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SPOTLIGHT

The traffic controller: GARLH4 dictates neuroligin synapse-type preference

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Neuroligin isoforms are commonly thought to intrinsically specify synapse identity. In this issue, Yamasaki et al. (https://doi.org/10.1083/jcb.202507190) show that the auxiliary protein GARLH4 (LHFPL4) instead dictates neuroligin preference via competitive hierarchy, enabling dynamic reassignment between excitatory and inhibitory postsynaptic domains.

Introduction

Excitatory and inhibitory synapses must remain molecularly distinct even as circuits assemble and undergo continual remodeling. Neuroligins (NLs) are key postsynaptic organizers (1), and their isoform-enriched distributions have often been treated as a proxy for synapse identity. NL1 is typically associated with excitatory synapses (2), whereas NL2 is concentrated at inhibitory synapses (3). NL4 contributes to inhibitory synapse organization in a cell- and circuit-dependent fashion (4, 5). NL2 has been linked to inhibitory postsynaptic assembly through gephyrin/collybistin scaffolding pathways.

Concurrently, receptor auxiliary proteins have emerged as decisive determinants of inhibitory receptor nanoscale organization. The tetraspan protein LHFPL4 (GARLH4) is required for synaptic clustering of $GABA_A$ receptors ($GABA_A$Rs) and forms a core element of native inhibitory receptor assemblies (6, 7, 8). This raises a central issue: are NL isoforms intrinsically "assigned" to synapse type, or can receptor-associated factors redirect where an NL isoform resides?

The work highlighted here supports the second view. By mapping how GARLH4-containing $GABA_A$R assemblies engage different NL isoforms—and how isoforms compete for that engagement—Yamasaki et al. propose that synapse-type preference is a tunable outcome of preferential assembly and relative availability rather than a fixed address label (9).

Breaking the isoform "address code"

A major conceptual takeaway is that an NL classically considered excitatory can be recruited into inhibitory receptor complexes when inhibitory-preferred NLs are limiting. Blue native PAGE reveals increased incorporation of NL1 into high-molecular weight assemblies containing GARLH4 and $GABA_A$Rs when NL2/4 are absent (9), likely utilizing the conserved GARLH-binding interface identified in prior studies (7, 10).

This biochemical shift is mirrored anatomically. In experiments using glyoxal for improved antibody penetration and immunoreactivity, NL1 displays higher overlap with inhibitory synaptic markers in NL2-deficient tissue, indicating a redistribution toward inhibitory postsynaptic sites (9).

Importantly, the phenomenon is not limited to NL1. NL3, which normally occupies both synapse classes, also exhibits a bias toward inhibitory localization when NL2 is removed, consistent with a preferential assembly among NLs for access to inhibitory receptor–associated accessory proteins.

GARLH4 establishes a competitive hierarchy among NLs

If multiple NL isoforms can assemble with GARLH4/$GABA_A$Rs in heterologous systems, why do they segregate in vivo? The authors' competition experiments argue that NL2 assembles with the GARLH4/$GABA_A$R complex more efficiently than NL1, thereby predominating GARLH4-bound assemblies under wild-type conditions (Fig. 1). When NL2 (and in some settings NL4) is removed, GARLH4 becomes available to engage other/less-preferred partners, allowing NL1 and NL3 to populate inhibitory synapses.

This competition-based view helps reconcile why inhibitory transmission is reduced but not abolished in settings where NL2 is disrupted: the system can, within limits, repurpose other NLs to sustain GARLH4-dependent stabilization of synaptic $GABA_A$Rs.

Forced GARLH4–NL coupling is sufficient to redirect synaptic localization

A particularly clean sufficiency test comes from forced coupling. A GARLH4–NL1 fusion shifts away from PSD-95–positive excitatory sites and toward inhibitory terminals, indicating that the rerouting depends on specific NL-based assemblies rather than a generic inhibitory targeting signal. Crucially, this effect is specific: fusing GARLH4 to the non-synaptic transmembrane protein CD4 fails to drive inhibitory targeting. This negative control confirms that GARLH4 cannot simply drag any protein to the inhibitory postsynapse; rather, it requires a compatible NL interface to instruct synapse-type preference, further validating the stoichiometric competition model.

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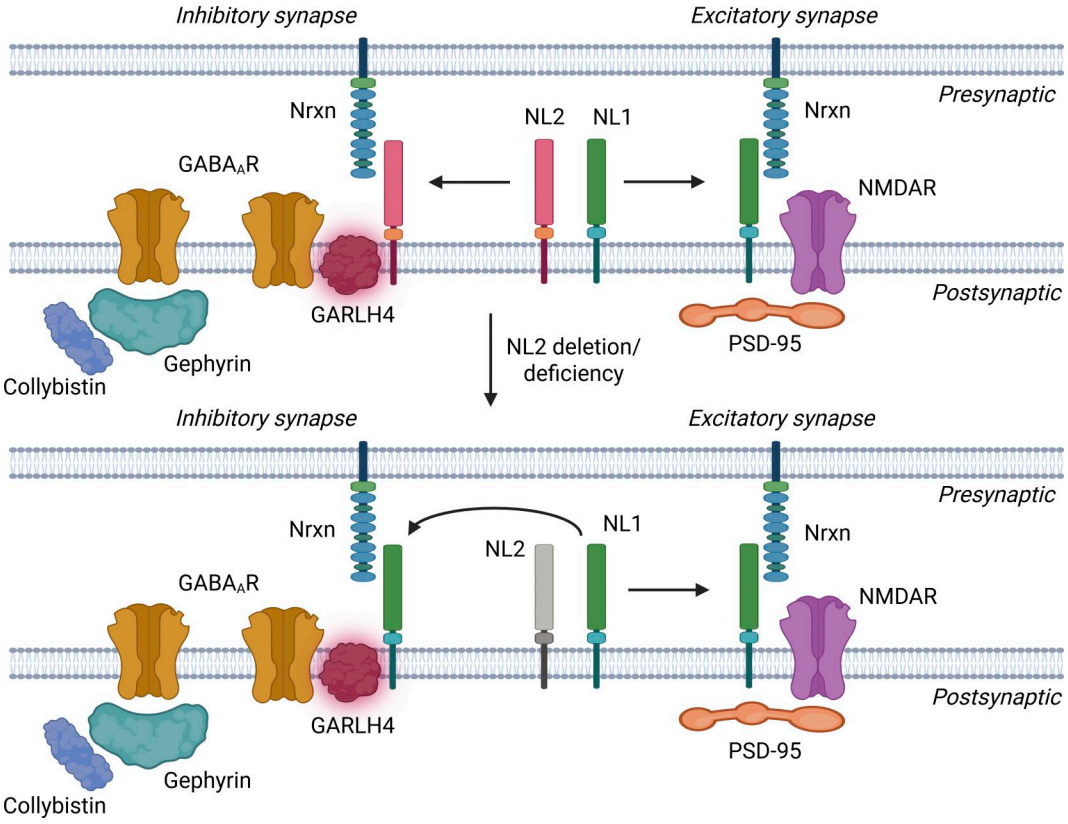

Figure 1. **GARLH4 establishes a competitive hierarchy to regulate NL synapse-type preference.** Under physiological conditions (top), neuroligin 2 (NL2) acts as the dominant partner for inhibitory synapses. Because NL2 preferentially assembles with the GARLH4-containing GABA$_A$R complex, it effectively outcompetes other isoforms, predominating the inhibitory sites and segregating neuroligin 1 (NL1) to excitatory synapses with NMDARs and PSD-95. In the absence of NL2 (deletion or deficiency [NL2 in grey]; bottom), this competitive hierarchy is removed, enabling NL1 to assemble with GARLH4/GABA$_A$R complexes and redistribute toward inhibitory postsynaptic sites. This illustrates that NL localization can be a tunable outcome of stoichiometry and competition rather than a fixed address label. NMDAR, NMDA receptor; Nrxn, neurexins; PSD-95, postsynaptic density-95.

A stoichiometric model with circuit-level implications

Taken together, the data support a local, quantitative model: NL deployment reflects GARLH4 availability and isoform-specific competitive strengths. Transcriptomic resources such as DropViz provide a practical way to identify neuronal contexts in which Lhfpl4 (GARLH4) abundance might bias NL utilization toward inhibitory synapses or, conversely, leave NL1 primarily in excitatory domains.

This framework also provides a mechanistic lens through which to interpret inhibitory phenotypes linked to NL4 and inhibitory circuit dysfunction. NL4 loss perturbs inhibitory synaptic inhibition and network oscillations in specific contexts (5), and NL4 is concentrated at glycinergic postsynapses in retina (4). The competitive model predicts that the impact of NL4 perturbation will depend not only on NL4 itself but also on the extent to which other NLs can be redeployed through GARLH4-dependent pathways to compensate.

Conclusion

Overall, Yamasaki et al. reposition GARLH4 from a stabilizing component of inhibitory receptor complexes to an instructive "traffic controller" for NL synapse-type choice. By linking NLs to GABA$_A$R assemblies and imposing a competitive hierarchy among isoforms, GARLH4 can reassign NL1/NL3 between excitatory and inhibitory synapses, suggesting new ways to think about how excitation–inhibition balance is maintained and perturbed in disease.

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