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'Identify' and 'lock in': molecular integration during synaptic target recognition

B. Hoang* and A. Chiba

B608 CLSL (CSB), Department of Cell and Structural Biology, 601 South Goodwin Avenue, University of Illinois, Urbana (Illinois 61801, USA), Fax + 1 217 244 8962, e-mail: hoang@uiuc.edu

Abstract. Synaptic target recognition is a complex molecular event. In a differentiating presynaptic terminal, relatively 'rare' molecules first detect the cell identity of the synaptic target. Subsequently, many 'common' molecules continue the process of synaptogenesis. We present a theoretical framework for understanding synaptic target recognition and discuss the features of its molecular components and their integration, drawing on the rapid progress made in recent studies.

Key words. Axon; chemoaffinity; growth cone; molecular integration; neural recognition; synaptogenesis.

The success of neural networking in a developing brain depends on the ability of individual neurons to recognize appropriate synaptic partners. This neural recognition, known more specifically as 'synaptic target recognition,' represents a unique case of cell recognition with a specific consequence, the initiation of a synapse. A number of new papers are dedicated to this topic each year, rapidly expanding the molecular vocabulary necessary to understand synaptic target recognition. These urge an updated theoretical framework by which such new knowledge may be organized.

In this review, we discuss several key studies and also outline a theoretical framework that integrates them. We hope this framework will help further our comprehensive understanding of the molecular integration underlying the basis for neural networking.

Molecular components of synaptic target recognition

Since Roger Sperry [1] inspired neurobiologists nearly three decades ago with his 'chemoaffinity' theory, numerous studies have supported the view that the secrets of neural networking in the brain can ultimately be explained in terms of specific genes and their regulation [2–8]. Many of the molecular players, unknown to Sperry and his contemporaries, are now known and continue to be identified.

There is good evidence that each synaptic partner has a relatively independent capacity to proceed with its own differentiation process. For example, agrin, a 'synapse organizer' molecule secreted from vertebrate motoneuron terminals, is sufficient for clustering neurotransmitter receptors on the postsynaptic membrane even after presynaptic terminals are removed [9–11]. Meanwhile, the presynaptic motoneuron terminals in *Drosophila* embryos can develop even when myoblasts are prevented from forming muscles [12]. It is possible, therefore, to separate molecular events at developing synapses either as presynaptic or postsynaptic. Since a number of recent reviews have concentrated mainly on postsynaptic differentiation and neurotransmitter receptor clustering [9–11, 13], we will focus on the presynaptic molecular integration during transformation of growth cones to presynaptic terminals.

At the presynaptic site, synaptic targeting involves a relatively complex molecular event that combines at least two sets of molecular integration (fig. 1). First, when an axon encounters the cues provided by its target, specific target recognition receptors on its surface will be activated (fig. 1A). It is important to note that the majority of cellular encounters between an axon and its surroundings that occur during its out-

* Corresponding author.

growth do not result in synapse initiation. This implies that relatively 'rare' molecules, positioned in specific sets of axons, are involved in each case of target recognition. Second, once initiated, axon terminals quickly engage a more or less 'common' set of molecules (fig. 1B), which then begin to recruit other presynaptic

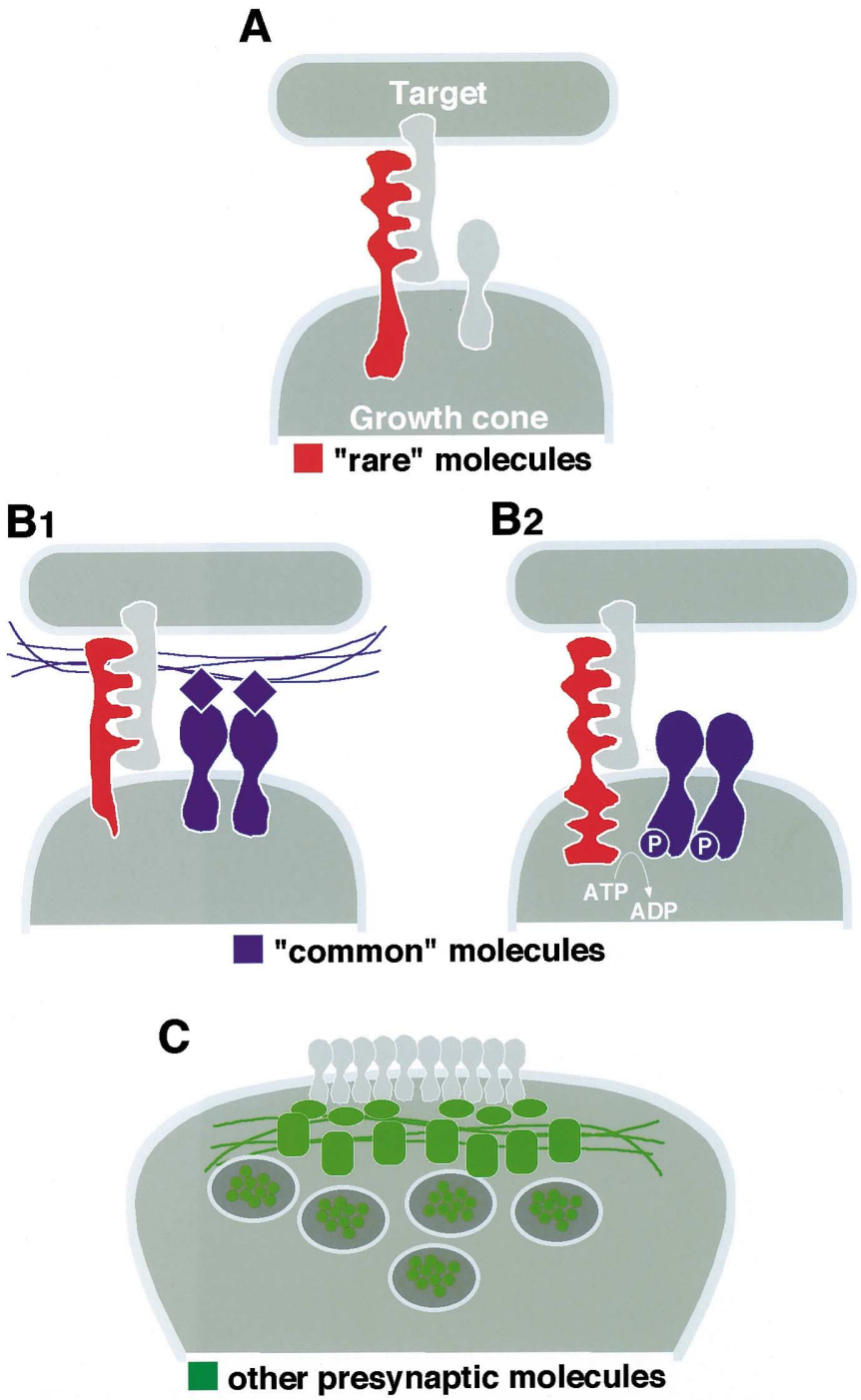

Fig. 1.

proteins such as neurotransmitter vesicles, vesicle release/recycle molecules, ion channels and various subsynaptic adapter proteins (fig. 1C) [14, 15]. These molecules are widely shared by many axons, and together convert motile growth cones into morphologically homogeneous presynaptic structures.

As a result, in each synaptic targeting event, both 'rare' and 'common' molecules are used by the axon terminal, with the former mainly to ensure cell specificity and the latter mostly to facilitate reliable development of synaptic connection. One can classify the participating molecules as 'rare' or 'common' based on both their appearance and functions.

An important question regarding synaptic target recognition

Realization of the scale of molecular diversity and integration during synaptic target recognition raises an important question. We have relatively little information about how the 'rare' molecules that detect the cell identity of the target and the 'common' molecules that initiate synaptogenesis are interfaced within each axon terminal. Surface receptors and sub-membrane molecular pathways are potential sites of signal integration within axon terminals, but the details of such molecular integrations remain undefined.

On a purely theoretical basis, one could argue that molecular integration is the only way through which massive neural evolution has ever been possible. While the number of synapses increases by nearly 10^{15} from the relatively simple nervous system of *Caenorhabditis elegans* to that of human, the number of genes in their respective genomes merely quadruples at most. Therefore, it seems reasonable to speculate that the addition of such an astonishing number of synapses in the human brain, and their seemingly uncompromised synaptic specificity [16], is accomplished not by the addition of new genetic raw materials but by the creative utilization of rather limited genetic resources.

Historically, there was a period during which developmental neurobiologists concentrated their attention on the molecules in the 'rare' category. Several genetic screens have been designed to isolate mutations that cause synaptic targeting errors in specific sets of neurons [17, 18]. In complementary studies that utilize the endogenous molecular expression patterns as entry points, the roles of genes expressed in specific subsets of neurons and/or their synaptic targets have been examined systematically [19–21].

However, the crucial question remains as to how these 'rare' molecules are coupled to a general machinery of synaptogenesis [5]. Some recent studies are beginning to provide insights into the question of what happens after initial target identification.

A theoretical framework for synaptic target recognition

We propose a theoretical framework in which synaptic target recognition as a whole is envisioned as a process that links two distinct molecular events of 'identifying' the synaptic target and 'locking in' the synaptic partners. We believe that constructing such a framework of thinking is especially useful because it will produce specific predictions regarding complex molecular integration which can be tested or applied to existing knowledge (table 1). The specific predictions are as follows.

First, the two classes of synaptic target recognition molecules likely exhibit different expression patterns. The 'rare' molecules, responsible for the first stage of synaptic target recognition, will be present only in a limited number of cells (fig. 1A). This is in contrast to the 'common' molecules that will be widely shared by many, if not all, neurons (fig. 1B). In addition, the presence of the 'rare' molecules will be required only

Figure 1. Molecular integration during synaptic target recognition. The main role of 'rare' molecules is to 'identify' the synaptic target (*A*), whereas that of 'common' molecules is to 'lock in' the synaptic partners (*B*) and subsequently recruit other presynaptic proteins necessary for maturation of the presynaptic structures (*C*). (*A*) First, synaptic target recognition will be triggered by relatively 'rare' growth cone receptor molecules. These 'rare' molecules are expressed uniquely on individual axon growth cones and are responsible for 'identifying' their synaptic target cells. The interactions between these 'rare' receptors and their corresponding ligands may be homophilic or heterophilic, and may also involve matching certain combinations of 'rare' molecules. (*B*) Next, a set of 'common' molecules will be quickly engaged within the axon growth cone that has experienced activation of its 'rare' molecules. These 'common' molecules are widely shared by many axons and are capable of self-clustering at the axon membrane. The two diagrams depict two alternative scenarios through which activation of 'rare' molecules may be interfaced to the 'common' molecules (*1*) Binding of 'rare' receptors to corresponding ligands will bring other target-derived molecules (e.g., extracellular-matrix-bound molecules) within easy access to the 'common' molecules on the growth cone. This will lead to extracellularly induced recruitment of these and other presynaptic proteins. (*2*) Alternatively, binding of 'rare' receptors will stimulate their cytoplasmic catalytic activities, which will then alter the phosphorylation status of certain membrane-associated 'common' proteins (here shown as single molecular entities, although they may involve molecular complexes). This will result in intracellularly induced recruitment of these and other presynaptic proteins. (*C*) Subsequently, the rapid recruitment of a set of 'common' molecules will cause an avalanche of molecular complexing among other presynaptic proteins such as neurotransmitter vesicles, vesicle release/recycle molecules, ion channels, and various subsynaptic adapter proteins. The 'rare' molecules may be downregulated by this stage.

during the very first stage of presynaptic differentiation, while the 'common' molecules may continue to play their subsequent roles even after the 'rare' molecules are downregulated. The subcellular localization of the 'rare' and 'common' molecules may differ somewhat. Due to their direct interaction with extrinsic cues, the 'rare' molecules are expected to be either transmembrane or membrane bound (fig. 1A). In contrast, the 'common' molecules could include both transmembrane and intracellular signaling molecules that are closely associated with the cell surface events triggered by the 'rare' molecules (fig. 1B).

Second, the phenotypes expected from genetic deletion of the genes of each class of molecules are distinct. The loss of a 'rare' molecule would lead to defects in only a specific set of neurons that normally express the gene. When 'common' molecules shared by many neurons are deleted, however, the phenotype may or may not be subtle but will likely involve many neurons. Furthermore, while genetic manipulations of a 'rare' molecule are expected to result in rather specific phenotypes because other growth cone receptors responsive to their specific ligands are still intact, the deletion of a 'common' molecule could produce variable synaptogenesis defects among many neurons.

The role of 'rare' molecules is to 'identify' the synaptic target

Studies from the last few years provide many examples of molecules that seem to fit the expected profiles of the two functional classes of molecules according to the theoretical framework described above. Here, we merely highlight the main conclusions concerning molecules in the 'rare' category, as reviews have appeared elsewhere that summarize these studies in detail [2–5, 22–24].

First, negative recognition is as important as positive recognition. A well-known case for locally provided cues from non-target cells that exert inhibitory influences on specific sets of axons comes from the Eph family of receptors in vertebrate retinotectal systems [25–27]. Though their identities are not yet known, the growth cone receptors for muscle-derived semaphorins, netrins, and Toll in the *Drosophila* neuromuscular system have also been proposed to mediate negative recognition of non-target muscles by specific subsets of motoneuron axons [28–31]. Retraction of axon growth cones caused by the cells or regions that are outside the appropriate synaptic targets is now considered to be a major mechanism by which synaptic targeting accuracy can be dramatically improved.

Second, for synaptic matching of the highest cellular resolution, positive recognition between an individual axon and its synaptic target is necessary. One means by which positive recognition is achieved is through a homophilic molecular match between the synaptic partners. This is probably the most succinct version of the 'chemoaffinity' theory [1]. Based on their rare, as well as synaptically matched, expression patterns, a number of neuronal cell surface molecules of diverse gene families have been implicated in establishing synaptic specificity. They include the immunoglobulin superfamily cell adhesion molecules (IgCAMs), Toll-like receptors (TLRs), cadherins, connexins, and neurexins [3, 5–8, 32–36]. As discussed in a recent review [4], currently the best demonstrations for homophilic recognition have been fasciclin III (IgCAM) and connectin (TLR) in the *Drosophila* neuromuscular system [19, 37–40].

Additionally, heterophilic molecular matching is also very likely. The vertebrate odorant receptors that constitute a large family of genes expressed heterogeneously by the olfactory neurons appear to contribute to idiosyncratic target recognition by individual olfactory axons [41, 42]. The ligands for these receptors during synaptic target recognition are not yet known.

The results show that a diverse population of proteins is utilized in different fashions to define the specificity of synaptic partners. Although the proteins are different in structure, their activations give rise consistently to a common synaptic apparatus.

The role of 'common' molecules is to 'lock in' the synaptic partners

Very little is known about how activation events mediated by these 'rare' cell surface molecules lead to re-

Table 1. Predictions for the two functional classes of molecules that are integrated during synaptic target recognition.

Class	Expression pattern		Consequences when deleted		Proposed role	Example candidate
	sites	timing	axons affected	phenotypes		
'Rare' molecules	specific axons	at first contact	specific axons	specific targeting errors	'identify' the synaptic target	Fas III, EPH, Toll, connectin
'Common' molecules	many axons	first contact and onward	many axons	synaptogenesis defects	'lock in' the synaptic partners	Late-bloomer, RTKs, RTPs, Fas II, cadherins, integrins

cruitment of the 'common' molecules of synaptogenesis. The situation is challenging since these 'rare' molecules apparently share no common features in their cytoplasmic structures [5, 6]. A key to resolving this puzzle may lie in the unique functional features of some members of the 'common' molecules. Before discussing why we think certain of these molecules are best suited to 'lock in' the process of synaptogenesis, we will first review the specific cases of 'common' molecules.

Two main features predicted from the two-stage model of synaptic target recognition are (i) that the 'common' interface molecules will be expressed by many axons, and (ii) their loss will lead to defects in synaptogenesis initiation by many axons (table 1). One such molecule is Late-bloomer, a tetraspanin expressed by all *Drosophila* motoneuron axons at the time of motoneuron-muscle interactions [43]. When Late-bloomer is genetically deleted, the motor axons still reach their respective targets but fail to initiate presynaptic differentiation in time. The extracellular domains of Late-bloomer are relatively small and are therefore not very likely to mediate initial interactions with target-provided cues. Furthermore, the phenotype of a null mutation in the *Late-bloomer* gene is not permanent and, given extra time, many motor axons appear to complete synaptogenesis. This suggests that other members of a hypothetical presynaptic complex may still function, although less efficiently. These observations are consistent with the idea that Late-bloomer and related proteins play the roles of a 'common' molecule.

Several other neural cell surface molecules are also good candidates for potent 'common' interface molecules that 'lock in' synaptogenesis initiation. The trk family of receptor tyrosine kinases (RTKs), receptor tyrosine phosphatases (RTPs), fasciclin II (IgCAM), cadherins, and integrins are all present in many axons [44–50]. Furthermore, fasciclin II, cadherins, and integrins are known to be enriched at the developing presynaptic terminals in a variety of animal systems [24, 48, 51–54]. The available data suggest that the loss of RTPs or integrins affects synaptogenesis initiation by many motoneurons in *Drosophila* embryos [55, 56]. Unfortunately, the phenotypic analyses of the loss of these molecules are still incomplete because these molecules have a number of other earlier functions including axon pathfinding before reaching the targets [47, 57].

What makes the cadherins and integrins particularly unique is the fact that they can feed into a number of different local cytoplasmic signaling cascades. For example, cadherins, through association with catenins, initiate cytoskeletal rearrangement [53, 58–60], while integrins complex with a number of cytoplasmic adapter/signaling molecules and exert a wide range of influences over cytoskeletal and cytoplasmic signaling [61–63].

While specific molecular partners of cadherins or integrins at synapse initiation have not been determined, ultrastructural studies in the *Drosophila* neuromuscular system have revealed that selective molecular complexing may be occurring during synaptic target recognition [E. Suzuki, D. Rose and A. Chiba, unpublished data]. Numerous spots of close membrane apposition that resemble focal adhesions are found between normal synaptic partners. Both sides of these presumptive focal adhesions accumulate electron-dense materials. Here the gap between the membranes becomes smaller (down to approximately 10 nm) compared to the ordinary situation among non-target partners (20–40 nm). Such electron-dense structures often result from accumulation of integrins, cadherins, and their associated molecules [64–66]. The selective cell adhesions appear to precede other signs of synaptogenesis initiation such as retraction of filopodia, accumulation of synaptic vesicle proteins, and electrophysiological evidence of evoked potentials. These observations suggest that recruitment of a specific set of molecules upon the initial contact of the synaptic partner cells is a common feature shared widely among neurons.

Possible scenarios with certain 'common' molecules

How could the cadherins, integrins, or other functionally similar molecules of the 'common' category, link directly or indirectly to a variety of 'rare' molecules and ultimately converge their activation onto a common molecular pathway of synaptogenesis? The answer may be found in the inherent natures of such cell surface molecules which will likely be well conserved across animal species.

Figure 1B depicts how certain of the 'common' molecules present a particularly interesting feature. Common to cadherins and integrins is that they can be activated by a number of different factors from outside and inside the cell. Integrins can be activated either by extrinsic ligands such as laminin and L1 [61–63] or intrinsic phosphorylation signals [51, 63, 67, 68]. They are therefore capable of interfacing either outside-in or inside-out signaling events [69, 70]. It is also an attractive possibility that activation of some of the RTKs or RTPs induces secondary integrin activation [44, 71]. As a consequence, any local event that promotes contact between integrins and their ligands or phosphorylation of FAK and other similar integrin-associated cytoplasmic proteins can potentially cause the same avalanche of molecular complexing at the axon membrane [68, 72]. For example, the former could result from an axon encountering a target cell that bears matching homophilic or heterophilic cell adhesion molecules (fig. $1B_1$), while the latter might occur when an axon runs

into target-provided cues that activate RTKs expressed by the axon (fig. $1B_2$). Slightly more limited, similar scenarios have been proposed for cadherins in their coordination with catenins [53, 58, 73].

We may therefore view these neural surface molecules as something analogous to a 'power amplifier' in a hi-fi stereo system. Different input devices such as a CD player, FM radio and cassette tape deck are connected to a common adapter which in turn feeds the amplified signals to the speakers. We suggest that successful interfacing between activation of structurally diverse 'rare' molecules to pan-neuronal process of synaptogenesis relies crucially on the inherent natures of some of the 'common' neural surface molecules, such as the cadherins, integrins, and possibly Late-bloomer, that can respond widely and sensitively to a number of local signaling events.

Concluding remarks

Within the recent papers on the topic of synaptic target recognition is an increased appreciation that the molecular events governing establishment of specific synapses are relatively complex. We have summarized the major conclusions from recent years and provide a theoretical framework through which the current and future data may be reconstructed. It is hoped that the theoretical framework of a two-stage molecular integration outlined here will help us achieve comprehensive understanding of synaptic target recognition, one of the fundamental topics in developmental neurobiology.

We have proposed that synaptic target recognition may be viewed as a process of integrating two distinct molecular events, that of 'identifying' the synaptic target by the 'rare' molecules and that of 'locking in' the synaptic partners by the 'common' molecules. A major unresolved question concerns the integration mechanism itself. While it remains a possibility that a family of genes that share a unique cytoplasmic domain possesses the specific function of linking diverse extracellular recognitions to the common synaptogenesis pathway, the current evidence seems to point to an alternative scenario. There may exist a group of commonly shared cell surface molecules whose principal task during synaptic target recognition is to converge the activation signals of the 'rare' receptors onto a common cytoplasmic pathway of presynaptic differentiation.

The field of synaptic target recognition has been maturing rapidly in recent years. While new molecular players continue to be identified, more emphasis must now be placed on understanding how these molecules are integrated. We anticipate new and exciting revelations of the intricacy of molecular integration during neural network formation.

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1 Sperry R. W. (1963) Chemoaffinity in the orderly growth of nerve fiber patterns and connections. Proc. Natl. Acad. Sci. USA **50:** 703–710
2 Goodman C. S. (1996) Mechanisms and molecules that control growth cone guidance. Ann. Rev. Neurosci. **19:** 341–377
3 Tessier-Lavigne M. and Goodman C. S. (1996) The molecular biology of axon guidance. Science **274:** 1123–1133
4 Chiba A. and Rose D. (1998) 'Painting' the target: how local molecular cues define synaptic relationships. BioEssays **20:** 941–948
5 Chiba A. and Keshishian H. (1996) Neuronal pathfinding and recognition: roles of cell adhesion molecules. Dev. Biol. **180:** 424–432
6 Garrity P. A. and Zipursky S. L. (1995) Neuronal target recognition. Cell **83:** 177–185
7 Varela-Echavarria A. and Guthrie S. (1997) Molecules making waves in axon guidance. Genes Dev. **11:** 545–557
8 Neito M. A. (1996) Molecular biology of axon guidance. Neuron **17:** 1039–1048
9 Denzer A. J., Hanger D. M., Gesemann M. and Ruegg M. A. (1997) Synaptic differentiation: the role of agrin in the formation and maintenance of the neuromuscular junction. Cell Tissue Res. **290:** 357–365
10 Bowe M. A. and Fallon J. R. (1995) The role of agrin in synapse formation. Ann. Rev. Neurosci. **18:** 443–462
11 Burden S. J. (1998) The formation of neuromuscular synapses. Genes Dev. **12:** 133–148
12 Prokop A., Landgraf M., Rushton E., Broadie K. and Bate M. (1996) Presynaptic development at the *Drosophila* neuromuscular junction: assembly and localization of presynaptic active zones. Neuron **17:** 617–626
13 Craig A. M. (1998) Activity and synaptic receptor targeting: the long view. Neuron **21:** 459–462
14 Prokop A. Integrating bits and pieces: synapse structure and formation in *Drosophila* embryos. Cell Tissue Res., in press
15 Meier T. and Wallace B. G. (1998) Formation of the neuromuscular junction: molecules and mechanisms. BioEssays **20:** 819–829
16 O'Leary D. D. M., Yates P. A. and McLaughlin T. (1999) Molecular development of sensory maps: representing sights and smells in the brain. Cell **96:** 255–269
17 Van Vactor D., Sink H., Fambrough D., Tsoo R. and Goodman C. S. (1993) Genes that control neuromuscular specificity in *Drosophila*. Cell **73:** 1137–1153
18 Seeger M., Tear G., Ferres-Marco D. and Goodman C. S. (1993) Mutations affecting growth cone guidance in *Drosophila*: genes necessary for guidance toward or away from the midline. Neuron **10:** 409–426
19 Nose A., Mahajan V. B. and Goodman C. S. (1992) Connectin: a homophilic cell adhesion molecule expressed on a subset of muscles and the motoneurons that innervate them in *Drosophila*. Cell **70:** 553–567
20 Keshishian H., Chiba A., Chang T. N., Halfon M. S., Harkins E. W., Jarecki J. et al. (1993) Cellular mechanisms governing synaptic development in *Drosophila melanogaster*. J. Neurobiol. **24:** 757–587.
21 Landgraf M., Roy S., Prokop A., VijayRaghavan K. and Bate M. (1999) *even-skipped* determines the dorsal growth of motor axons in *Drosophila*. Neuron **22:** 45–52
22 Chiba A. (1999) Early development of *Drosophila* neuromuscular junction: a model for studying neuronetwork development. In: Neuromuscular Junctions in *Drosophila*, pp. 1–24, Budnik V. and Gramates S. (eds), Academic Press, San Diego
23 Walsh F. S. and Doherty P. (1997) Neural cell adhesion molecules of the immunoglobulin superfamily: role in axon growth and guidance. Ann. Rev. Cell Biol. **13:** 425–456

24 Redies C. (1997) Cadherins and the formation of neural circuitry in the vertebrate CNS. Cell Tissue Res. **290:** 405–413
25 Holt C. E. and Harris W. A. (1998) Target selection: invasion, mapping and cell choice. Curr. Opin. Neurobiol. **8:** 98–105
26 Tessier-Lavigne M. (1995) Eph receptor, tyrosine kinases, axon repulsion, and the development of topographic maps. Cell **82:** 345–348
27 Holt C. and Harris W. A. (1993) Position, guidance, and mapping in the developing visual system. J. Neurobiol. **24:** 1400–1422
28 Rose D., Zhu X., Kose H., Hoang B., Cho J. and Chiba A. (1997) Toll, a muscle cell surface molecule, locally inhibits synaptic initiation of the RP3 motoneuron growth cone in *Drosophila*. Development **124:** 1561–1571
29 Mitchell K. J., Doyle J. L., Serafini T., Kennedy T. E., Tessier-Lavigne M., Goodman C. S. et al. (1996) Genetic analysis of netrin genes in *Drosophila*: netrins guide CNS commissurral axons and peripheral motor axons. Neuron **17:** 203–215
30 Matthes D. J., Sink H., Kolodkin A. L. and Goodman C. S. (1995) Semaphorin II can function as a selective inhibitor of specific synaptic arborizations. Cell **81:** 631–639
31 Winberg M. L., Mitchell K. J. and Goodman C. S. (1998) Genetic analysis of the mechanisms controlling target selection: complementary and combinatorial functions of netrins, semaphorins, and IgCAMs. Cell **93:** 581–591
32 Shishido E., Takeichi M. and Nose A. (1998) *Drosophila* synapse formation: regulation by transmembrane protein with Leu-rich repeats, CAPRICIOUS. Science **280:** 2118–2121
33 Ullrich B., Ushkaryov Y. A. and Sudhof T. C. (1995) Cartography of neurexins: more than 1000 isoforms generated by alternative splicing and expressed in distinct subsets of neurons. Cell **14:** 497–507
34 Dodd J. and Schuchardt A. (1995) Axon guidance: a compelling case for repelling growth cones. Cell **81:** 471–474
35 Keynes R. and Cook G. M. W. (1995) Axon guidance molecules. Cell **83:** 161–169
36 Gallo G. and Letourneau P. C. (1998) Axon guidance: GTPases help axons reach their targets. Curr. Biol. **8:** R80–R82
37 Nose A., Takeichi M. and Goodman C. S. (1994) Ectopic expression of connectin reveals a repulsive function during growth cone guidance and synapse formation. Neuron **13:** 525–539
38 Nose A., Umeda T. and Takeichi M. (1997) Neuromuscular target recognition by a homophilic interaction of connectin cell adhesion molecules in *Drosophila*. Development **124:** 1433–1441
39 Chiba A., Snow P., Keshishian H. and Hotta Y. (1995) Fasciclin III as a synaptic target recognition molecule in *Drosophila*. Nature **374:** 166–168
40 Kose H., Rose D., Zhu X. and Chiba A. (1997) Homophilic synaptic target recognition mediated by immunoglobulin-like cell adhesion molecule fasciclin III. Development **124:** 4143–4152
41 Momberts P., Wang F., Dulac C., Chao S. K., Nemes A., Mendelsohn M. et al. (1996) Visualizing an olfactory sensory map. Cell **87:** 675–686
42 Wang F., Nemes A., Mendelsohn M. and Axel R. (1998) Odorant receptors govern the formation of a precise topographic map. Cell **93:** 47–60
43 Kopczynski C. C., Davis G. W. and Goodman C. S. (1996) A neural tetraspanin, encoded by late bloomer, that facilitates synapse formation. Science **271:** 1867–1870
44 Van Vactor D. (1998) Protein tyrosine phosphatases in the developing nervous system. Curr. Opin. Cell Biol. **10:** 174–181
45 Fannon A. M. and Colman D. R. (1996) A model for central synaptic junctional complex formation based on the differential adhesive specificities of the cadherins. Neuron **17:** 423–434
46 Serafini T. (1997) An old friend in a new home: cadherins at the synapse. Trends Neurosci. **20:** 322–323
47 Hoang B. and Chiba A. (1998) Genetic analysis of the role of integrin during axon guidance in *Drosophila*. J. Neurosci. **18:** 7847–7855
48 Grabham P. W. and Goldberg D. J. (1997) Nerve growth factor stimulates the accumulation of $\beta 1$ integrin at the tips of filopodia in the growth cones of sympathetic neurons. J. Neurosci. **17:** 5455–5465
49 Wang X. H. and Poo M. M. (1997) Potentiation of developing synapses by postsynaptic release of neurotrophin-4. Neuron **19:** 825–835
50 Gallo G., Lefcort F. B. and Letourneau P. C. (1997) The trkA receptor mediates growth cone turning toward a localized source of nerve growth factor. J. Neurosci. **17:** 5445–5454
51 Wu D. Y., Wang L. C., Mason C. A. and Goldberg D. J. (1996) Association of $\beta 1$ integrin with phosphotyrosine in growth cone filopodia. J. Neurosci. **16:** 1470–1478
52 Redies C. and Takeichi M. (1996) Cadherins in the developing central nervous system: an adhesive code for segmental and functional subdivisions. Dev. Biol. **180:** 413–423
53 Uchida N., Honjo Y., Johnson K. R., Wheelock M. J. and Takeichi M. (1996) The catenin/cadherin adhesion system is localized in synaptic junctions bordering transmitter release zones. J. Cell Biol. **135:** 767–779
54 Schuster C. M., Davis G. W., Fetter R. D. and Goodman C. S. (1996) Genetic dissection of structural and functional components of synaptic plasticity. I. Fasciclin II controls synaptic stabilization and growth. Neuron **17:** 641–654
55 Desai C. J., Gindhart J. G., Goldstein L. S. B. and Zinn K. (1996) Receptor tyrosine phosphatases are required for motor axon guidance in the *Drosophila* embryo. Cell **84:** 599–609
56 Desai C. J., Krueger N. X., Saito H. and Zinn K. (1997) Competition and cooperation among receptor tyrosine phosphatases control motoneuron growth cone guidance in *Drosophila*. Development **124:** 1941–1952
57 Iwai Y., Usui T., Hirono S., Steward R., Takeichi M. and Uemura T. (1997) Axon patterning requires *D*N-cadherin, a novel neuronal adhesion receptor, in the *Drosophila* embryonic CNS. Neuron **19:** 77–89
58 Yap A. S., Brieher W. M. and Gumbiner B. M. (1997) Molecular and functional analysis of cadherin-based adherens junctions. Ann. Rev. Cell Dev. Biol. **13:** 119–146
59 Takeichi M. (1988) The cadherins: cell-cell adhesion molecules controlling animal morphogenesis. Development **102:** 639–655
60 Tomaselli K. J., Neugebauer K. M., Bixby J. L., Lilien J. and Reichardt L. F. (1988) N-Cadherin and integrins: two receptor systems that mediate neuronal process outgrowth on astrocyte surfaces. Neuron **1:** 33–43
61 Sastry S. K. and Horwitz A. F. (1993) Integrin cytoplasmic domains: mediators of cytoskeletal linkages and extra- and intracellular initiated transmembrane signaling. Curr. Opin. Cell Biol. **5:** 819–831
62 Arregui C. O., Carbonetto S. and McKerracher L. (1994) Characterization of neural cell adhesion sites: point contacts are the sites of interaction between integrins and the cytoskeleton in PC12 cells. J. Neurosci. **14:** 6967–6977
63 Guinebault C., Payrastre B., Racaud-Sultan C., Mazarguil H., Breton M., Mauco G. et al. (1995) Integrin-dependent translocation of phosphoinositide 3-kinase to the cytoskeleton of thrombin-activated platelets involves specific interactions of p85α with actin filaments and focal adhesion kinase. J. Cell Biol. **129:** 831–842
64 Weisberg E., Sattler M., Ewaniuk D. S. and Salgia R. (1997) Role of focal adhesion proteins in signal transduction and oncogenesis. Crit. Rev. Oncog. **8:** 343–358
65 Burridge K. and Chrzanowska-Wondnicka M. (1996) Focal adhesions, contractility, and signaling. Ann. Rev. Cell Dev. Biol. **12:** 463–519
66 Gomez T., Roche F. and Letourneau P. (1996) Chick sensory neuronal growth cones distinguish fibronectin from laminin by making substratum contacts that resemble focal contacts. J. Neurobiol. **29:** 18–34

67 Schlaepfer D. D. and Hunter T. (1998) Integrin signaling and tyrosine phosphorylation: just the FAKs? Trends Cell Biol. **8:** 151–157
68 Takagi Y., Ui-Tei K., Miyake T. and Hirohashi S. (1998) Laminin-dependent integrin clustering with tyrosine-phosphorylated molecules in a *Drosophila* neuronal cell line. Neurosci. Lett. **244:** 149–152
69 Kolanus W. and Zeitlmann L. (1998) Regulation of integrin function by inside-out signaling mechanisms. Curr. Top. Microbiol. Immunol. **231:** 33–49
70 Yamada K. M. and Miyamoto S. (1995) Integrin transmembrane signaling and cytoskeletal control. Curr. Opin. Cell Biol. **7:** 681–689
71 Van Vactor D. (1998) Adhesion and signaling in axonal fasciculation. Curr. Opin. Neurobiol. **8:** 80–86
72 Hanks S. K. and Polte T. R. (1997) Signaling through focal adhesion kinase. BioEssays **19:** 137–145
73 Daniel J. M. and Reynolds A. B. (1997) Tyrosine phosphorylation and cadherin/catenin function. BioEssays **19:** 883–891