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Review

Mutations of the synapse genes and intellectual disability syndromes

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ABSTRACT

Intellectual disability syndromes have been found associated to numerous mutated genes that code for proteins functionally involved in synapse formation, the regulation of dendritic spine morphology, the regulation of the synaptic cytoskeleton or the synthesis and degradation of specific synapse proteins. These studies have strongly demonstrated that even mild alterations in synapse morphology and function give rise to mild or severe alteration in intellectual abilities. Interestingly, pharmacological agents that are able to counteract these morphological and functional synaptic anomalies can also improve the symptoms of some of these conditions. This review is summarizing recent discoveries on the functions of some of the genes responsible for intellectual disability syndromes connected with synapse dysfunctions.

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1. Introduction

Psychiatric and neurological diseases are often characterized by the occurrence of aberrant synaptic formation, function and plasticity, or malformed dendritic spine (Blanpied and Ehlers, 2004) and it is now clear that an accurate control of synaptic formation and maturation is critical for the development of a correct active neuronal network essential for all brain functions.

Intellectual disability (ID) is one of the most common neurodevelopmental disorders; intelligence quotient of patients affected by ID is about 70 or below and deficits in behavior related to adaptive functioning including autism spectrum disorders (ASD) are often exhibited by these patients.

It has been demonstrated that 25% of ID patients are carrying genetic mutations (Rauch et al., 2006) while in up to 60% of cases the pathogenetic mechanisms have been not identified.

More than a few single-genes causing syndromic or nonsyndromic ID have been recognized over the past 20 yr. Interestingly several of these genes are located on the chromosome X and are responsible for X-linked intellectual disabilities (XLID). Fascinatingly more than 50% of the ID-gene codifies for proteins clearly located in the pre- or post-synaptic compartments and emerge to

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be implicated in synaptic functions by regulating synapse formation, actin cytoskeleton rearrangement, or synaptic plasticity (Ropers and Hamel, 2005).

The synapse-related proteins associated with ID can be separated into two groups, one that localizes fully at synapses and whose deletions and mutations directly impede with synaptic formation, and a second cluster that indirectly controls neuronal development and synapse formation by regulating synthesis and degradation of major synaptic proteins or the synaptic actin cytoskeleton assembly or disassembly. In this review we will describe some molecular mechanisms by which dysfunctions in several of these proteins contribute to ID.

2. Mutations in the synaptic scaffold proteins

2.1. Mutations and deletions in the SHANK gene family

A partial and variable in size distal deletion of chromosome 22 involves an important region that contains *SHANK*3 gene which codifies the large postsynaptic scaffold protein Shank3. This deletion causes in humans the Phelan-McDermid syndrome (PMS, also called 22q13.3 deletion syndrome) which is characterized by strong intellectual impairment, absent or delayed speech, autistic-like behavior, hypotonia, and mild dysmorphic features (Bonaglia et al., 2001; Manning et al., 2004; Phelan et al., 2001; Wilson et al., 2003).

Thus *SHANK*3 haploinsufficiency is considered to be the major cause of the neurological symptoms of PMS, even if other genes may also be missing by the chromosomal deletion especially when the deletion is particularly large (Bonaglia et al., 2001; Delahaye et al., 2009; Durand et al., 2007; Wilson et al., 2003). In reality, a number of *de novo* mutations in *SHANK*3 (Durand et al., 2007; Gauthier et al., 2009; Moessner et al., 2007), but also in the other member of the *SHANK* family, *SHANK*1 (Sato et al., 2012) and *SHANK*1 (Berkel et al., 2010) have been identified in individuals with ASD and ID. All these data strongly suggest that deletion and mutations in the *SHANK* genes are always associated to severe cognitive diseases.

The functions of the three SHANK genes have been recently well studied using genetic mutations in mice. The first described mouse was the *SHANK*1 full knock out, that showed small dendritic spines, weakened synaptic transmission, enhanced learning (Hung et al., 2008), and defects in social communication (Wöhr et al., 2011). For *SHANK*3 a number of mutant mice have been recently described in order to highlight the importance of Shank3 haploinsufficiency in the pathogenesis of ID and Phelan-McDermid syndrome (Bozdagi et al., 2010; Peça et al., 2011; Wang et al., 2011). The *SHANK*3 gene has several splice variants and consequent specific knocks have been created. The genetic deletion of two major *SHANK*3 splice variants causes self-injurious repetitive grooming and alterations in social relations correlating with major modification in striatal synapses and cortico-striatal circuits, but not in hippocampal synapses, suggesting that the remaining *SHANK*3 splice variant(s) may be enough to preserve normal synapse organization and function in hippocampus (Peça et al., 2011). In other two independent mice, where only longest splice variant has been deleted, defects in social behavior, alterations in learning, in memory formation and in synaptic transmission have been described (Bozdagi et al., 2010; Wang et al., 2011). These animals had markedly impaired basal synaptic transmission in CA3–CA1 connections, reduced GluR1 clusters and protein levels in the hippocampus, and an altered activity-dependent AMPAR synaptic plasticity (Bozdagi et al., 2010; Wang et al., 2011).

In our laboratory we recently knocked down all major Shank3 splice variants in rodent neuronal cultures by RNA interference (shRNA) and demonstrated that Shank3 absence in hippocampal cells specifically reduced the expression of mGlu5 receptors, and also impaired DHPG-induced phosphorylation of ERK1/2 and CREB (Verpelli et al., 2011). We thus propose that mGlu5-dependent synaptic plasticity is altered in absence of Shank3.

Finally, similarly to *SHANK*3, also the *SHANK*2 full knockout mice shows abnormalities in behavior tests, impairment in social activities, hyperactivity, and defects in synaptic transmission (Bockers et al., 2004; Schmeisser et al., 2012; Won et al., 2012).

Altogether, these studies show that in mice mutations in the *SHANK* genes cause alterations in both synaptic morphology and signalling and behavior characteristics, therefore, these mice are a good animal model to study ASD and ID although the specific role of the various splice variants of the SHANK1–3 genes remains to be determined with more sophisticated genetic experiments.

2.2. The MAGUK family of proteins

PSD-95, codifies by *DLG*4 gene in humans, is the most abundant scaffold protein at the PSD that belongs to the MAGUK family of proteins. Although polymorphisms and mutations have been extensively searched in *DLG*4 in association with neurodevelopmental pathologies, only one major study suggests, up to now, an association between a *DLG*4 gene variation and ASD and Williams syndrome (Feyder et al., 2010). A second study demonstrated an haplotype derived from 2 polymorphic markers at the core promoter region of *DLG*4 gene has been associated to schizophrenia (Cheng et al., 2010).

On the contrary, *DLG*3 – the human gene that encodes for synapse-associated protein 102 (SAP102) – is clearly linked with ID (Tarpey et al., 2004; Zanni et al., 2010). Some mutations identified in this gene cause premature stop codons within or before the third PDZ domain. These mutations damage the ability of the probable truncated SAP102 protein to bind with the NMDA receptors and other proteins regulating in NMDA receptors signalling pathways (Chen et al., 2011).

3. Mutations in the X chromosome genes

The majority of the XLID are attributable to the Fragile X and Rett syndromes, however deletions and mutations of several other genes on chromosome X have been found strongly associated with ID. Mutations of the *NLGN*3 and *NLGN*4 genes (Jamain et al., 2003) were the first to be clearly associated with alterations in synaptic function.

Neuroligin proteins, originally identified as binding partners of neurexins, are the prototype of the synaptic adhesion molecules that regulate and promote synaptogenesis in the brain. The neuroligins/neurexins association forms the trans-synaptic complex which is important for both excitatory and inhibitory synapse formation in brain (Südhof, 2008). In the recent years several other XLID genes have been associated to synaptic function and indeed it has been estimated that about 50% of the XLID gene codifies for synaptic proteins (Laumonnier et al., 2007). Here we will describe the function of some of these genes.

3.1. The IL1RAPL1 gene

A number of mutations in the interleukin-1 receptor accessory protein-like 1 gene (*IL*1*RAPL*1) have been found in patients with cognitive impairments ranging from nonsyndromic ID to ASD (Bhat et al., 2008; Carrie et al., 1999; Franek et al., 2011; Piton et al., 2008). The IL1RAPL1 protein belongs to a new Toll/IL-1 receptor family and shares 52% homology with the IL-1 receptor accessory protein (IL-1RacP) and it is structurally formed by three

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