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Review article

The LGI1–ADAM22 protein complex in synaptic transmission and synaptic disorders

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ABSTRACT

Physiological functioning of the brain requires fine-tuned synaptic transmission, and its dysfunction causes various brain disorders such as autism, dementia, and epilepsy. It is therefore extremely important to identify and characterize key regulators of synaptic function. In particular, disease-related synaptic proteins, such as autism-related neurexin–neuroligin and psychiatric disorder-related NMDA receptor, have attracted considerable attention. Recent basic and clinical research has highlighted critical roles of a ligand–receptor complex, LGI1–ADAM22, in synaptic transmission and brain function, as mutations in the LGI1 gene cause autosomal dominant lateral temporal lobe epilepsy and autoantibodies to LGI1 cause limbic encephalitis which is characterized by memory loss and seizures. Here, we will review our current knowledge about LGI1 and ADAM22, and discuss their patho-physiological roles in synaptic transmission and synaptic disorders.

Contents

1. Introduction

The leucine-rich glioma-inactivated protein 1 (LGI1) gene was originally cloned from the human glioblastoma cell line, in which its gene expression is down-regulated or absent due to the t(10;19)(q24;q13) balanced chromosome translocation (Chernova et al., 1998). Although LGI1 was thus suggested as a possible tumor suppressor gene product, its role in progression of glioma remains controversial (Gu et al., 2005). LGI1 is a 60-kDa secretory protein and predominantly expressed in neuronal cells in the brain (Kalachikov et al., 2002; Ohkawa et al., 2013; Senechal et al., 2005). LGI1 has the N-terminal leucine-rich repeat (LRR) domain and the C-terminal β-propeller EPTP-repeat domain, both of which are expected to mediate protein–protein interactions (Fig. 1A). Q3

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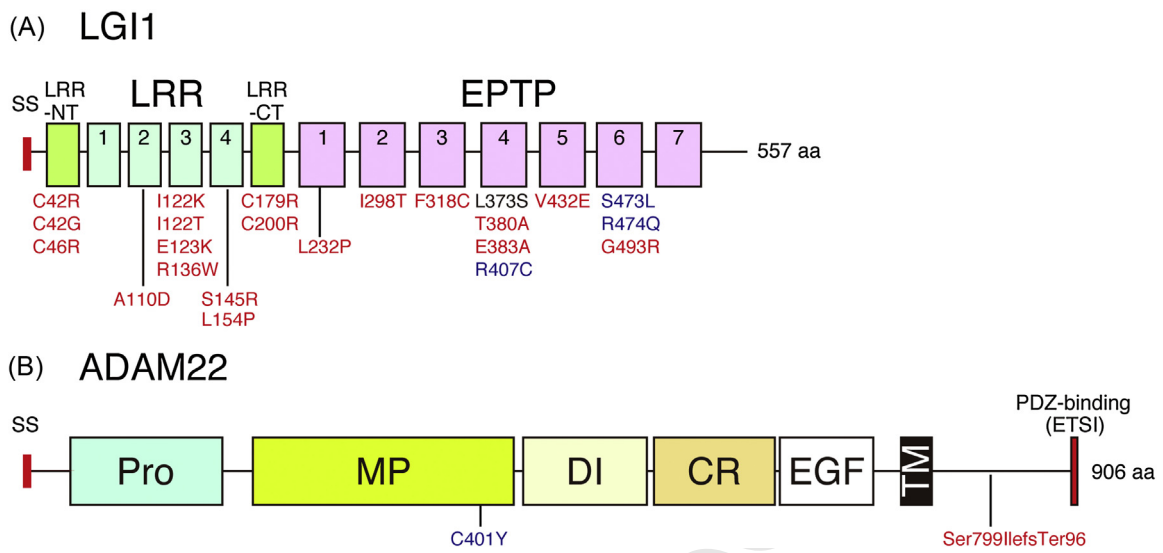

Fig. 1. Domain organization and reported human mutations of LGI1 (A) and ADAM22 (B). (A) SS, signal sequence; LRR, leucine-rich repeat; EPTP, epitempin repeat; NT, N-terminal; CT, C-terminal. Red and blue letters represent secretion-defective and secretion-competent missense mutations, respectively [modified from Yokoi et al. (2015)]. Secretion of L373S mutation is not examined. (B) Pro, prodomain; MP, metalloprotease domain; DI, disintegrin domain; CR, cysteine-rich domain; EGF, EGF-like domain; TM, transmembrane domain. 'ETSI' represents type I PDZ binding motif. Ser799IlefsTer96, a frameshift mutation; C401Y mutation, no LGI1-binding activity (Muona et al., 2016). Note that the metalloprotease activity of ADAM22 subfamily (ADAM22, ADAM23 and ADAM11) is inactive. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

In 2002, three groups reported several heterozygous mutations in the LGI1 gene in families with autosomal dominant lateral temporal lobe epilepsy [ADLTE, also known as autosomal dominant partial epilepsy with auditory features (ADPEAF)] (Gu et al., 2002; Kalachikov et al., 2002; Morante-Redolat et al., 2002). ADLTE is a rare inherited epileptic syndrome characterized by partial seizures with prominent auditory symptoms (OMIM 600512). So far, at least 35 LGI1 mutations have been reported in ADLTE families, including 12 truncation or deletion and 23 missense mutations (Fig. 1A) (Nobile et al., 2009; Rosanoff and Ottman, 2008; Yokoi et al., 2015). Given that most of genes which are mutated in inherited epileptic disorders encode ion channel subunits [so called channelopathy concept for idiopathic (inherited) epilepsies] (Noebels, 2003; Reid et al., 2009; Scheffer and Berkovic, 2003; Steinlein, 2004), LGI1 is a unique epilepsy-related gene encoding a secretory protein and thereby has attracted considerable attention of researchers.

In 2006, proteomic analyses by immunoisolation from the brain tissue identified LGI1 as a component of synaptic protein complexes. First, Schulte et al. (2006) identified LGI1 as a subunit of the Kv_1 (Shaker-related) voltage-gated potassium channel, which is a major constituent of presynaptic A-type potassium channels. Using the *Xenopus* oocyte expression system, they showed that LGI1 prevents N-type inactivation of the Kv_1 channel mediated by the cytoplasmic Kvβ subunit. However, it remains unclear how extracellularly secreted LGI1 antagonizes cytoplasmic actions of Kvβ. Almost at the same time, we identified LGI1, a disintegrin and metalloprotease 22 (ADAM22), and stargazin as major components of *in vivo* protein complexes mediated by PSD-95, a representative postsynaptic scaffolding protein (Fukata et al., 2006). Interestingly, all three proteins that associate with PSD-95 are genetically linked to epileptic disorders. Stargazin, a member of transmembrane AMPA receptor regulatory protein (TARP) family (Tomita et al., 2003), is mutated in *stargazer* mice with absence epilepsy and cerebellar ataxia (Letts et al., 1998) and regulates AMPA receptor trafficking and gating (Chen et al., 2003; Tomita et al., 2005). ADAM22 belongs to the transmembrane ADAM metalloprotease family but is catalytically inactive (Novak, 2004; Sagane et al., 2005) (Fig. 1B). ADAM22 knockout (KO) mice show ataxia with peripheral nerve hypomyelination and premature death before weaning due to multiple seizures (Sagane et al., 2005). We found that extracellularly secreted LGI1 functions as a ligand for ADAM22 that directly binds to PSD-95, and that LGI1 controls AMPA receptor-mediated synaptic transmission through its ADAM22-binding (Fukata et al., 2006).

Recent clinical findings on autoimmune-mediated encephalitis have further expanded the critical function of LGI1 in the adult human brain. Autoimmune forms of encephalitis have been associated with autoantibodies against synaptic cell-surface antigens including metabotropic glutamate receptor 1 (mGluR1) and NMDA-, AMPA-, $GABA_A$-, $GABA_B$-, and glycine receptors (Crisp et al., 2016; Lancaster and Dalmau, 2012). In 2010, Dalmau's and Vincent's groups found LGI1 autoantibodies in patients with limbic encephalitis, a specific entity of encephalitis with acute or subacute onset of cognitive impairment, confusion and mesial temporal lobe seizures (Irani et al., 2010; Lai et al., 2010). Overall biochemical, genetic, and clinical evidence strongly suggests important participation of LGI1 in synaptic regulation and pathogenesis of brain disorders such as epilepsy.

2. Physiological roles of LGI1–ADAM22 in the brain

2.1. Expression pattern of LGI1–ADAM22

The expression of LGI1 and ADAM22 is developmentally regulated (Fukata et al., 2006). In the rat or mouse brain, the expression of LGI and ADAM22 is very low in embryos and newborn pups, and is gradually increased around postnatal day 7 (P7) to reach the highest level in the adult stage. Accordingly, the amount of PSD-95-mediated protein complex containing LGI1, ADAM22, and stargazin is increased after P7, when major synaptic proteins begin to be expressed to contribute to synapse maturation. In addition, this PSD-95 protein complex is ubiquitously observed over whole regions of the brain. The *in situ* hybridization data show that mRNAs of LGI1 and ADAM22 are widely expressed in the brain: *e.g.*, neocortex and limbic regions including hippocampus and amygdala. In the hippocampus, the amount of LGI1 mRNA is highest in granule cells of the dentate gyrus (DG) and CA3 pyramidal neurons, and ADAM22 mRNA is relatively highly expressed

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