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Invited review

Cell adhesion and homeostatic synaptic plasticity

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ABSTRACT

At synapses, pre- and post-synaptic cells get in direct contact with each other via cell adhesion molecules (CAMs). Several CAMs have been identified at the neuromuscular junction and at central synapses, where they regulate synaptic strength, by recruiting scaffolding proteins, neurotransmitter receptors and synaptic vesicles in response to the binding of counter-receptors across the synaptic cleft. Many synapses are also surrounded by astrocytic processes and embedded in conspicuous extracellular matrix (ECM). It is now widely recognized that astrocytes play a central role in regulating the synaptic machinery by exchanging information with the neuronal elements via diffusible molecules and direct physical interactions; this has lead to the concept of the 'tri-partite synapse'. More recently, the term 'tetra-partite synapse' has been introduced to underlie the importance of ECM in shaping synaptic function by mediating interaction and signaling between neurons and astrocytes.

Here, we will review how this integrated view of the synapse can help us understand homeostatic synaptic plasticity at the neuromuscular junction and in the central nervous system. We will explore how synaptic CAMs regulate two forms of homeostatic plasticity: (i) postsynaptic scaling of synaptic currents to counteract changes in neuronal network activity and (ii) the compensatory modulation of presynaptic neurotransmitter release in response to changes in postsynaptic efficacy. We will discuss recent findings on activity-dependent *trans*-synaptic signaling events and the role of cell adhesion in the feedback control of network activity.

This article is part of the Special Issue entitled 'Homeostatic Synaptic Plasticity'.

If we want things to stay as they are, things will have to change

(Se vogliamo che tutto rimanga come è, bisogna che tutto cambi)

Spoken by Tancredi in The Leopard (Il Gattopardo; by di Lampedusa; 1958)

1. Synaptic cell adhesion: a molecular perspective

The term 'synaptic cell adhesion molecule' (CAM) refers to proteins spanning the synaptic cleft and directly connecting pre- and post-synaptic terminals. Some CAMs, such as Neuroligins, SynCAMs and β1 integrin, are enriched at the center of the synapse (Mortillo et al., 2012); others, typically members of the Cadherin family, are preferentially localized at the outer rims of presynaptic active zones and postsynaptic densities (Uchida et al., 1996). Furthermore, there are CAMs that mediate neuron–astrocyte interactions at the synapse. Direct evidence for their existence is presently limited to the EphA4/ephrinA3 complex between dendritic spines and astrocytic processes (Filosa et al., 2009; Murai et al., 2003) (Fig. 1). Although adhesion complexes between astrocytes and nerve terminals do not cross the synaptic cleft, and are therefore not strictly synaptic, they are likely to be as important as *trans*-synaptic CAMs in determining synaptic structure and function (Volterra and Meldolesi, 2005).

CAMs are usually divided between those mediating homophilic interactions (like with like) and those mediating heterophilic interactions between two different types of CAMs (Fig. 1). Recent findings have however shown that such distinctions are not always so clear-cut. For example, it is well appreciated that some CAMs (e.g. many members of the immunoglobulin superfamily) bind homophilically in some cases and heterophilically in others (Dityatev et al., 2008). Furthermore, *trans*-synaptic interactions

Abbreviations: ADAM, a disintegrin and metalloprotease; AMPAR, 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propanoic acid receptor; BDNF, brain-derived neurotrophic factor; CAM, cell adhesion molecules; CaMKIV, calcium/calmodulin-dependent protein kinase IV; Cdk5, cyclin-dependent kinase 5; ECM, extracellular matrix; GABA, gamma-aminobutyric acid; GAP, GTPase-activating protein; GEF, guanine nucleotide exchange factor; LTD, long-term depression; LTP, long-term potentiation; MHC, Major histocompatibility complex; NMDAR, *N*-Methyl-D-aspartate receptor; PDZ, postsynaptic density protein/Drosophila disc large tumor suppressor/zonula occludens-1 protein; TNFα, tumor necrosis factor alpha.

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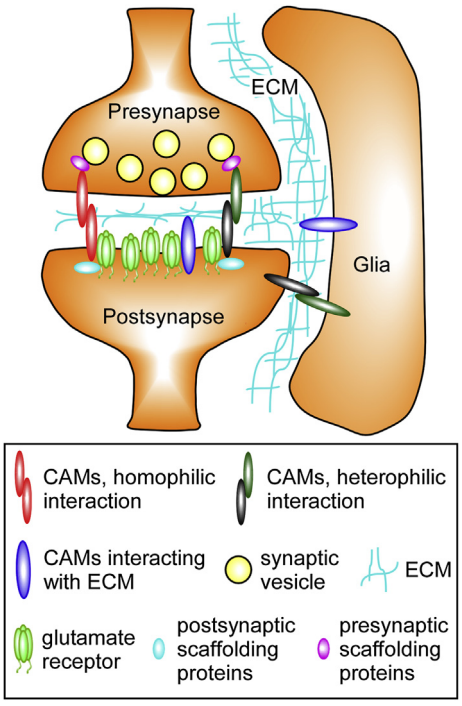

Fig. 1. Synaptic CAMs mediate interactions between different compartments of the synapse. Synaptic CAMs orchestrate structural and functional aspects of synaptic connections by recruiting scaffolding proteins and neurotransmitter receptors in response to the binding of specific counter-receptors and ligands. They mediate direct and indirect interactions between pre- and post-synaptic terminals, and between neurons and astrocytes. CAM interactions are either homophilic (red) or heterophilic (green/black) or with ECM proteins (blue).

between pre- and post-synaptic CAMs can occur indirectly through interposed ECM proteins (Fig. 2). Besides the many examples provided by integrins (Humphries et al., 2006; McGeachie et al., 2011), it has recently been shown that, at the parallel fiber-Purkinje cell synapses, presynaptic β-Neurexins bind to the postsynaptic orphan glutamate receptor δ2 (GluD2) via cerebellin 1, a member of the C1q tumor necrosis factor super-family, secreted by presynaptic cerebellar granule cells (Uemura et al., 2010). This ménage à trois between β-Neurexin, cerebellin 1 and GluD2 is an essential bidirectional synaptic organizer for the parallel fiber-Purkinje cell synapses; similar tripartite complexes involving cerebellins are likely to control synaptic structure and function also in the forebrain (Matsuda and Yuzaki, 2011). In an analogous manner, the secreted factor leucine-rich, glioma-inactivated protein-1 (LGI1) might coordinate pre- and post-synaptic functions of hippocampal synapses by bridging between two CAMs, the presynaptic ADAM23 and the postsynaptic ADAM22 (Fig. 2) (Fukata et al., 2006, 2010; Zhou et al., 2009).

Synaptic CAMs contribute to most aspects of synaptic function. During synapse formation, they are critically involved in determining synapse specificity by mediating the initial target recognition between pre- and post-synaptic neurons (Sanes and Yamagata, 2009; Williams et al., 2010, 2011). In the initial stages of synapse development, they recruit synaptic components in response to the consolidation of their interactions, thereby promoting the coordinated maturation of pre- and post-synaptic terminals (Chavis and Westbrook, 2001; Dalva et al., 2007; Zhou et al., 2009). During the later stages of synapse development and in mature synapses, they regulate synaptic structure and function. Some synaptic CAMs are involved in activity-dependent positive feedbacks, thus contributing to Hebbian forms of synaptic plasticity, as extensively reviewed elsewhere (Benson et al., 2000; Dityatev et al., 2008; McGeachie et al., 2011). Here, we discuss more recent work highlighting the role of some CAMs in activity-dependent negative feedbacks and the regulation of homeostatic forms of synaptic plasticity.

2. Cell adhesion molecules in synaptic scaling

One of the best-understood forms of homeostatic synaptic plasticity is synaptic scaling, which was initially characterized in primary cultures of excitatory and inhibitory neurons. In this system, manipulations that elevate or reduce the activity of the full neuronal network induce robust compensatory changes in the strength of excitatory and inhibitory synapses that restore action potential firing rate within a dynamic range and prevent runaway potentiation or depression (Hartman et al., 2006; Kilman et al., 2002; O'Brien et al., 1998; Turrigiano et al., 1998). As opposed to Hebbian-type synaptic plasticity, which is input specific and fast in onset, synaptic scaling in response to global changes in neuronal **network activity** entails uniform adjustments in the strength of all synapses on a neuron. At least in primary cultures, all synaptic currents appear to scale up or down according to a multiplicative function that retains the relative differences in synaptic weights (Turrigiano et al., 1998). Synaptic scaling is a slow process, being detectable after 1 h and reaching a plateau within 1–2 days (Ibata et al., 2008; Sutton et al., 2006). The slow onset of homeostatic

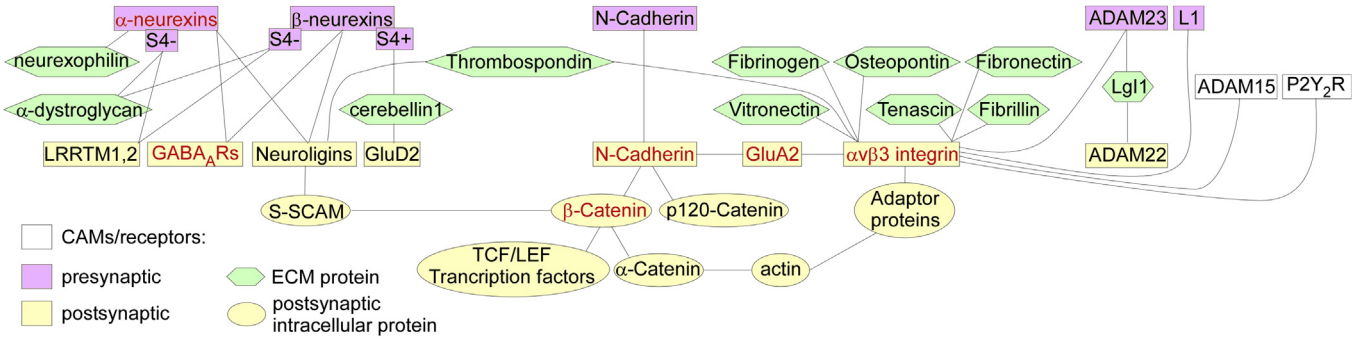

Fig. 2. Neuronal CAMs neurexins, N-Cadherin and αvβ3 integrin, and their major interactions. Intracellular proteins are depicted as ovals, ECM molecules as green hexagons and transmembrane proteins as rectangles. Presynaptic proteins are shown in pink and postsynaptic ones in yellow. Localization for ADAM15 and P2Y$_2$R is not specified; ADAM15 could be either pre- or post-synaptic, P2Y$_2$R neuronal or glial. Molecules implicated in homeostatic synaptic plasticity have a red font. For α- and β-neurexins, the cartoon specifies when the presence (S4+) or absence (S4−) of the insert at the splicing site 4 (S4) is important for determining protein–protein interactions. The model is based on data from studies in various systems. In addition to the references cited in the main text, the following works have been used: Baudouin and Scheiffele (2010), Krueger et al. (2012) and Zhang et al. (2010).