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Cell adhesion in *Drosophila*: versatility of cadherin and integrin complexes during development

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Abstract

We highlight recent progress in understanding cadherin and integrin function in the model organism *Drosophila*. New functions for these adhesion receptors continue to be discovered in this system, emphasising the importance of cell adhesion within the developing organism and showing that the requirement for cell adhesion changes between cell types. New ways to control adhesion have been discovered, including controlling the expression and recruitment of adhesion components, their posttranslational modification, recycling and turnover. Importantly, even ubiquitous adhesion components can function differently in distinct cellular contexts.

Introduction

Cell adhesion plays vital roles during the development and adult life of multicellular organisms. Two types of adhesion can be distinguished: adhesion between adjacent cells (cell-cell adhesion) and adhesion between cells and the extracellular matrix (cell-ECM adhesion, but also cell-ECM-cell adhesion). The canonical receptors for cell-cell adhesion are classical cadherins, which bind to other cadherins from neighbouring cells through homodimerization of their extracellular domains [recently reviewed in 1,2,3]. Cell-ECM adhesion occurs primarily with integrin receptors, each a heterodimer of α and β subunits, which bind specific ECM proteins [recently reviewed in 4].

In this review we describe recent advances in our understanding of these adhesion receptors as they function in the model organism *Drosophila*. In particular, we wish to highlight the emerging insights that arise from being able to study adhesion mechanisms in a variety of developmental and cellular contexts within the intact organism (Table 1). Using *Drosophila*, one can compare functions in diverse cell types, but also the same cell types in different developmental contexts, e.g. forming different organs, such as the eye or wing, or at different stages in the life cycle. Using *Drosophila* as a model system also has the advantage of the reduced gene number relative to vertebrates, which makes it more straightforward to remove completely the function of a particular type of protein. Thus, *Drosophila* has only 3 classical cadherins (E- and two N-cadherins, from a total of 17 proteins in the genome with cadherin repeats [5]), 5 integrin α subunits (αPS1-5) and 2 integrin β subunits (βPS and βν) [6]. Both cadherins and integrins recruit cytoplasmic proteins to form adhesion complexes that link their intracellular domains with the actin cytoskeleton, and each type of cytoplasmic protein is also encoded by fewer genes in *Drosophila* relative to vertebrates.

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We now focus on recent findings in *Drosophila* that have revealed how cell adhesion is adjusted to the requirements of different cell types and developmental events by changes in adhesion complex composition and dynamics.

Novel cadherin and integrin functions in *Drosophila*

New functions for cadherins and integrins continue to be discovered at a steady rate, as investigators test whether these adhesion receptors contribute to their favorite biological process. We have collated the known functions to demonstrate the breadth of activities of these receptors (Table 1, recently discovered functions are in bold). For cell biologists, these can be viewed as a range of assays that may reveal the mechanistic diversity of adhesion complexes. Just to highlight a few of the functions discovered recently: negative regulation of myoblast fusion by N-cadherin, counteracting an Arf-GEF [7]; E-cadherin-dependent proliferation and apoptosis in the absence of actin capping protein [8]; assembly of an ECM by integrins that is used by other cells as a track for their integrin-dependent migration [9]; repulsion between sensory neuron dendrites by integrins to ensure a non-overlapping field [10,11]. Not only do these discoveries aid the understanding of each developmental process, but they also provide new paradigms for the function of these receptors. Looking at Table 1 it is clear that integrins and cadherins are involved in many similar processes in the building of an organism, however, if you look at any individual tissue the two receptors are doing different things, supporting the view that they have distinct roles. The diversity of functions raises the question of whether they can be achieved by a single adhesive function for each type of receptor, or whether they require tailor-made adhesion complexes. As we shall discuss, the range of adhesive functions provided by *Drosophila* development and physiology has begun to reveal that their are different flavours of the adhesion machinery, and different modes of regulation of these diverse machines.

Regulation of adhesion by differential expression of the receptors

The easiest way to modulate adhesion is by controlling the expression of adhesion receptors, to control whether a cell has cadherins or integrins and also selecting the type of receptor. With integrins, 10 possible heterodimers can be formed with the 5 α subunits and 2 β subunits. While βPS is probably ubiquitously expressed, the rest show tightly controlled expression patterns, and have quite distinct functions (Table 1). A good example regulating adhesion by changing expression is in the follicular epithelium, where the cells switch from laminin-binding to RGD-binding integrins [12] (of note, a change in the composition of cadherins occurs simultaneously, with N-cadherin turned off, while E-cadherin remains on [13]). In the cases where it has been tested, the functional differences of the integrins α subunits map solely to the extracellular domains [14], even when it comes to recruiting a specific intracellular protein [12]. This suggests that the main reason different α subunits are employed is to generate heterodimers that bind particular matrix components. A number of integrin extracellular matrix ligands have been identified in *Drosophila*, and they also have distinct distributions [reviewed in 6]. The recruitment of many of them appears to be independent of integrins, but two require integrins for their stability and/or recruitment [9,15]. Thus, changing the expression of different integrin subunits and recruiting ligands by multiple mechanisms permits the generation of a variety of interactions with matrix proteins, creating diverse adhesion contexts throughout the developing organism.

There are multiple examples of important developmental regulation of E-cadherin. For example, elevation of E-cadherin synthesis by Src42A kinase is required for tracheal morphogenesis [16], while inhibition of E-cadherin transcription by talin ensures a differential adhesion between oocyte and follicle cells to establish the correct positioning of the oocyte and future embryo axis [17]. Actin-capping protein reduces E-cadherin synthesis

in the majority of the presumptive wing cells, therefore, promoting wingless and inhibiting JNK signaling in these cells [8].

E- and the two N-cadherins have complex patterns of expression, with some cells having single receptors and others a mixture. For example, during the epithelial-mesenchymal transition of the presumptive mesoderm during gastrulation, E-cadherin transcription is downregulated, while N-cadherin is upregulated [18], and as mentioned, N-cadherin becomes downregulated in the follicular epithelium [13]. A good example of how regulation of cadherin expression in time and space can regulate cell architecture is provided by the developing eye [19,20]. Cadherin extracellular interactions can also be regulated. N-cadherin is regulated by alternative splicing, with a more adhesive isoform expressed during early developmental stages [21], suggesting that splicing is used to regulate the strength of adhesion. E-cadherin exists in different conformations in a reproducible spatial pattern in the embryo, as documented using monoclonal antibody staining of unfixed embryos during dorsal closure [22]. Although the nature of these different conformations and how they are induced is not known, it seems likely that they are different homophilic binding states with different adhesive strengths [22,23]. Finally, the degredation of cadherins can also be regulated, as the turnover of E-cadherin decreases as embryonic development progresses [24].

Regulating the synthesis and turnover of adhesion complexes

Another mechanism to modulate adhesive function is to regulate the endocytosis and recycling of the transmembrane adhesion receptors. This appears to be the main mechanism used to move E-cadherin from one membrane to another [24,25]. E-cadherin endocytosis has been found to be increased in tissues undergoing active remodelling. Src42A and Pak1 elevate E-cadherin endocytosis in trachea and salivary glands to ensure the morphogenesis of these systems [16,26]. RhoGEF2 promotes E-cadherin endocytosis specifically at the junctions that are targeted for disassembly during germ band elongation [27]. The mechanisms that control E-cadherin endocytosis can be very different between tissues; the small GTPase Cdc42 has opposite effects on E-cadherin endocytosis, promoting E-cadherin endocytosis in the pupal notum and eye, but inhibiting endocytosis in the embryonic epidermis [28-30].

In contrast to cadherins, few recent studies have analysed the endocytosis and recycling of integrins in *Drosophila*. The pathways targeting integrins to adhesion sites can be specific to tissues, as revealed by a novel membrane trafficking pathway in the follicular epithelium [31]. The dynamic turnover of integrins and several associated proteins at muscle attachment sites reduces as larval development proceeds [32], suggesting that stabilisation of attachment as contraction strength increases. Integrin recruitment and turnover in pupal muscles is regulated by Myotubularin, which controls the balance of phosphoinositides at the membrane [33], suggesting a link between membrane composition and integrin localization and/or turnover. Future analysis of integrin and cadherin dynamics should provide a better understanding of how these large complexes of proteins can be modulated to accommodate different requirements of cells for adhesion throughout development.

The adhesome: regulating the link between adhesion receptors and the cytoskeleton

The term adhesome encapsulates the idea that it would be useful to identify the full set of proteins involved in the function of cadherins and integrins [34]. In particular, identifying all cytoplasmic proteins required for the function of these proteins is an ongoing task. Conceptually we can divide the intracellular adhesome components into 4 classes (Fig. 1

and Tables 2 and 3). Class 1 is cytoplasmic proteins that are always required for adhesion receptor function, the so-called “core” components. However, there are at least three possible ways to define such core components: 1) co-purifying with the receptor, 2) co-localising with the receptor in all types of cellular contexts, or 3) a genetic one, where the loss of core components produces the same set of defects as loss of the receptor (Fig. 1).

For classical cadherins, criterion 1 has worked well as they can be purified tightly bound to three intracellular proteins: β-catenin and p120catenin bind to cadherins directly; and α-catenin binds β-catenin [for references see 1,3]. The 3 catenins also co-localise with cadherins in a wide variety of cells, fulfilling criterion 2. However, while loss of α- and β-catenin causes strong lethal phenotypes very similar to loss of cadherins, loss of p120catenin results in viable and fertile flies [Table 2, 35,36,37].

There does not appear to be a similar “core” of intracellular proteins that can be co-purified with integrins; this may due to the technical difficulties of purifying integrins bound to the insoluble extracellular matrix, or it may reflect a lower affinity in the interactions, with chemical cross-linking being required to co-purify any of the integrin-associated proteins from cultured cells [38]. A large number of proteins fulfill criterion 2 (Table 3). Comparing muscle attachment sites (the major site of integrin adhesion in the embryo) to the focal adhesion structures that form on the basal surface of the follicular epithelium revealed that 7 of the 9 components examined were present in both systems [12]. Using criterion 3, talin has emerged as the sole core component, as it is the only integrin-associated protein absolutely required for integrin adhesion [see Table 3 and 39], and it is also essential for the recruitment of many of the other associated proteins [40]. Mutants in other components have subsets of the integrin/talin phenotype, or in the case of some, no detectable phenotype.

Thus, the work characterising the cadherin and integrin adhesomes has revealed associated proteins that are always colocalised with the adhesion receptor, but not always essential for its function. We term these class 2 proteins, and divide them into 3 subgroups, A-C (Fig. 1, Table 2 and 3). Classes 2A and 2B are defined by always being present but having a mutant phenotype that only show some overlap with the cadherin or integrin mutant phenotype. The difference between 2A and 2B is that 2A is partially required for all processes, but some processes only require a partial activity of the adhesion receptor so that no defect is observed, while 2B would only be functioning in some processes. These two classes are difficult to distinguish, but one prediction is that the mutant phenotype of class 2A components should resemble that caused by a mutation that uniformly reduces adhesion receptor activity, while this would not be expected for class 2B. Class 2C consists of proteins that are always present but do not share any phenotypes with mutants in the adhesion receptors.

The class 2 components highlight the issue of redundancy: we imagine that some of the components may show a weak phenotype when removed because another protein, similar in sequence and/or function, is able to substitute fully or partially. To date, it has been difficult to identify examples of this for some of the highly conserved proteins, e.g. p120catenin, vinculin and FAK, which lack strong phenotypes, and Rsu-1 and tensin, which only contribute to integrin adhesion in the wing. The recent discovery that Rsu-1 mutants become lethal in combination with a viable site-directed mutation in PINCH, which eliminates PINCH binding to ILK [41], shows that the powerful genetic approaches in *Drosophila* can identify these redundant functions.

Class 3 proteins are defined as being only associated with the receptor in some cell types or developmental stages. These are of particular interest, because they suggest that the integrin adhesion complex has specific requirements in different contexts. Finally, class 4 proteins

are those that do not become concentrated at sites of adhesion, and therefore do not localise or copurify, but nonetheless are required for adhesion function; these are not discussed further here.

Integrin-associated class 3 proteins are tensin and Wech. Wech is present in muscles, but not in follicle cells, while the recruitment of tensin to follicle cell focal adhesions requires the switch from αPS1βPS to αPS2βPS, with the specificity unexpectedly mapping to the extracellular domain of αPS2 [12]. The mechanism is unknown, but our favorite model is that the αPS2βPS-ECM link is a stronger attachment, and the ability to apply a stronger force uncovers binding sites for tensin.

A number of new cadherin adhesome class 3 proteins have been described recently (Table 2). Mutations in the genes encoding these proteins revealed novel and unexpected functions of cadherins that could not be uncovered by studying core components, as their absence causes severe phenotypes that mask these more subtle defects. For example, the study of MyoIB demonstrated the involvement of E-cadherin in establishing left/right asymmetry of the organism [42]; and Schizo/Loner has revealed the inhibitory role of N-cadherin on myoblast fusion [7]. Class 3 proteins also coordinate cadherin function with other pathways. Nemo kinase physically connects E-cadherin with the planar cell polarity proteins Strabismus and Prickle, contributing to ommatidial rotation [43].

While the class 3 proteins provide a clear way to regulate adhesion in different cell types or developmental stages, what has also emerged recently is that even class 1 and 2 proteins, which are always present, may function in a variety of ways. Talin is a scaffolding protein that binds the integrin β subunit cytoplasmic domain and actin, activating integrins and providing a link between integrins and the cytoskeleton. The major actin-binding domain and the two integrin-binding sites of talin are each required differently for the different integrin functions during development [44,45]. This suggests that, although talin is generally required for integrin function, the different types of cell-ECM adhesions do not rely equally on the same domains of talin. The class 2B protein Zasp has at least 13 potential splice variants and some of these are specifically expressed in muscles [46], suggesting that the apparent ubiquitous expression is in fact the tissue specific expression of multiple proteins with distinct functions, making Zasp a set of class 3 proteins. This diversity fits with data showing that point mutations in the integrins themselves can result in tissue-specific defects [47,48]. These results emphasize that even though a protein may be present in an adhesion complex at all times, we should not assume that it is molecularly or functionally identical at all times.

Diversity in the function of class 1 core components has also emerged for cadherin adhesion, with recent work emphasising the importance of β-catenin phosphorylation. In the developing eye, p21-activated kinase Mbt (D-Pak2) phosphorylates β-catenin, which destabilizes its binding to E-cadherin and reduces cell-cell adhesion strength, allowing correct cell rearrangement and morphogenesis during retina development [49,50]. A reduction in this inhibition of adhesion by Mbt could explain the observed increase in binding affinity between E-cadherin and β-catenin in the embryonic epidermis as development progresses [24], as *mbt* mRNA gradually decreases during embryogenesis [51]. If this is the case, it would however suggest that the Mbt-dependent reduction of affinity is not critical, as null *mbt* mutants are viable and fertile with rough eyes [52]. Another example is Nemo kinase, which phosphorylates β-catenin in a subset of developing photoreceptors to promote its function in ommatidial rotation [43]. Finally, Abl tyrosine kinase promotes phosphorylation of β-catenin to regulate the asymmetry of cadherin adhesion site localization and the dynamics in the epidermal cells of gastrulating embryos linked to convergent extension [53].

Conclusions

Recent work on cell adhesion in *Drosophila* has expanded our appreciation of the complexities of the adhesion machinery and the many possible ways to regulate its function. This model organism provides numerous adhesion events in the development and homeostasis of the animal. Each event may provide a paradigm for a particular variety of adhesive mechanism. We anticipate that advances in genetic and imaging tools will aid the elucidation of these mechanisms and reveal the importance of such variety of mechanism.

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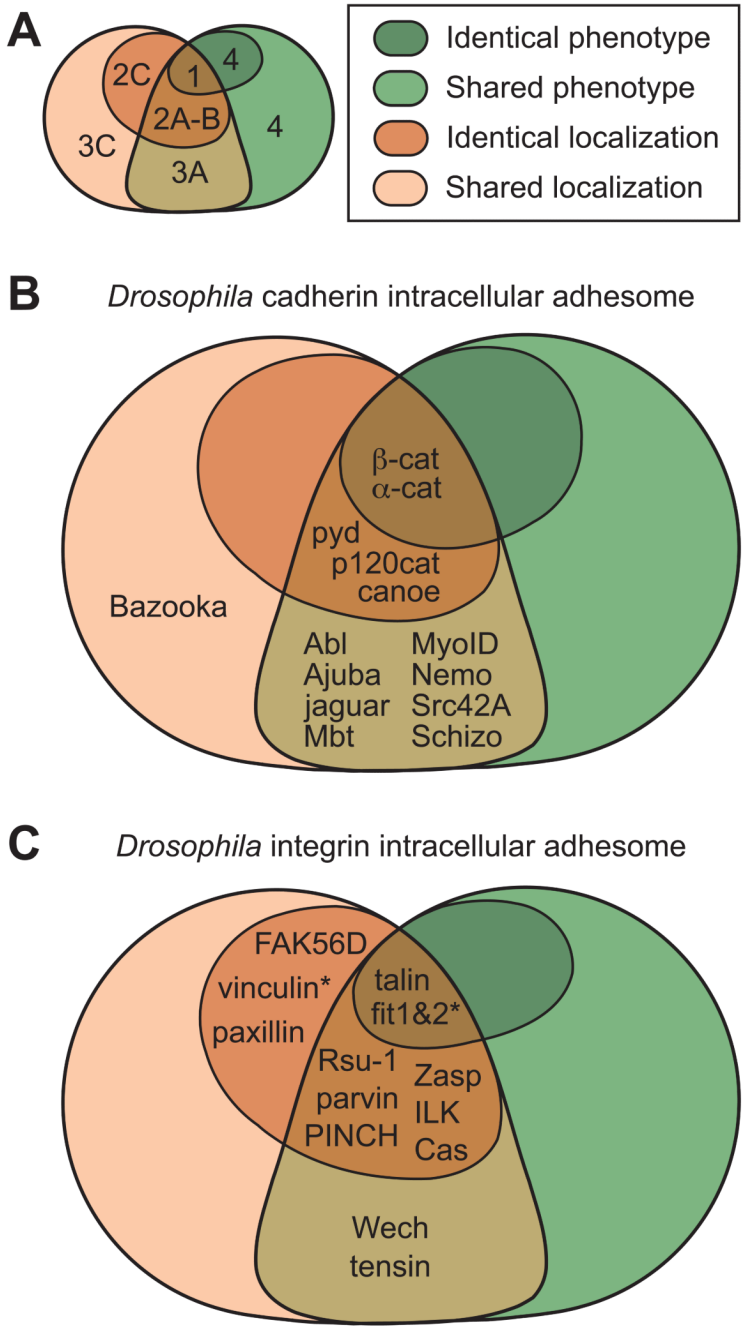

Figure 1.

Classes of intracellular adhesome proteins in general (A); in cadherin adhesion (B); and integrin adhesion (C). The proteins are divided in classes depending on their overlap in phenotype and colocalization with the adhesion receptor. Class 1, 2A-B and 2C proteins colocalize with receptor in all cases, and loss of class 1 proteins shares all phenotypes with the loss of receptor, loss of class 2A-B shares some phenotypes, and loss of class 2C does not share any. Class 3A and 3C proteins colocalize with receptor in some cases, and loss of class 3A proteins results in some common phenotypes with loss of receptor, while loss of class 3C proteins does not. We include a class 4 of proteins that do not colocalize with receptor, and loss of these proteins results in all or some phenotypes caused by loss of

receptor. * indicates that the class of the protein was predicted based on indirect data or data from other model systems. For detailed description of the proteins and references to literature see Tables 2 and 3.

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Table 1

Cadherin and Integrin functions in *Drosophila*

Tissue/system	Cadherin functions	Integrin functions
Amnioserosa	Adhesion between cell layers (between leading edge epidermis cells and amnioserosa) E – Gorfinkiel 2007	*Cell spreading* αPS3βPS – Schock 2003 Adhesion between cell layers (yolk cell/amnioserosa cells) αPS3 and βPS – Narasimha 2004 *ECM assembly* βPS – Narasimha 2004
Border cells	Cell migration E – Tepass 1999	Collective cell movement βPS – Llense 2008
Embryonic epidermis	*Cell-cell adhesion* (all) E – Tepass 1999 **Cell intercalation** (germband elongation) E – Levayer 2011; Tamada 2012 Collective cell movement (dorsal closure) E – Gorfinkiel 2007 *Modulation of signaling* (Wingless) E – Sanson 1996 **Organization of the actin cytoskeleton** (germband elongation) E – Gorfinkiel 2007; Rauzi 2010	Cell migration (dorsal closure) αPS1βPS, αPS2βPS, αPS3 – Leptin 1989; Roote 1995; Stark 1997 Collective cell movement (germband retraction) αPS1βPS, αPS2βPS – Leptin 1989; Roote 1995
Follicle cells	*Differential adhesion* (follicle cells/oocyte) E – Tepass 1999 Monolayer maintenance E – Godt 1998	Monolayer maintenance αPS1βPS – Fernandez-Minan 2007 Organization of the actin cytoskeleton (stress fibres) βPS – Delon 2009 *Organization of the microtubule cytoskeleton* (mitotic spindle) αPS1βPS – Fernandez-Minan 2007 Planar cell polarity βPS – Delon 2009 Stem cell maintenance αPS1βPS – O'Reilly 2008
Intestine	Stem cell maintenance E – Maeda 2008 *Modulation of signaling* (Notch) E – Maeda 2008	Cell migration αPS1βPS, αPS2βPS, αPS3βPS, βv – Brown 1994; Martin-Bermudo 1999; Devenport 2004
Muscle cells	***Cell fusion*** N – Dottermusch-Heidel 2012	Organization of the actin cytoskeleton (sarcomeres) βPS – Volk 1990; Rui 2010 *Muscle attachment* αPS2βPS – Leptin 1989; Brabant 1993 *ECM assembly* αPS2βPS – Devenport 2007
Nervous system	***Differential adhesion*** (neuron/glia) E – Slováková 2011 Tissue patterning (axons) N – Iwai 1997	**Adhesion between cell layers** (glial cell layers) αPS2βPS, αPS3βPS – Xie 2011 Axon guidance αPS2βPS, αPS3βPS – Hoang 1998 **Tissue patterning** (dendrites) αPS1βPS – Han 2012; Kim 2012
Retina	*Cell geometry* E, N – Hayashi 2004 Cell intercalation E – Carthew 2005 *Modulation of signaling* (EGF) E – Dumstrei 2002 Planar cell polarity E, N – Mirkovic 2006 *Cell-cell adhesion* E, N – Hayashi 2004 Tissue patterning N – Lee 2001; E – Grzeschik 2005	Adhesion between cell layers βPS – Zusman 1990
Salivary gland	***Cell geometry*** E – Pirraglia 2010	Cell migration αPS1βPS – Bradley 2003
Testis	Stem cell maintenance (somatic) E – Voog 2008	Stem cell maintenance (germline) βPS – Tanentzapf 2007
Trachea	*Cell-cell adhesion* E – Tepass 1999	Cell migration αPS1βPS – Boube 2001
Wing	***Cell death*** (JNK) E – Jezowska 2011 ***Modulation of signaling*** (Wingless) E – Jezowska 2011 *Cell-cell adhesion* E – Tepass 1999	Adhesion between cell layers αPS1βPS, αPS2βPS – Brower 1989, 1995; Wilcox 1989
Malpighian tubules	*Cell-cell adhesion* E – Tepass 1999	
Sensory organs	***Modulation of signaling*** (Notch) E – Benhra 2011	
Hemocytes		**Cell migration** αPS2 – Siekhaus 2010 ***Phagocytosis*** βv – Nagaosa 2011
Mesoderm		**Cell migration** αPS1βPS, αPS3βPS – Urbano 2011 *ECM assembly* αPS2βPS – Martin-Bermudo 1999; Urbano 2011 **Cell intercalation** βPS – McMahon 2010

Overview of the functions discovered for cadherins and integrins in *Drosophila*. The specific cadherins or integrins characterized are indicated (E: E-cadherin, N: N-cadherin). Recently discovered functions are in bold and functions specific to cadherins or integrins are in italic. References: **Benhra** (2011) *Curr. Biol.* 21 87-95; **Boube** (2001) *Genes Dev.* 15 1554-1562; **Brabant** (1993) *Dev. Biol.* 157 49-59; **Bradley** (2003) *Dev. Biol.* 257 249-262; **Brower** (1995) *Development* 121 1311-1320; **Brower** (1989) *Nature* 342 285-287; **Brown** (1994) *Development* 120 1221-1231; **Carthew** (2005) *Curr. Opin. Genet. Dev.* 15 358-363; **Delon** (2009) *J. Cell Sci.* 122 4363-4374; **Devenport** (2004). *Development* 131 5405-5415; **Devenport** (2007) *Dev. Biol.* 308 294-308; **Dottermusch-Heidel** (2012) *Dev. Biol.* ahead of print; **Dumstrei** (2002) *Development* 129 3983-3994; **Fernandez-Minan** (2007) *Curr. Biol.* 17 683-688; **Godt** (1998) *Nature* 395 387-391; **Gorfinkiel** (2007) *J. Cell Sci.* 120 3289-3298; **Grzeschik** (2005) *Development* 132 2035-2045; **Han** (2012) *Neuron* 73 64-78; **Hayashi** (2004) *Nature* 431 647-652; **Hoang** (1998) *J Neurosci.* 18 7847-7855; **Iwai** (1997) *Neuron* 19 77-89; **Jezowska** (2011) *Dev. Biol.* 360 143-159; **Kim** (2012) *Neuron* 73 79-91; **Lee** (2001) *Neuron* 30 437-450; **Leptin** (1989) *Cell* 56 401-408; **Levayer** (2011) *Nat. Cell Biol.* 13 529-540; **Llense** (2008) *Curr. Biol.* 18 538-544; **Maeda** (2008) *Gen. Cells* 13 1219-1227; **Martin-Bermudo** (1999) *Development* 126 5161-5169; **McMahon** (2010) *Development* 137 2167-2175; **Mirkovic** (2006) *Development* 133 3283-3293; **Nagaosa** (2011) *J. Biol. Chem.* 286 25770-25777; **Narasimha** (2004) *Curr. Biol.* 14 381-385; **O'Reilly** (2008) *The J. Cell Biol.* 182 801-815; **Pirraglia** (2010) *Development*; **Rauzi** (2010) *Nature* 468 1110-1114; **Roote** (1995) *Dev. Biol.* 169 322-336; **Rui** (2010) *PLoS Genet.* 6 e1001208; **Sanson** (1996) *Nature* 383 627-630; **Schock** (2003) *Genes Dev.* 17 597-602; **Siekhaus** (2010) *Nat. Cell Biol.* 12 605-610; **Slováková** (2011) *Development* 138 1563-1571; **Stark** (1997) *Development* 124 4583-4594; **Tamada** (2012) *Dev. Cell* 22 309-319; **Tanentzapf** (2007) *Nat. Cell Biol.* 9 1413-1418; **Tepass** (1999) *Curr. Opin. Cell Biol.* 11 540-548; **Urbano** (2011) *PLoS ONE* 6 e23893; **Volk** (1990) *Cell* 63 525-536; **Voog** (2008) *Nature* 454 1132-1136; **Wilcox** (1989) *Development* 107 891-897; **Xie** (2011) *Development* 138 3813-3822; **Zusman** (1990) *Development* 108 391-402

Table 2

Cadherin-associated intracellular proteins in *Drosophila*

Drosophila protein	Mammalian orthologue	Protein domains	Class	L	I	Ph	Tissue (L/Ph)	Function	References
β-catenin	β-catenin	12 armadillo-like repeats	1	■	+	■	All (L/Ph)	All	N, E – Tepass 1999
α-catenin	α-catenin	α-catenin/vinculin conserved site	1	■	+	●	All (L/Ph)	All	E – Sarpal 2012
p120catenin	p120catenin	3 armadillo-like repeats	2A-B	■	+	◉	All (L), embryonic epidermis and retina (Ph)	Tissue integrity, tissue patterning	N, E – Myster 2003; Larson 2008
Canoe	Afadin	2 Ras-associating, PDZ, forkhead-associated and Dilute domains	2A-B	■	+	◉	All (L), midline glia and retina (Ph)	Differential adhesion, organization of cytoskeleton, cell geometry, tissue patterning	E – Matsuo 1997, 1999; Slováková 2011
Polychaetoid (pyd)	TJP1/ZO-1	3 PDZ, Guanylate kinase-like, SH3 and ZU5 domains	2A-B	■	P	◉	Embryonic epidermis (L), retina (L/Ph)	Cell migration, cell shape, tissue patterning	E – Seppa 2008; Choi 2011; Djiane 2011
Abl	ABL	Tyrosine protein kinase, SH2, SH3 and F-actin binding domains	3A	◧	+	◉	Embryonic epidermis (L/Ph), nervous system (Ph)	Cell intercalation, tissue patterning	E –Tamada 2012 N – Tepass 1999
Ajuba	AJUBA	3 LIM domains	3A	◧	P	◉	Embryonic epidermis, wing (L)	None described	E – Sabino 2011
Bazooka	Par-3	Oligomerization domain and 3 PDZ domains	3C	◧	+	○	Embryonic epidermis (L, late stages), wing (L)	None described	E – Wei 2005
jaguar	MYO6	Myosin tail 2, Myosin head motor domains and IQ motif	3A	◧	+	◉	Border cells (L/Ph)	Cell migration	E – Geisbrecht 2002
Mbt	PAK7	CRIB and Serine/Threonine protein kinase domains	3A	◧	+	◉	Retina (L/Ph)	Tissue patterning, organization of the cytoskeleton	E – Menzel 2007
MyoID	MYOID	Myosin tail 2, Myosin head motor domains and IQ motif	3A	◧	+	◉	Genital discs (L/Ph)	Left/right asymmetry	E – Petzoldt 2012
Nemo	Nemo-like kinase	Serine/Threonine protein kinase	3A	◧	+	◉	Retina (L/Ph)	Planar polarity	E – Mirkovic 2011
Src42A	fyn-related kinase	Tyrosine protein kinase, SH2 and SH3 domains	3A	◧	+	◉	Embryonic epidermis, trachea (L/Ph)	Tissue integrity	E – Takahashi 2005; Shindo 2008
Schizo/Loner	IQSEC1	Sec7 and PH domains, IQ motif	3A*	□	+	◉	Muscle (L/Ph)	Cell fusion	N – Dottermusch-Heidel 2012

Cadherin-associated intracellular proteins in *Drosophila*. “Class” indicates whether the proteins: always co-localize with their receptor and are required for all functions (1 – core components) or for some functions (2A-B) of the receptor; co-localize with their receptor in certain contexts and are required for some functions (3A) or for no described function (3C) of the receptor. See text and figure 1 for more details. “L” (co-Localization) indicates whether the proteins localize with their receptors in all (full black) or some tissues (half black). “I” (Interaction) indicates whether the *Drosophila* proteins have been shown to (+) or are predicted to (P) interact biochemically with their receptor. “Ph” (Phenotype) indicates whether the protein is required for more functions (full black), all functions (●), some functions (◉) or for no described function (○) of its receptor. “Tissue” describes in which tissue the protein localizes (L) and shares phenotypes (Ph) with its receptor. “Function” describes the relevant processes described requiring the protein for its receptor function. References: **Choi** (2011) *Mol. Biol. Cell* 22 2010-2030; **Djiane** (2011) *J. Cell Biol.* 192 189-200; **Dottermusch-Heidel** (2012) *Dev. Biol.* ahead of print; **Geisbrecht** (2002) *Nat. Cell Biol.* 4 616-620; **Larson** (2008) *Mech. Dev.* 125 223-232; **Matsuo** (1997) *Development* 124 2671-2680; **Matsuo** (1999) *Cell Tiss. Res.* 298 397-404; **Menzel** (2007) *Mech. Dev.* 124 78-90; **Mirkovic** (2011) *Nat. Struc. Mol. Biol.* 18 665-672; **Myster** (2003) *The J. Cell Biol.* 160 433-449; **Petzoldt** (2012) *Development* 139 1874-1884; **Sabino** (2011) *J. Cell Sci.* 124 1156-1166; **Sarpal** (2012) *J. Cell Sci.* 125 233-245; **Seppa** (2008) *Dev. Biol.* 318 1-16; **Shindo** (2008) *Development* 135 1355-1364; **Slováková** (2011) *Development* 138 1563-1571; **Takahashi** (2005) *Development* 132 2547-2559; **Tamada** (2012) *Dev. Cell* 22 309-319; **Tepass** (1999) *Curr. Opin. Cell Biol.* 11 540-548; **Wei** (2005) *Dev. Cell* 8 493-504

Table 3

Integrin-associated intracellular proteins in *Drosophila*.

Drosophila protein	Mammalian orthologue	Protein domains	Class	L	I	Ph	Tissue (L/Ph)	Function	References
talin	talin	FERM domain and 2 integrin-, >10 vinculin-, 2 actin-binding sites	1	■	P	■	All (L/Ph)	All	Brown 2002
fermitin 1 & 2	kindlin 1, 2 & 3	FERM and PH domain	1*		P		Embryonic muscles (Ph)	Muscle attachment (RNAi)	Bai 2008
Cas	p130Cas	SH3 domain	2A-B	■		◉	Embryonic muscles (L) and CNS (L/Ph)	Axon guidance	Huang 2007
ILK	ILK	Pseudo-kinase domain, ankyrin repeats	2A-B	■		◉	All (L), embryonic muscles and wings (Ph)	Muscle attachment Adhesion between cell layers	Zervas 2001
parvin	parvin	2 Calponin-Homology domains	2A-B	■		◉	All (L), embryonic muscles and wings (Ph)	Muscle attachment Adhesion between cell layers	Vakaloglou 2012
PINCH	PINCH	LIM domains	2A-B	■		◉	All (L), embryonic muscles and wings (Ph)	Muscle attachment Adhesion between cell layers	Clark 2003
Rsu-1	Rsu-1	7 leucine-rich repeats	2A-B	■		◉	Embryonic muscles (L) and wings (L/Ph)	Adhesion between cell layers	Kadrmas 2004
Zasp	Zasp	ZM motif, 1 PDZ and 4 LIM domains	2A-B	■		◉	Embryonic muscles (L/Ph)	Muscle attachment	Jani 2007
paxillin	paxillin	LIM domains	2C	■		○	All (L)	Cell fusion (not known if integrin-dependant)	Bataille 2010
vinculin	vinculin	talin- and actin-binding domains	2C*	■		○		None described	Alatortsev 1997
FAK56D	FAK	FERM, Tyrosine kinase and FAT domains	3A	◧		○	All (L)	Optical stalk structure (not known if integrin-dependant)	Grabbe 2004; Murakami 2007
tensin	tensin	SH2 and PTB domains	3A	◧		◉	Embryonic muscles (L) and wings (L/Ph)	Adhesion between cell layers	Torgler 2004
Wech	Wech	B-box zinc-finger, coiled-coil and NHL domains	3A	◧		◉	Embryonic muscles (L/Ph)	Muscle attachment	Loer 2008

Integrin-associated intracellular proteins in *Drosophila*. “Class” indicates whether the proteins: always co-localize with their receptor and are required for all functions (1 – core components), for some functions (2A-B) or for no described function (2C) of the receptor; co-localize with their receptor in certain contexts and are required for some functions of the receptor (3A). See text and figure 1 for more details.

* indicates that the class is predicted. “L” (co-Localization) indicates whether the proteins localize with their receptors in all (full black) or some tissues (half black). “I” (Interaction) indicates whether the *Drosophila* proteins have been shown to (+) or are predicted to (P) interact biochemically with their receptor. “Ph” (Phenotype) indicates whether the protein is required for more functions (full black), some functions (◉) or for no described function (○) of its receptor. “Tissue” describes in which tissue the protein localizes (L) and shares phenotypes (Ph) with its receptor. “Function” describes the relevant processes described requiring the protein for its receptor function. “RNAi” indicates functions observed when the gene is down-regulated by RNAi in some tissues. References: **Alatortsev** (1997) *FEBS Lett.* 413 197-201; **Bai** (2008) *Development* 135 1439-1449; **Bataille** (2010) *Dev. Cell* 19 317-328; **Brown** (2002) *Dev. Cell* 3 569-579; **Clark** (2003) *Development* 130 2611-2621; **Grabbe** (2004) *Development* 131 5795-5805; **Huang** (2007) *Development* 134 2337-2347; **Jani** (2007) *J. Cell Biol.* 179 1583-1597; **Kadrmas** (2004) *J. Cell Biol.* 167 1019-1024; **Loer** (2008) *Nat. Cell Biol.* 10 422-428; **Murakami** (2007) *Development* 134 1539-1548; **Torgler** (2004) *Dev. Cell.* 6 357-369; **Vakaloglou** (2012) *J. Cell Sci.* ahead of print; **Zervas** (2001) *J. Cell Biol.* 152 1007-1018