



Adhesion G-protein Coupled Receptors in Autism

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Editorial

Despite extensive research efforts, the exact etiologic-pathologies of autism are still inadequately understood [1-3]. The current diagnosis of autism is only based on the evaluation of behavior and social communication skills. The absence of a specific biomarker renders the diagnosis potentially subjective. The search for biomarkers to provide a valid help in diagnosis and to identify novel therapies is a priority in autism research and care [4].

Due to their unique pivotal role in immune and nervous system, the adhesion-class G protein-coupled receptor (a-GPCR) proteins show a promising novel target for both autism biomarker discovery and novel drug design.

Adhesion-class G protein-coupled receptors

The adhesion-class G protein-coupled receptors (a-GPCRs) are formed by hybrid molecular structure: a large extracellular cell-adhesion domain containing an extended array of protein folds useful for interactions, together with a GPCR-like seven-pass transmembrane domain (7TM). The term adhesion GPCR arises from the fact that the N-terminus often shares structural homology with cell-adhesion proteins, such as lectins and immunoglobulins [5]. This class of receptors is the second largest GPCR subfamily and comprises 33 proteins in humans; it is widely distributed, as they are normally expressed in the central nervous, immune, and reproductive systems. The genomic structure is very complex with multiple introns and splice variants [6]. Their hybrid molecular architecture could explain the several cellular functions of this class of receptors. The extracellular domain is responsible for cell type/tissue specific functions through cellular adhesion, and the 7TM domain drives the signal transduction; indeed, they are key players in signal transduction mechanisms, cell adhesion (cell-cell and cell-matrix interactions), immune responses, but also in orientation and positioning during development and tumor formation [7]. The capacity of a-GPCRs to activate several downstream signaling pathways makes these receptors potentially important drug targets for novel therapeutic agents [8]. The modulation of their signaling mechanisms could be an effective way to address also some of the autism-related cellular and molecular changes.

F4/80 protein

Adhesion-GPCRs show an interesting role in immune system regulation. Immune system is greatly affected and dysregulated in autism pathology [9]. It has been demonstrated that the epidermal growth factor (EGF)-TM7 adhesion-GPCR subfamily members are involved in controlling both the innate and acquired immune

responses [10]. Moreover, the F4/80 protein, a specific member of this subclass of a-GPCRs, is able to activate the efferent CD8⁺ regulatory T cells responsible for peripheral immune tolerance [11]. F4/80 protein molecular structure is hybrid, consisting of two different domains: the EGF-like motif is located at the extracellular N-terminus, whereas the TM7 domain is located at the COOH terminus [12]. Interestingly, F4/80 protein is a macrophage-specific adhesion-GPCR and the identification of cellular signaling pathway could be helpful to elucidate the strong dysregulation of autistic macrophages. Indeed, in autism these macrophagic cells are addressed toward autoimmunity probably by local tissue microenvironment signaling [13].

Brain-specific Angiogenesis Inhibitor (BAI) subfamily

Among the adhesion-GPCRs, the brain-specific angiogenesis inhibitor (BAI) receptor subfamily shows probably the strongest involvement in autism. This subfamily comprises BAI-1, -2, -3 genes; whereas they share similar cell and tissue expression, only BAI1 is transcriptionally regulated by p53 [14,15]. Their molecular structure comprises a 7TM-linked GPCR proteolysis site (Cys-rich motif) in the extracellular domain, followed by one hormone-binding domain and five thrombospondin type-1 repeats; several N-linked glycosylation sites complete the extracellular domain structure [14]. The inner cytoplasmic domain is constituted by a relatively long cytoplasmic tail at the end of the 7TM region containing a QTEV motif able to interact with PDZ domain-containing proteins [16]. BAI1 was first studied for its ability to inhibit angiogenesis and tumor formation [17]. BAI1 is involved in apoptotic cell phagocytosis and myoblast fusion [18,19], but it has been recently elucidated that BAI1 has roles in regulation of synaptogenesis and dendritic spine formation (spinogenesis), open the way for its studying in psychiatric diseases [17,20]. Moreover, BAI3 signaling regulates dendrite morphogenesis in neurons through RhoGTPase/actin pathways [21]. Autism pathology shows cortical abnormalities [22], together with abnormal formation of neuronal networks and connectivity, likely due to dysregulation in dendrite morphogenesis [23]. Indeed, reduced dendritic spine plasticity through dysregulated Rho GTPases pathway has been noted in an experimental model of autism [24].

Lectomedin (LEC) Receptor Subfamily

The molecular structure of this subfamily (three members) comprises a conserved GPS proteolytic site in extracellular domain, following by a hormone binding domain and an olfactomedin (OLF) domain [6]. Very interesting for autism pathology is the fact that LEC-1 and -2 are able to interact with shank scaffolding protein, enhancing post-synaptic density and plasticity.

Indeed, the proteins of Shank family are scaffolding proteins of the post-synaptic density and have a key role in autism disorders, as well as in other neuropsychiatric diseases [25]. Moreover, Shank mouse mutants are considered one of the experimental model of autism, as Shank mutations provokes synaptic dysfunction in mice [26]. Shank3 mutant mice exhibit impaired social interaction and repetitive behaviors like autism [27]. This member Shank3 is a scaffolding protein strictly associated with the cell adhesion proteins neuroligins (NLGN), which in turn are involved in the formation and maintenance of synapses between neurons [27]. It has been demonstrated that specific mutations in the genes encoding NLGN 3 and NLGN 4 are associated with autism [28].

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