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A Two-Immunoglobulin-Domain Transmembrane Protein Mediates an Epidermal-Neuronal Interaction to Maintain Synapse Density

Highlights

- The IgSF protein ZIG-10 is required to maintain synapse density
- ZIG-10 mediates an interaction between excitatory neurons and epidermis
- ZIG-10 signals through Src kinase to regulate phagocytosis in epidermis
- ZIG-10 activity modulates epileptic-like convulsions

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In Brief

Maintenance of synapses is required for robust circuit function during the lifetime of an animal. Cherra and Jin have identified a novel two-Ig-domain transmembrane protein that mediates the interaction between neurons and epidermis to maintain synapse density through phagocytosis in *C. elegans*.

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A Two-Immunoglobulin-Domain Transmembrane Protein Mediates an Epidermal-Neuronal Interaction to Maintain Synapse Density

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SUMMARY

Synaptic maintenance is essential for neural circuit function. In the *C. elegans* locomotor circuit, motor neurons are in direct contact with the epidermis. Here, we reveal a novel epidermal-neuronal interaction mediated by a two-immunoglobulin domain transmembrane protein, ZIG-10, that is necessary for maintaining cholinergic synapse density. ZIG-10 is localized at the cell surface of epidermis and cholinergic motor neurons, with high levels at areas adjacent to synapses. Loss of *zig-10* increases the number of cholinergic excitatory synapses and exacerbates convulsion behavior in a seizure model. Misexpression of *zig-10* in GABAergic inhibitory neurons reduces GABAergic synapse number, dependent on the presence of ZIG-10 in the epidermis. Furthermore, ZIG-10 interacts with the tyrosine kinase SRC-2 to regulate the phagocytic activity of the epidermis to restrict cholinergic synapse number. Our studies demonstrate the highly specific roles of non-neuronal cells in modulating neural circuit function, through neuron-type-specific maintenance of synapse density.

INTRODUCTION

Maintenance of synaptic connections throughout the lifetime of an organism is important for learning, memory, decision making, and adaptive behavioral outputs. Synaptic connectivity is regulated not only by neurons, but also by adjacent non-neuronal cells. Glial cells enhance synaptogenesis to guide the formation of discrete circuits in the developing nervous system (Colón-Ramos, 2009; Corty and Freeman, 2013). Astrocytes and microglia modulate synapse formation through many secreted factors, such as hevin, thrombospondins, BDNF, TNFα, and glypican (Bessis et al., 2007; Clarke and Barres, 2013; Stellwagen and Malenka, 2006). Direct contact between glial cells and axons, partly mediated by protocadherins, integrins, and nectins, is also required for efficient synapse formation (Garrett and Weiner, 2009; Hama et al., 2004; Togashi et al., 2009). Conversely, glial cells can reduce synapse density through various mechanisms. Astrocytic secretion of SPARC opposes synapse formation by antagonizing hevin-enhanced synaptogenesis (Kucukdereli et al., 2011). Furthermore, microglia and astrocytes directly eliminate excitatory and inhibitory synapses through distinct phagocytic programs using the complement cascade or MEGF10, respectively (Chung et al., 2013; Schafer et al., 2012). These functions of non-neuronal cells promote an optimal level of excitatory and inhibitory synapses that is essential for circuit function; deviation from an excitation and inhibition balance has been associated with neurological disorders (Lisman, 2012; Rubenstein, 2010; Stafstrom, 2006). While many types of interactions between neurons and non-neuronal cells can modulate synaptic connectivity, a gap in our knowledge remains to be how neuron-specific synapse maintenance is achieved at the molecular level.

The immunoglobulin (Ig) domain superfamily (IgSF) is a large, well-conserved family of proteins that regulates many aspects of neural circuit formation, including neurite outgrowth, target identification, and synaptogenesis. Secreted and transmembrane IgSF proteins guide axons and dendrites to precise target areas for synapse formation (Aurelio et al., 2002; Dickson and Gilestro, 2006; Zipursky and Grueber, 2013). Once pre- and postsynaptic compartments arrive at their target areas, distinct members of IgSF subfamilies, such as Sidekicks and Dscams, specify synaptic connections between neurons in discrete laminae of the retina (Millard et al., 2010; Yamagata and Sanes, 2008; Yamagata et al., 2002). Additional homophilic and heterophilic interactions between pre- and post-synaptic IgSF molecules, such as SynCAM, NCAM, and nectins, further assist in the formation of synapses (Togashi et al., 2009). In the mouse cortex, the L1CAM family of proteins expressed in glial cells facilitates inhibitory synapse formation (Ango et al., 2008). To date, many cell adhesion molecules, including members of the IgSF, have been identified as intrinsic factors for synapse formation and specification; however, far less is known regarding the roles of IgSF proteins expressed in non-neuronal cells.

C. elegans has a simple nervous system and a small number of non-neuronal cells. Previous studies have shown that expression of the IgSF member SYG-2/Nephrin in the vulval epidermis