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Review article

Activity-dependent proteolytic cleavage of cell adhesion molecules regulates excitatory synaptic development and function

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ABSTRACT

Activity-dependent remodeling of neuronal connections is critical to nervous system development and function. These processes rely on the ability of synapses to detect neuronal activity and translate it into the appropriate molecular signals. One way to convert neuronal activity into downstream signaling is the proteolytic cleavage of cell adhesion molecules (CAMs). Here we review studies demonstrating the mechanisms by which proteolytic processing of CAMs direct the structural and functional remodeling of excitatory glutamatergic synapses during development and plasticity. Specifically, we examine how extracellular proteolytic cleavage of CAMs switches on or off molecular signals to 1) permit, drive, or restrict synaptic maturation during development and 2) strengthen or weaken synapses during adult plasticity. We will also examine emerging studies linking improper activity-dependent proteolytic processing of CAMs to neurological disorders such as schizophrenia, brain tumors, and Alzheimer's disease. Together these findings suggest that the regulation of activity-dependent proteolytic cleavage of CAMs is vital to proper brain development and lifelong function.

Contents

1. Introduction 61
2. Proteolytic cleavage in the developing brain 61
   2.1. Permitting synaptic maturation 61
   2.2. Driving synaptic maturation 63
   2.3. Restricting synaptic maturation 63
   2.4. When proteolytic cleavage goes amiss in the developing brain – schizophrenia and brain tumors 64
3. Proteolytic cleavage in the adult brain 65
   3.1. Hebbian plasticity 65
   3.2. Homeostatic plasticity 65
   3.3. When proteolytic cleavage goes amiss in the adult brain – Alzheimer's disease 66
4. How does neuronal activity regulate proteolytic processing? 66
5. Concluding remarks and future questions 67
Funding sources 68
References 68

Abbreviations: Aβ, amyloid-β; ADAM, a disintegrin and metalloproteinase; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; APP, amyloid precursor protein; CAM, cell adhesion molecule; CaMK, calcium-calmodulin dependent kinase; DCC, deleted in colorectal cancer; ECM, extracellular matrix; GABA, γ-aminobutyric acid; ICAM, intercellular adhesion molecule; LTD, long term depression; LTP, long term potentiation; MMP, Matrix metalloproteinase; mTOR, mechanistic target of rapamycin; NCAM, neural cell adhesion molecule; NGL, netrin G-ligand; NMDA, *N*-methyl-D-aspartate; NMJ, neuromuscular junction; PI3K, phosphoinositide 3-kinase; PSD, postsynaptic density; SIRP, signal regulatory protein.

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1. Introduction

Neuronal activity is at the heart of information transfer and processing in the brain. Neuronal activity, in the form of synaptic transmission, also regulates synaptic development, strength, and remodeling. An important question is how neuronal activity is detected and then converted into the molecular signals that regulate synaptic connectivity and function. One answer to this question is the proteolytic cleavage of Cell Adhesion Molecules (CAMs). Proteolytic cleavage is the process by which proteins are cut into fragments in a rapid and sequence-specific manner by enzymes known as proteases. The two major classes of extracellular proteases that have been heavily linked to brain development and function are Matrix Metalloproteinases (MMPs) and A Disintegrin and Metalloproteinases (ADAMs). A number of *in vivo* studies demonstrate the clear importance of these proteases in both synapse development and function (Nagy et al., 2006; Michaluk et al., 2011; Zhuang et al., 2015; reviewed in Sonderegger and Matsumoto-Miyai, 2014).

There are several reasons why proteolytic cleavage of CAMs is an effective regulator of activity-dependent signaling. 1) Numerous CAMs undergo proteolytic cleavage in an activity-dependent manner in the developing as well as the adult brain (Table 1). 2) Proteolytic cleavage can activate or inactivate CAM-mediated signaling and also generate novel, bioactive fragments to influence a broad range of signaling pathways. 3) In response to synaptic transmission, activity-dependent CAM cleavage can occur rapidly (seconds to a few minutes) and in a spatially restricted manner (Conant et al., 2010; Peixoto et al., 2012). In this review, we will discuss the role of proteolytic cleavage of CAMs during synaptic development and then in the adult brain. In particular, we will focus on the different yet coordinated ways by which activity-dependent proteolytic cleavage can permit, drive and then restrict the maturation of active synapses during development. Then, we will survey the mechanisms by which proteolytic cleavage can strengthen or weaken synapses in response to neuronal activity during synaptic plasticity in the adult brain. We will also discuss how unregulated cleavage can result in neurological disorders such as schizophrenia, brain tumors, and Alzheimer's disease. Finally, we will examine the possible mechanisms by which neuronal activity regulates the proteolytic cleavage of CAMs.

2. Proteolytic cleavage in the developing brain

Synapses develop *via* multiple stages: 1) axon elongation and targeting, 2) synaptic differentiation, and 3) synaptic refinement, which includes both the maturation of active synapses and the elimination of inactive ones (Sanes and Lichtman, 1999; Fox and Umemori, 2006; Johnson-Venkatesh and Umemori, 2010). The first two stages are thought to be largely activity independent, but activity is critical for the synaptic refinement stage (Fig. 1). Proteolytic cleavage regulates each of these stages of synaptic development. The regulation of axon elongation and targeting by proteolytic cleavage is well established. The ectodomain cleavage of proteins such as DCC, Robo, and Ephrin A has been shown to be a critical step during axon elongation and targeting (reviewed in Bai and Pfaff, 2011). The cleavage of these proteins acts as a mechanism to switch between the attraction and repulsion signals required to guide an axon to its appropriate target. Blocking proteolytic cleavage during this stage results in axon guidance defects such as the aberrant outgrowth and improper midline crossing of axons (Galko and Tessier-Lavigne, 2000; Hattori et al., 2000; Nguyen Ba-Charvet et al., 2001).

Proteolytic cleavage, specifically the cleavage of Collagens, a family of Extracellular Matrix (ECM) proteins, is implicated in the synaptic differentiation stage as well. Many Collagens undergo proteolytic cleavage to generate bioactive fragments (termed matricryptins; Davis et al., 2000; reviewed in Ricard-Blum and Vallet, 2016). At the neuromuscular junction (NMJ), Collagen IV-derived matricryptins direct the assembly of motor nerve terminals (Fox et al., 2007). In the cerebellum, the cleaved product of Collagen XVIII is both necessary and sufficient to drive the differentiation of climbing fiber synapses (Su et al., 2012). In the neocortex, the C-terminal peptide from Collagen XIX promotes inhibitory nerve terminal formation (Su et al., 2016). Proteolytic cleavage during these two initial stages of synaptic development is activity-independent.

During the final, activity-dependent stage of synaptic development, the synaptic refinement stage, activity-dependent proteolytic cleavage occurs. Cleavage of CAMs, in response to neuronal activity, plays three distinct, but coordinated roles in orchestrating the structural and functional maturation of active synapses during synaptic refinement. Namely, proteolytic cleavage 1) creates a permissive environment for maturation by switching off signals that prevent maturation; 2) drives maturation by switching on maturation-promoting signals and; 3) restricts synaptic maturation to maintain synapses at a stable state once the synapse is sufficiently mature (Fig. 2).

2.1. Permitting synaptic maturation

During the refinement process, active and functional synapses undergo maturation, while inactive ones are eliminated. During synaptic maturation, immature synapses undergo structural and functional reorganization to form mature synapses. Relative to the immature synapse, the mature synapse is characterized by increases in the number of glutamatergic vesicles in the presynaptic active zone and neurotransmitter receptors in the postsynaptic density (PSD). Additionally, both the active zone and PSD widen, and immature, dendritic filopodia morph into mature, mushroom-like spines (Fiala et al., 1998; Li and Sheng, 2003; Yuste and Bonhoeffer, 2004). Synaptic maturation can also involve an increase in the ratio of AMPA to NMDA receptors, changes to NMDA receptor subunits, and changes to the types of presynaptic calcium channels (Reviewed in Yasuda and Umemori, 2009).

Given that only active synapses may undergo "activity-dependent" maturation, there likely are signals that keep the synapse in an immature state until that synapse is able to detect neuronal activity. Once activity is detected, the brake on maturation is removed, allowing synaptic maturation to occur. Full-length ICAM-5 (also known as Telencephalin) is one signal maintaining the synapse in an immature state (Fig. 2, top). At immature synapses, full-length ICAM-5-mediated signaling has been shown to be a negative regulator of postsynaptic maturation (Benson et al., 1998; Matsuno et al., 2006). ICAM-5 is enriched in dendritic filopodia, the immature form of a dendritic spine, and is excluded from mature spines. Overexpression of ICAM-5 increases the number of immature dendritic filopodia, while the loss of ICAM-5 drives spine maturation *in vitro* (Matsuno et al., 2006). ICAM-5 inhibits maturation *via* its interaction with presynaptic β1-integrin. ICAM-5 co-immunoprecipitates with β1-integrin, and the application of a β1-integrin blocking antibody to cultured neurons demonstrates enhanced spine maturation similar to the effect of blocking ICAM-5 function (Ning et al., 2013). When the synapse is ready for maturation, ICAM-5 is likely eliminated from active, functional filopodia *via* the disruption of the ICAM-5 and β1-integrin interaction followed by the activity-driven proteolytic cleavage of ICAM-5. The pharmacological activation of NMDA receptors results in increased MMP-9-driven cleavage of the ICAM-5 extracellular domain (Tian et al., 2007; Ning et al., 2013). In MMP-9 null animals, ICAM-5 is not reduced at spines even after the age of maturation, sup-