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The Ins and Outs of GluD2—Why and How Purkinje Cells Use the Special Glutamate Receptor

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Abstract The δ2 glutamate receptor (GluD2) is predominantly expressed in cerebellar Purkinje cells and plays crucial roles in cerebellar functions. Indeed, the number of synapses between parallel fibers (PFs) and Purkinje cells is specifically and severely reduced in GluD2-null cerebellum. In addition, long-term depression (LTD) at PF−Purkinje cell synapses is impaired in these mice. Nevertheless, the mechanism by which GluD2 regulate these two functions—morphological and functional synaptic plasticity at PF synapses—has remained unclear. Recently, we found that Cbln1, a glycoprotein released from granule cells, was bound to the N-terminal domain of GluD2 and regulated formation and maintenance of PF–Purkinje cell synapses. Furthermore, we found that D-Ser released from Bergmann glia bound the ligand-binding domain of GluD2 and mediated LTD in a manner dependent on the C-terminus. These findings indicate how GluD2 is activated and regulates functions at PF–Purkinje cell synapses. A hypothesis about why GluD2 is employed by PF synapses is also discussed.

Keywords Cerebellum · Parallel fiber · Synapse · D-serine · Cbln1

The δ2 glutamate receptor (GluD2) belongs to the ionotropic glutamate receptor (iGluR) family, but has long been referred to as an "orphan" receptor since it does not bind to conventional glutamate analogs [1]. The membrane topology of GluD2 is thought to be similar to that of other iGluRs: an N-terminal domain (NTD) and a bipartite ligand-binding domain (LBD) on the extracellular side of the plasma membrane, four transmembrane domains, and a cytoplasmic C-terminal domain. GluD2-null mice (i.e., *hotfoot* and genetically engineered GluD2 knockout mice) show marked reduction in the number of parallel fiber (PF)–Purkinje cell synapses in the cerebellum. In addition, the length of the postsynaptic density is often disproportionally longer than that of the opposing presynaptic active zone in the remaining PF–Purkinje cell synapses, indicating that GluD2 plays an essential role in aligning and maintaining the postsynaptic density with the presynaptic element at PF–Purkinje cell synapses. Furthermore, GluD2-null mice show the abrogated long-term depression (LTD) of PF–Purkinje cell synaptic transmission, which normally occurs following repeated PF stimulation combined with the depolarization of Purkinje cells and serves as the basis for motor learning. These findings indicate that GluD2 plays two essential roles—morphological and functional synaptic plasticity—at PF synapses. However, how and why GluD2 regulates these functions has remained largely unclear.

A breakthrough occurred with the serendipitous finding that Cbln1-null mice show strikingly similar behavioral, physiological, and anatomical phenotypes to those of GluD2-null mice, indicating that Cbln1 and GluD2 might share signaling pathways [2]. Cbln1 belongs to the C1q family, whose members, including C1q, adiponectin, and collagen X, are secreted and involved in various intercellular functions. In the cerebellum, Cbln1 is released from granule cells. We found that recombinant Cbln1 specifically binds to the NTD of GluD2 in vitro and in vivo [3]. Furthermore, Cbln1 specifically binds to neurexin that contains a splice-site 4 [4, 5]. Therefore, we propose that Cbln1 released from granule cells binds to its presynaptic receptor neurexin and its postsynaptic receptor GluD2, and the tripartite complex serves as a synaptic organizer at PF–Purkinje cell synapses [6]. We also hypothesize that Cbln1

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may be retained on the PFs via neurexin before synapses are formed between PFs and Purkinje cells. Since dendritic spines are autonomously formed in the absence of PFs according to the Sotelo's spinogenesis model [7], Cbln1 on PFs may initiate bidirectional synaptogenesis once it make contacts with GluD2 located on Purkinje cell spines [6]. In this way, the neurexin/Cbln1/GluD2 signaling may be suited for the unique synaptogenesis mechanism at PF–Purkinje cell synapses.

Although the purified LBD of GluD2 was shown to bind to D-Ser [8], its physiological significance has remained unclear. We have recently shown that although D-Ser binding to the LBD of GluD2 does not induce ion flows through GluD2, it induces endocytosis of AMPA receptors, and thereby reduces PF-evoked excitatory postsynaptic currents in Purkinje cells [9]. Furthermore, PF stimulation evoked release of endogenous D-Ser from Bergman glia and enhanced induction of LTD in the cerebellum of immature mice. Interestingly, such D-Ser-mediated effects required the C-terminus of GluD2, indicating that D-Ser binding to the LBD may induce conformational changes at the cytoplasmic region of GluD2.

Conflicts of interest The author declares that no potential conflicts of interest exist.

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