is mainly expressed in the heart, skeletal muscle and brain[69], produces a mild muscular dystrophy when deleted in mice[70], but no human disorder has so far been reported to involve this molecule.

Models of cardiovascular diseases. Mutations in the gene encoding metavinculin (MV), a muscle-specific splice variant of vinculin (VCL) that localizes to intercalated discs and the Z-line[71], have been associated with dilated cardiomyopathy (DCM) in humans[72,73]. Additionally, mutations in the gene that encodes VCL, which also affect its muscle specific splice variant MV, are linked to hypertrophic cardiomyopathy (HCM)[73,74]. In patients with HCM, VCL localization to intercalated discs was reduced, but it is not clear whether this was due to the mutation or to a secondary feature of the disease[75]. Although constitutive deletion of VCL is embryonic lethal[76], mice that express a single *Vcl* allele showed ultrastructural defects and developed cardiomyopathy in response to increased haemodynamic load[77]. Mice that express a cardiac-specific deletion of VCL developed DCM, which is characterized by the dissolution of intercalated discs[78]. Interestingly, skeletal muscle weakness has not been reported in patients or mice with *VCL* mutations, which implies a specific cardiac phenotype.

In addition to MV, alterations in the Z-line protein LIM domain-binding 3 (LDB3; also known as cypher or ZASP)[79], are linked to DCM in humans[80]. In patients that carry mutations in *LDB3*, peripheral muscle weakness was also observed, which indicates that this protein also has a role in skeletal muscle[81,82]. Mice in which LDB3 is constitutively deleted exhibit severe myopathy, which confirms the role of this protein in muscle function[83]. A cardiac-specific ablation of LDB3 in mice leads to severe DCM and premature death before 23 weeks of age[84]; conversely, mice that express a patient-relevant point mutation in *Ldb3* (S196L) develop DCM at a slower rate, and therefore might be a useful model for LDB3-linked DCM in humans[85].

Models of skin blistering disorders. Dermatological diseases that are caused by mutations in adhesome genes best highlight the need for cell adhesion in the maintenance of organismal homeostasis. The α6β4 integrin, which is encoded by *ITGA6* and *ITGB4*, is a component of hemidesmosomes — epithelial adhesion structures that interact with laminin 332 within the basement membrane [86] (FIG. 3a). In contrast to other integrins, which form connections with the actin cytoskeleton, α6β4 integrin connects the ECM to intermediate filaments[86]. Gene mutations in either of these integrin subunits

Myotendinous junction
A specialized region located at the muscle–tendon interface that represents the primary site of force transmission.

Intercalated discs
Specialized cardiac muscle structures that join adjacent cardiomyocytes, mainly through adherens-type junctions.

Z-line
A region at the boundaries of muscle sarcomeres in which the actin filaments are anchored. It appears as a dark transverse line in electron micrographs.

Intermediate filaments
Cytoplasmic and nuclear proteins that polymerize into stable filaments of ~10 nm in diameter. Their ability to form very stable filaments enables them to confer mechanical strength to the cytoskeleton.

in humans leads to a blistering disorder called pyloric atresia associated with junctional epidermolysis bullosa (PA-JEB), which is characterized by the detachment of basal keratinocytes from the underlying basement membrane (reviewed in REF. 87; FIG. 3b). Complete ablation of the β4 or α6 subunit in mice leads to perinatal lethality with severe skin blistering, which is reminiscent of extreme cases of JEB[88–90]. Conditional, inducible deletion of α6 integrin from the mouse epidermis is tolerated, although it produces blistering, alopecia, inflammation and hyperproliferation of keratinocytes as seen in patients with JEB[91,92]; mosaic deletion of β4 integrin results in blistering and inflammation in areas where it is absent[93].

Homozygous mutations in the gene encoding α3 integrin have been identified in three patients with nephrotic syndrome, pulmonary disease and skin fragility, which resulted in death during infancy[94,95]. These findings are in agreement with the phenotype of mice lacking the α3 subunit, which manifests in lung and kidney malformations due to aberrant branching morphogenesis[96] and a skin blistering phenotype[97]. However, blisters from mice and patients contain basement membrane deposits on both the dermal and epidermal sides of the blister, which suggests a role for α3 integrin in assembling and remodelling the basement membrane, rather than in anchoring cells to it; α6β4 integrins anchor cells to this site[98].

Kindler syndrome, which was first described by Theresa Kindler in 1954 (REF. 99), is caused by mutations in the *FERMT1* gene, which encodes kindlin 1 (REFS 100,101) (FIG. 3c). This disorder is characterized by skin blistering and atrophy in early life, which is followed by poikiloderma and photosensitivity. It is the first skin disorder known to involve a defective actin–ECM linkage[100]. Studies in mice and kindlin 1-deficient keratinocytes have shown that the defect occurs at the level of the interaction between basal keratinocytes and the epidermal basement membrane, which is consistent with the role of kindlin 1 as an integrin activator[18,102]. Kindlin 1-deficient skin cells display a loss of polarity and proliferation, and increased apoptosis[102]. Kindlin 1 deficiency in keratinocytes also results in the partial loss of the epithelial phenotype, which underlines the importance of adhesome signalling in maintaining the differentiated state[103]. Intriguingly, patients with Kindler syndrome tend to have a higher incidence of skin cancer[104].

From these and other studies, it is clear that inherited gene mutations in adhesome components are a marked source of disease and disability. However, dysregulated functioning of signalling components and inappropriate expression of adhesome molecules, independent of genetic mutation, is also an important contributor to disease.

Altered functions of the adhesome

Changes in the expression pattern and activity of adhesome components have been implicated in various diseases. As the physiological consequences of adhesome dysregulation on physiology are often spatiotemporally dependent, only a few animal models accurately reproduce the same disorders as seen in human patients. Furthermore, the involvement of adhesome-associated kinases and GTPases in disease progression has, in many cases, not been definitively proven to arise from adhesome-specific functions, and adhesion-independent functions may also be involved.

Aberrant expression of adhesome components. Changes in the expression levels of integrins and upregulation of integrins that are not normally expressed on quiescent cells are hallmarks of cancer. These changes enable cancer cells to acquire migratory and invasive properties, to alter their signalling profile and to survive in a foreign extracellular milieu that would normally trigger apoptosis in the untransformed cell. Moreover, the expression of certain integrins may enable tumour cells to acquire radioresistance[105]. Likewise, pathological angiogenesis is characterized by the expression of integrins such as αvβ3 on the tumour endothelium, which is absent on the quiescent endothelium[106]. The role of integrins in cancer and pathological angiogenesis is the subject of recent reviews[107–109]. The involvement of other adhesome components, including both scaffolding and signalling molecules, in cancer and pathological angiogenesis has also recently been discussed[110–114].

Specific growth factors have been shown to alter the expression of integrins in human chondrosarcoma cells. IL-8 and tumour necrosis factor (TNF) increased the transcription of the αv and β3 subunits, which was dependent on the transcription factors activator protein 1 (AP1) and nuclear factor-κB (NF-κB), respectively; the α5 and β1 subunits are upregulated by insulin-like growth factor 1 (IGF1) in an NF-κB-dependent manner[115–117]. The transcription factor ZEB2 (zinc-finger E-box binding homeobox 2; also known as SIP1 and ZFHX1B) was shown to increase the transcription of α5 integrin in colorectal cancer cells, in cooperation with the transcription factor SP1 (REF. 118). The seemingly paradoxical effect of MYC overexpression on suppressing invasion and metastasis has recently been explained by direct downregulation of the expression of αv, α5, β1, β3 and β5 integrins in several breast cancer cell lines and in retinal pigment epithelial cells, which is an established model for MYC signalling[119].

MicroRNAs (miRNAs) also regulate integrin expression in tumours. For example, loss of let-7a and overexpression of miR-214 led to an increase in β3 and a decrease in α3 integrin, respectively, in malignant melanoma[120,121]. miR-31, which is downregulated in many cancers, was shown to regulate the expression of α2, α5, αv and β3 integrins[122]. Downregulation of miR-124a in glioblastoma increased the expression of β1 integrin and correlated with increased migration and invasion, and decreased survival[123]. As dysregulated miRNA expression is a hallmark of cancer, direct examination will surely uncover many more examples of integrin regulation by this family of non-coding RNAs. Taken together, the expression profile of integrins on tumour cells is controlled by a complex interplay of growth factor signalling, transcription factor expression and miRNA regulation.

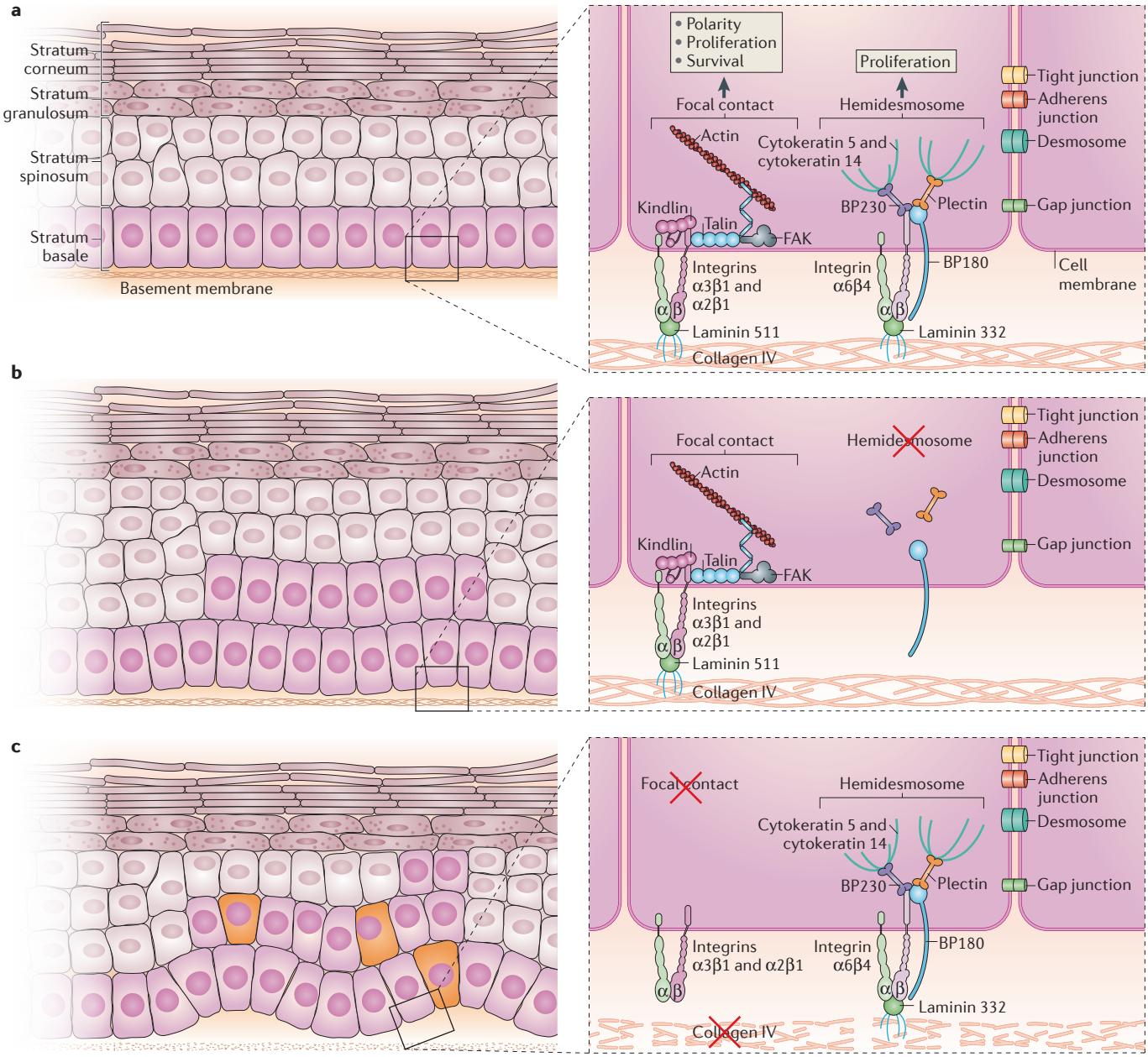

Figure 3 | **Adhesome-related skin blistering disorders: junctional epidermolysis bullosa and Kindler syndrome.** **a** | Normal epidermis architecture. The epidermis is a stratified epithelium that consists of four distinct layers of keratinocytes (left panel). Only keratinocytes in the stratum basale are in contact with the basement membrane, to which they adhere to through focal contacts that contain α3β1 and α2β1 integrins and hemidesmosomes that contain α6β4 integrin (right panel). Focal contacts link laminin 511 and type IV collagen to the actin cytoskeleton through talin and other actin-binding adhesome components (not shown); conversely, hemidesmosomes link laminin 332 to cytokeratin 5 and cytokeratin 14 through the structural molecules plectin and bullous pemphigoid 230 (BP230). BP180 binds to plectin, BP230 and β4 integrin, and is an essential component of the hemidesmosome. In addition to structural functions, signalling from focal contacts (for example, through focal adhesion kinase (FAK)) contributes to proliferation, survival and the establishment of cell polarity; signalling from hemidesmosomes is important for proliferation. Cell–cell adhesions through tight junctions, adherens junctions, desmosomes and gap junctions are not considered in this article. **b** | In junctional epidermolysis bullosa (JEB), mutation in the genes encoding either α6 or β4 integrin results in the loss of integrin expression at the cell surface and the absence of hemidesmosomes. Although focal contacts are intact, cells lose contact with the basement membrane, and the hyperproliferation of basal keratinocytes that follows leads to thickening of the epidermis. Although the underlying basis for hyperproliferation is unknown, it may be a secondary effect of inflammatory cell infiltration, as genetic deletion of *ITGB4* (which encodes β4 integrin) in mice normally results in hypoproliferation[184]. Despite detachment of the epidermis from the basement membrane, the architecture of the basement membrane seems normal. **c** | In Kindler syndrome, mutations in the gene encoding kindlin 1 prevent the activation of β1-containing integrins, which leads to the detachment of the epidermis from the basement membrane. The structure of the basement membrane is disrupted as basal keratinocytes are unable to remodel it. In the absence of signalling from focal contacts, keratinocytes display a lack of polarity, decreased proliferation and increased apoptosis (orange cells), which leads to thinner and more fragile skin. Although increased apoptosis is a hallmark of the human disease, it is not observed in kindlin 1-null mice. Disease progression leads to the thickening of the stratum corneum and hyperpigmentation.

Furthermore, altered expression of adhesome components has been shown to assist in the development of pathological cardiac hypertrophy and focal segmental glomerulosclerosis (FSGS). Left ventricular hypertrophy is a compensatory mechanism in response to volume or pressure overload from hypertension or aortic insufficiency. In human biopsy samples, increased expression of integrin-linked kinase (ILK) and focal adhesion kinase (FAK) has been detected[124,125]. These molecules probably directly contribute to hypertrophy, as cardiomyocyte-specific transgenic overexpression of ILK in mice phenocopies the human disease[124], and a siRNA-mediated reduction in FAK expression *in vivo* attenuates hypertrophy in a mouse model of volume overload[126]. ILK may cause hypertrophy by inducing cardiomyocyte proliferation[127,128], whereas FAK overexpression is mainly detected in cardiac fibroblasts[125], and it is possible that these cells may be in the process of differentiating into myofibroblasts[129].

The role of FAK in cardiac hypertrophy seems to be complicated: one study demonstrated that the deletion of FAK in cardiomyocytes prevents hypertrophy[130], whereas another study showed that hypertrophy was promoted in the absence of FAK[131]. One reason behind the discrepancy may be the age of the organism at which maximal FAK deletion was detected. In the study in which loss of FAK was protective, FAK remained detectable for three months, whereas in the study in which FAK loss promoted hypertrophy, FAK protein was undetectable two weeks after birth. These studies point to a potentially protective role of FAK during the early stages of life, perhaps by regulating the growth or function of the heart when the organism is young.

FSGS is a progressive renal disease in which the intimate contacts between podocytes and capillaries are lost, in a process known as foot process effacement (FIG. 4). Regulation of the actin cytoskeleton by RHO-family GTPases (mainly RHOA, RAC1 and CDC42) must be tightly controlled to maintain the delicate foot process. Mouse models showed that disrupting the balance of RHO GTPase activity leads to changes in the actin cytoskeleton and establishment of FSGS in mice[132,133]. Recently, a mutation in an adhesome-associated RACGAP gene, *ARHGAP24* (encoding RHOGAP24; also known as FILGAP and $p73^{RHOGAP}$), was identified in humans, establishing RHO GTPase dysregulation as an important mediator of FSGS[133].

The ILK–PINCH (particularly interesting new Cys-His; also known as LIMS1)–parvin complex may also be important in podocyte function through its role as an integrin adaptor and a GTPase regulating protein complex[134–136]. Biopsy material from patients with FSGS show increased ILK expression[137], and cultured podocytes show an increase in ILK-related activity when they are exposed to plasma from patients with FSGS[138]. This intriguing finding may help to explain the high rate of recurrent FSGS (20–30%) in patients that receive kidney transplants[139]. In mouse models, the actin adaptors tensin 1 (TNS1) and TNS2 have been implicated in FSGS, but so far no involvement for these proteins in human disease has been reported[140,141].

Adhesome-associated infectious diseases. Viruses have developed a number of strategies to infect cells through the involvement of integrins and other adhesome proteins. Although the adhesome is not considered dysregulated in this case, a large number of viruses and bacteria exploit integrins to facilitate cell attachment and uptake (Supplementary information S5 and S6 (tables)). Integrins that contain αv subunits seem to be favoured by many viruses, accounting for 50% of described virus–integrin interactions, and whereas αvβ3 integrin recognizes RGD (Arg-Gly-Asp)-containing ligands, some viruses can bind to this integrin in the absence of an RGD sequence[142–144]. In some cases, binding to integrins promotes the cellular uptake of the virus. Kaposi's sarcoma-associated herpes virus (KSHV), which binds to α3β1, αvβ5 and αvβ3 integrins, requires the activation of FAK or the FAK-related kinase Pro-rich Tyr kinase 2 (PYK2; also known as PTK2B) to enter cells, implicating adhesome signalling in virus uptake[145]. Human echo-virus 1 (EV1) prefers to bind the inactive form of α2β1 integrin, such that signalling pathways specific for 'activated integrins' are not involved in its uptake. However, EV1 promotes α2β1 integrin clustering and the activation of protein kinase Cα (PKCα), both of which are required for viral entry[146,147]. In the case of human cytomegalovirus (HCMV), αvβ3 integrin functions as a co-receptor, together with epidermal growth factor receptor (EGFR), to promote viral uptake by a mechanism dependent on PI3K and SRC activity[148]. Likewise, adenovirus requires the involvement of αvβ3 and αvβ5 integrins to facilitate cell entry through RAC1-mediated reorganization of the actin cytoskeleton downstream of PI3K, but neither of these integrins is required for cell attachment; they function only as co-receptors in this case[149–152].

Bacteria exploit integrins by directly interacting with them or by binding to the ECM and attaching to cells indirectly[153,154]. In contrast to viruses, bacteria show a marked preference for interacting with their hosts through β1 integrins. The reasons for this are unclear, but may be due to the increased resistance to force that β1 integrins exhibit as compared to β3 integrins, which may be important for bacterial uptake[155].

The molecular mechanisms by which bacteria enter cells differ in their details, but all require the manipulation of adhesome components, which results in the dynamic reorganization of the cytoskeleton. The binding of *Staphylococcus aureus* to α5β1 integrin stimulates the cytosolic assembly of a fibrillar adhesion-like adhesion, and subsequently the internalization of this bacterium in a FAK- and cortactin-dependent process[156]. Large membrane invaginations were observed around sites of cell attachment, which seemed to be involved in the engulfment process[154]. The molecular details of how these invaginations form are not known but may involve cortactin-mediated regulation of the actin-nucleating actin-related protein 2/3 (ARP2/3) complex[157]. Similar involvement of FAK–SRC signalling and cortactin has been observed in the invasion of *Neisseria meningitidis*[158] and *Shigella* spp.[159].

Focal segmental glomerulosclerosis
(FSGS). A kidney disease that is characterized by gradual disintegration of the glomerular filtration units as a result of a loss of attachment between podocytes and the glomerular basement membrane.

Podocytes
Cells in the kidney that have a crucial function in the filtration of solutes in the blood to form urine.

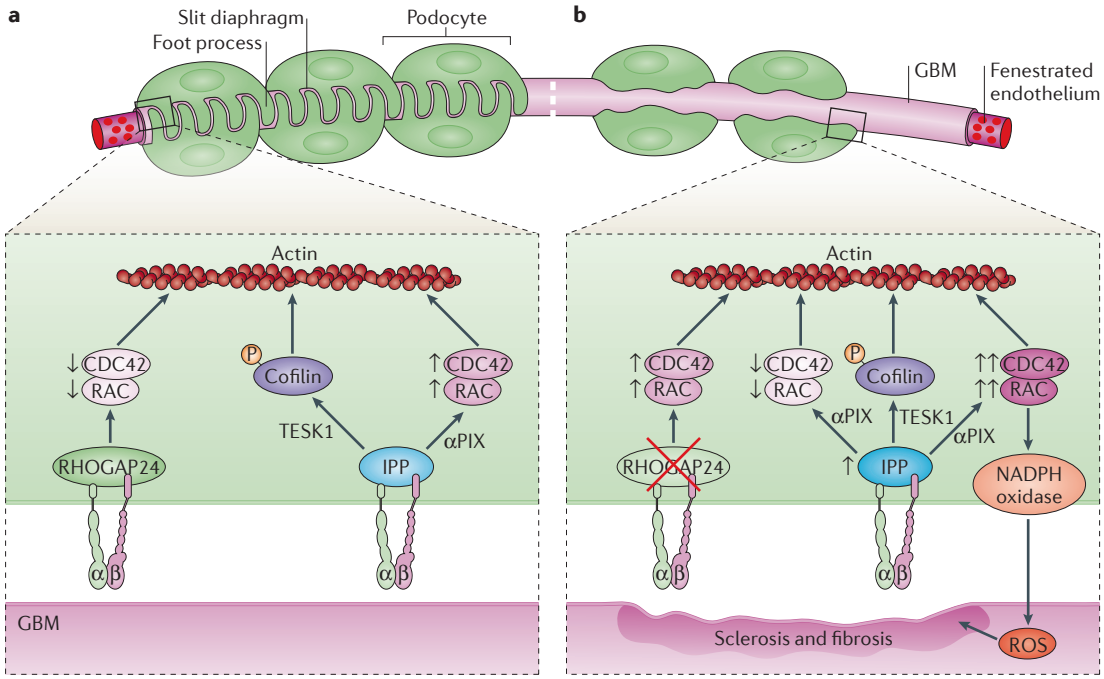

Figure 4 | **Focal segmental glomerulosclerosis.** Efficient blood filtration is dependent on intimate contacts between glomerular capillaries and podocytes. Glomerular capillaries are composed of a specialized fenestrated endothelium, which allows the passage of fluids and proteins but not blood cells, and a glomerular basement membrane (GBM). Podocytes bind to the GBM and encapsulate the capillary in a dense network of interdigitating foot processes, between which are slit diaphragms that permit the filtration of small solutes while preventing the loss of large proteins. **a** | In the normal kidney, the formation and maintenance of foot processes are dependent on balancing actin cytoskeleton dynamics by regulating the activity of the RHO GTPases CDC42 and RAC. The integrin-linked kinase (ILK)–PINCH (particularly interesting new Cys-His)–parvin (IPP) complex promotes the activity of CDC42 and RAC through the guanine nucleotide exchange factor PAK-interacting exchange factor-α (αPIX), which binds to α-parvin. Actin may also be regulated through the phosphorylation of cofilin through the Ser/Thr kinase testis-specific kinase 1 (TESK1), which also interacts with α-parvin. The GTPase activating protein (GAP) RHOGAP24, which localizes to the adhesome by binding the integrin- and actin-binding protein filamin (not shown), downregulates CDC42 and RAC activity. **b** | Impaired actin regulation within the podocyte leads to focal segmental glomerulosclerosis (FSGS), which is characterized by the effacement of foot processes and loss of the filtration barrier. Dysregulation of matrix deposition and remodelling, together with the production of reactive oxygen species (ROS) by RAC-mediated activation of NADPH oxidase, leads to progressive sclerosis and fibrosis of the capillary basement membrane. Mutations in the GAP domain of *ARHGAP24* (the gene encoding RHOGAP24) have been identified in humans with FSGS, which suggests that a failure to downregulate RHO GTPase activity contributes to this disease. Patients with FSGS frequently display increased ILK expression, which may lead to the enhanced activation of CDC42 and RAC with the concomitant dysregulation of actin dynamics. In mice, genetic deletion of IPP components in the podocyte also leads to progressive FSGS. The observation that alterations in molecules that both positively and negatively regulate the activity of RHO GTPases lead to the same outcome highlights the importance of maintaining a fine balance of GTPase activity to retain the delicate structure of the podocyte foot process.

A combination of gene knockout, siRNA knockdown and dominant-negative gene expression has enabled the dissection of the molecular mechanism that underlies *Campylobacter jejuni* cell invasion. It was revealed that β1 integrin-mediated cell attachment causes the activation of FAK, which leads to the activation of the RAC GEFs dedicator of cytokinesis protein 1 (DOCK1, also known as DOCK180) and T lymphoma invasion and metastasis-inducing 1 (TIAM1), and subsequently RAC-mediated actin rearrangements[160]. In addition, downregulation of ILK expression or activity was shown to impair the invasion of *Staphylococcus pyogenes*, *S. aureus* and *Yersinia* spp.[161]. The mechanism behind this inhibition is unknown but may involve the prevention of actin rearrangements induced by the ILK–PINCH–Parvin signalling complex[134].

The host defence against bacterial infection involves the rapid shedding of infected epithelia before it can cause severe pathology. Not surprisingly, bacteria have evolved mechanisms to overcome this host defence. Intracellular *Shigella* spp. secrete a virulence factor, outer surface protein E (OspE), which has recently been shown to bind ILK and to stabilize its association with the cell membrane[162]. The OspE–ILK complex increased the surface expression and activation of β1 integrin, which reduces cell detachment. As OspE is conserved across many pathogenic bacteria, blocking epithelial exfoliation by strengthening cell adhesion may be a general mechanism by which many bacteria evade this host defence.

Neisseria gonorrhoeae adopt a different strategy to prevent epithelial shedding. Through binding carcinoembryonic antigen-related cell adhesion molecules

Fab fragment
(Fragment antigen-binding). The antigen-binding portion of an antibody, which consists of the light chain and the heavy chain before the hinge region.

(CEACAMs) they increase the expression of cluster of differentiation 105 (CD105; also known as endoglin), a member of the TGFβ1 receptor family[163]. CD105 sequesters zyxin away from integrin attachments, in which CD105 functions as a negative regulator of adhesion, thus increasing integrin activation[164,165].

The adhesome as a therapeutic target

As changes in the adhesome are highly represented in human disease, interventions targeting adhesome components represent a potentially important therapeutic approach. Due to their surface exposure, compounds targeting integrins are the most developed. Currently, five integrin targeting drugs have been applied in the clinic[166]. These include the antibody natalizumab (Tysabri; Biogen Idec/Élan), which targets α4 integrin and is used to treat multiple sclerosis and Crohn's disease[167,168]; the antibody efalizumab (Raptiva; Genentech/Merck Serono), which is directed against αLβ2 integrin[169]; and abciximab (ReoPro; Janssen Biologics BV/Eli Lilly), a Fab fragment (fragment antigen-binding) that targets β3 integrin and is used to counter platelet activation in coronary disease and ischaemia[170]. Moreover, eptifibatide (Integrilin; Millennium Pharmaceuticals/Schering-Plough) and tirofiban (Aggrastat; Medicure Pharma), two small-molecule integrin antagonists, are in use to treat unstable angina[170]. Natalizumab and efalizumab have been linked to occurrences of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection. As a result, efalizumab was withdrawn from the market in 2009 and natalizumab was withdrawn temporarily before its use was reapproved in 2010.

In addition to these existing integrin antagonists, there are at least 260 additional compounds currently in clinical trials[166]. Among the most promising of these are vedolizumab (Entyvio; Millennium Pharmaceuticals), an antibody against α4β7 integrin that to date has not been shown to cause PML and could be used to replace natalizumab in the treatment of Crohn's disease[171] and multiple sclerosis; and cilengitide (Impetreve; Merck), a small-molecule that targets αv integrins and is currently in a Phase III clinical trial for glioblastoma treatment and in Phase II trials for other cancers[172].

Conclusions

There is ample evidence that components of the integrin adhesome have crucial roles in cell and tissue physiology; hence, gene mutations in key adhesome components can induce a disease state. This idea is clearly seen in the monogenetic diseases identified in the OMIM database. For genetically associated genes, the correlation between gene malfunction and the disease itself is far more complex. Further studies are needed to understand the gene–disease connection and the molecular mechanisms underlying the disease state.

Our analysis highlights the central role of the adhesome in cancer. It is clear that the adhesive and migratory ability of cancer cells is essential for disease development and should be therapeutically targeted. By combining novel insights obtained in siRNA screens for genes encoding protein products that have a role in adhesion and migration[13,15] with relevant animal models, it is likely that new information on adhesome genes that are involved in cancer development and metastasis will become available. Moreover, our knowledge of adhesome function can help to identify therapeutic targets in signalling pathways known to be important to disease development. It is noteworthy that the identification of new disease-related gene mutations in adhesome components can also clarify our understanding of the physiological functions of the adhesome in healthy cells and tissues.

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Competing interests statement
The authors declare no competing interests.

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