

## PDZ Domain-containing Proteins at Autotypic Junctions in Myelinating Schwann Cells

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A type of cell junction that is formed between different parts within the same cell is called autotypic cell junction. Autotypic junction proteins form tight junctions found between membrane lamellae of a cell, especially in myelinating glial cells. Some of them have postsynaptic density-95/disk large/zonula occludens-1 (PDZ) domains, which interact with the carboxyl (C)-terminal PDZ-binding motif of other proteins. PDZ domains are protein-protein interaction modules that play a role in protein complex assembly. The PDZ domain, which is widespread in bacteria, plants, yeast, metazoans, and *Drosophila*, allows the assembly of large multi-protein complexes. The multi-protein complexes act in intracellular signal transduction, protein targeting, and membrane polarization. The identified PDZ domain-containing proteins located at autotypic junctions include zonula occludens-1 (ZO-1), ZO-2, pals-1-associated tight junction protein (PATJ), multi-PDZ domain proteins (MUPPs), membrane-associated guanylate kinase inverted 2 (MAGI2), and protease-activated receptor (PAR)-3. PAR-3 interacts with atypical protein kinase C and PAR-6, forming a ternary complex, which plays an important role in the regulation of cell polarity. MAGI2 interacts with  $\alpha$ -amino-3-hydroxyl-5-methyl-4-isoxazole propionate (AMPA) receptor at excitatory synapses. PATJ is detected in paranodal loops associated with claudin-1. On the other hand, MUPP1 is found in mesaxons and Schmidt-Lanterman incisures with claudin-5. ZO-1, ZO-2, and PAR-3 are found at all three sites. Different distributions of PDZ domain-containing proteins affect the development of autotypic junctions. In this review, we will describe PDZ domain-containing proteins at autotypic tight junctions in myelinating Schwann cells and their roles.

**Key words** : Autotypic junction, cell junctions, PDZ domain, scaffold protein, schwann cell

### Introduction

There are innumerable cells in human body, and also a lots of cell junctions to communicate between the cells. In general, cell junctions are categorized into several types: gap junctions, adherens junctions, desmosomes, and tight junctions [25]. But in the other aspect, cell junctions also can be divided by whether the junction structure ranges between two different adjacent cells or not. One of the interesting examples in latter view is autotypic cell junction. Autotypic cell junction is defined as a type of cell junction that is formed between two structural parts in the same cell [2].

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These junctions are usually located in Schwann cells and myelinating glial cells, especially in non-compact myelin area like Schmidt-Lanterman incisures, paranodal loops, mesaxons and the outer aspect of the nodal gap, formed between adjacent plasma membrane lamellae of the same cell (Fig. 1) [2, 24]. Like other types of cell junctions, there are several proteins to maintain functions of autotypic cell junctions. For example, autotypic adherens junctions have cytoplasmic proteins called catenins to connect the calcium-sensitive adhesive molecule E-cadherin to the actin filaments [24, 105].

One of the important subtypes of autotypic cell junctions in myelinating cells is autotypic tight junctions [2]. These junctions are thought to function as a linking part and permeability controller, setting the extracellular spaces apart from the intramyelinic space between plasma membrane lamellae [44, 77]. Despite decades of studies, the constituents that construct autotypic tight junction are still not clear. However, the composition of the junction can be inferred

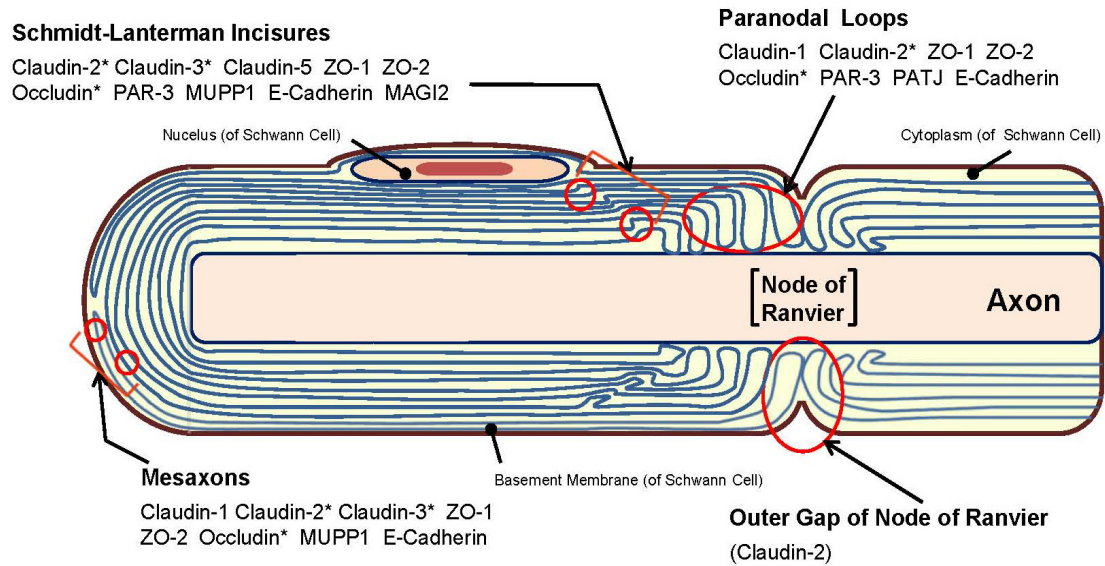


Fig. 1. Expression of autotypic junction proteins in myelinating Schwann cell. The location of autotypic junctions in the Schmidt-Lanterman incisures, mesaxons, paranodal loop regions, and the outer collar of gap of node of Ranvier are marked with circles. A variety of autotypic junction proteins in this review article are listed with their detailed expression sites. The proteins that are detected only in the rodent nerves are put in parentheses, and the proteins that are detected only in the human nerves with asterisks. Note that the various kinds of proteins are enriched in non-compact myelin sites except for the outer side of nodal gap. There are also some differences with the kind of junction proteins between the locations of autotypic junctions, suggesting that junctions formed in distinct sites have differences with their unique structural compositions.

not only according to the previous studies but also from the components of general type of tight junctions in epithelia and endothelia. Tight junctions have very intricate structure, consisting of a variety of functional molecules and several adhesive proteins: claudin family, one of the most important tight junction proteins with paracellular barrier function that controls the molecular flow of intercellular space [84, 90, 98]; occludin, the integral membrane protein establishing barrier function of tight junctions with four putative membrane-spanning segments [27, 96]; peripheral membrane proteins including zonula occludens-1 (ZO-1), ZO-2, and ZO-3, which are the connector proteins that link tight junction strands to cytoskeletal actin filaments [37, 81]; and junctional adhesion molecules (JAMs), the immunoglobulin superfamily proteins found at tight junctions that act as an adhesive ligands for interacting with a variety of cell types [17, 30, 66]. In addition, the proteins with postsynaptic density-95/disks large/zonula occludens-1 (PDZ) domain can also affect the function of adhesive tight junction proteins through PDZ domain-mediated interactions with specific PDZ-binding motif in the carboxyl (C)-terminal end of the interacting proteins [35]. The PDZ domain is also important for pathogenetic aspects because if there are some mutations

on PDZ domain, some specific diseases can be occurred. For example, some of the mutations of PDZ domain can cause an autosomal recessive type of Charcot-Marie-Tooth disease (CMT), a demyelinating neuropathy characterized by chronic motor weakness and sensory loss of distal extremities [33, 65]. Furthermore, previous study proved that diverse types of cancers can occur by the mis-localization and mutation of the PDZ domain-containing proteins DLG1 and Scribble, decreasing the adhesive strength of cell-cell junction sites followed by increasing level of cytoplasmic proteins [20].

There were some previous studies about PDZ domain-containing proteins and autotypic tight junctions individually, but there were not many integrated studies about the interaction between them. In this review, we focused on the biochemical characteristics of the autotypic tight junction proteins and how PDZ domain-mediated interactions can make an influence on these protein functions.

### PDZ domains

PDZ domains play an important role in protein-protein interactions and often recognize the C-terminal motif [86] or internal sequence motif of target proteins [34]. They are widespread through all eukaryotes and eubacteria [78]. For

example, there are 918 PDZ domain-containing proteins found in human and 771 PDZ domain-containing proteins found in mouse which are selected to regulate protein-protein interactions [88]. Furthermore, there are many kinds of PDZ domain-containing proteins such as multi-PDZ domain proteins (MUPPs), pals-1-associated tight junction protein (PATJ), and protease activated receptor (PAR)-3 (Fig. 2). They are linking the transmembrane proteins of tight junctions to the underlying cytoskeleton [71]. Moreover, PDZ domain-containing proteins regulate the protein-protein interactions, transport the micro-molecules which are take a role in signal cascade of the junctions and generate adhesion-complexes such as receptors or channels [48].

Studies of the structures of PDZ domains using crystallographic and proteomic methods have provided the newest sight of PDZ domain-mediated interactions and their regulatory mechanism. They revealed that PDZ domains usually have 80-100 amino acid residues and consist of 5 to 6  $\beta$ -strands and 2 to 3  $\alpha$ -helices [21]. More specifically, canonical PDZ domains are made up of 6  $\beta$ -strands and 2  $\alpha$ -helices, one of which is short and the other one is long [55, 56]. In previous report, more than 200 structures of PDZ domains have been reported, which represents the specificity of recognition between PDZ domain-containing proteins and their

ligands at the molecular level [16, 72]. One of the recent studies insisted discovered 16 structures of PDZ domains by their affinity to ligands, moreover, identified four additional structures by assembling existing database [19]. Most PDZ domains are found as isolating monomers, but some of PDZ domains form dimer. Remarkably, the dimer form does not interrupt the binding process of PDZ domains with their ligands because the specific peptides which are needed for conjugation still open [41]. Some PDZ domains are tandemly arranged with other PDZ domains and the tandem arrangement is needed for proper folding of the PDZ domain-containing proteins, which are considered to play important roles in supramodular formations [62].

Since the number of discovered PDZ domain-containing proteins is rapidly growing, some studies make the classification depending on features of amino acid residues on the specific position. The first class protein like postsynaptic density-95 (PSD-95), disks large (Dlg), ZO-1, which are the origin of their name, has serine/threonine residue at their (-2) position. The second class protein has the hydrophobic residues at the same position and  $\alpha$ -B1 position of the PDZ domain. The third class protein, including nNOS, has a preference for negatively charged amino acid residue at the same position [16, 57]. Since PDZ domain-containing proteins me-

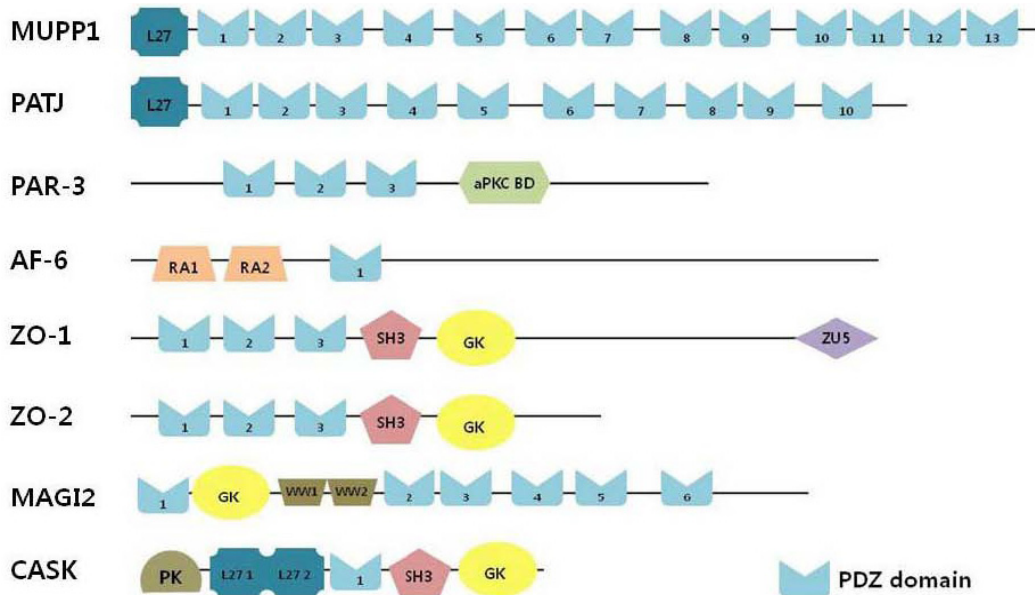


Fig. 2. Structures of PDZ domain-containing proteins in autotypic tight junctions. MUPP1 and PATJ have similar domains. While MUPP1 has an L27 domain and 13 PDZ domains, PATJ has an L27 domain and 10 PDZ domains. PAR-3 has 3 PDZ domains and an aPKC binding domain which interacts with aPKC to form the PAR-3-aPKC-PAR-6 complex. AF-6 has one PDZ domain and two Ras associated domains which inhibit insulin induced promoter activities. ZO-1 and ZO-2 have 3 PDZ domains, one SH3 domain and one GK domain in common. They both directly interact with F-actin. Only ZO-1 has ZU5 domain. MAGI2 has 6 PDZ domains with 2 WW domains and one GK domain.

diate many biological processes, it is very important to understand the regulatory mechanism of their own. Interaction of PDZ domain-containing proteins with binding partners can be regulated by phosphorylation of the C-terminal PDZ-binding motif and influence the whole interaction between the molecules [43, 95]. Besides the phosphorylation, intramolecular disulfide bond formation of PDZ domain-containing proteins can affect the interaction with binding partners as well [61, 70].

### ZO-1/-2/-3

ZO-1, ZO-2 and ZO-3 are tight junction-associated proteins that belong to the membrane-associated guanylate kinase (MAGUK) family [31]. They interact with JAMs which are expressed on leukocytes and localize on epithelial or endothelial cells functioning in cell-to-cell interaction [97]. JAM has two major roles: the first one is mediating inflammatory reaction between the leukocyte and endothelium, the second one is regulating cell polarity [92]. ZO-1 contains three PDZ domains, one Src homology (SH3), and one guanylate kinase-like (GUK) domain and they make the connection with JAM-A PDZ domain-dependently in epithelial cells and directly associates with membrane and cytosolic proteins such as occludin, claudins, ZO-2 (Fig. 1, Fig. 2) [97]. Also, it binds to the F-actin through actin-binding region (ABR) [23]. ZO-1 helps JAMs to recruit other JAMs to build macro-molecule complexes [81]. In the study about expression of ZO-1 and other JAMs, ZO-1 is localized widely in human myelinating Schwann cells [97]. It is strongly expressed in paranodal areas, Schmidt-Lanterman incisures and mesaxon (Table 1)

Table 1. Localization of tight junction proteins in myelinated schwann cells in rodents

Proteins	Schmidt-Lanterman incisures	Paranodal loops	Mesaxons	Reference
MUPP1	+++	-	+++	[77]
PATJ	-	+++	-	[77]
ZO-1	+++	+++	+++	[77]
ZO-2	+++	+++	+++	[77]
Par-3	+++	+++	-	[60]
AF-6	-	-	-	[77]
JAM	-	-	-	[47]
Occludin	-	-	-	[74]
Claudin-1	-	+++	+++	[77]
Claudin-5	+++	-	-	[77]
Pals-1	-	-	-	[45]
E-cadherin	+++	+++	+++	[47]

[2]. There are no ZOs at the node of Ranvier, neither are any other JAMs [80]. ZO-1 and JAMs' functions in human neuroglial cells are still not clear. ZO-2 does not only interact with C-terminal domains, but also contact with nuclear proteins and play a specific role in central dogma of proteins [93]. ZO-3 binds to PDZ7 of MUPP1 and PDZ6 of PATJ with its C-terminal amino acids (-A-T-D-L) connecting both of them (Fig. 3) [1]. But there are still some doubts about the existence and location of ZO-3 because it has no exact evidence. In addition, ZOs have a distinct C-terminal amino acids sequence which modulates these proteins act as scaffold proteins and associate with transmembrane tight junction strands. It means ZOs take a part in the signaling production between cytoskeleton and adaptor proteins and influence the gene expression [22]. In previous studies, it is revealed that ZOs are involved in intracellular signaling process as well as in gathering other proteins. ZO-1 is related with ZONAB/DbpA, which promotes proliferation of epithelial cells. When cells meet and develop intercellular junctions, ZO-1 is accumulated at junctions and recruits ZONAB/DbpA so that it is removed from the nucleus [5]. In contrast, ZO-2 actively shuttle between nucleus and tight junction. Nuclear localization and exporting signal are ZO-2's functions [32, 42]. Transcription factors AP-1 and C/EBP, the DNA-binding protein SAF-B, and the p120ctn family member ARVCF interact with ZO-2 [7, 46]. So that more close research is required to clarify ZO-1 functions, especially in human neuroglial cells and their distinct distribution. There is specific gene to express ZO-2/-3 proteins to function at the adherence junction. Interestingly, ZO-2 gene is very vital for mammalian survival so that ZO-2 knock-out mice cannot make a full development and die on the gastrulation step. In contrast, ZO-3 is dispensable [100]. This study also suggests that ZOs has variable roles in the transcription and some of them play an irreplaceable role in the living.

### MUPP1

MUPP1 has 13 PDZ domains and a Lin2/lin7 (L27) domain in its amino (N)-terminal region without any catalytic domains (Fig. 2). MUPP1 exists mainly in tight junctions and cell membranes of various organs [35]. There are signs of MUPP1 in heart, brain, placenta, skeletal muscles, liver, kidney and pancreas [94]. PDZ domain binds to other molecules or proteins, so multiple PDZ domains of MUPP1 can interact with several partners. MUPP1 can serve as a scaffold protein

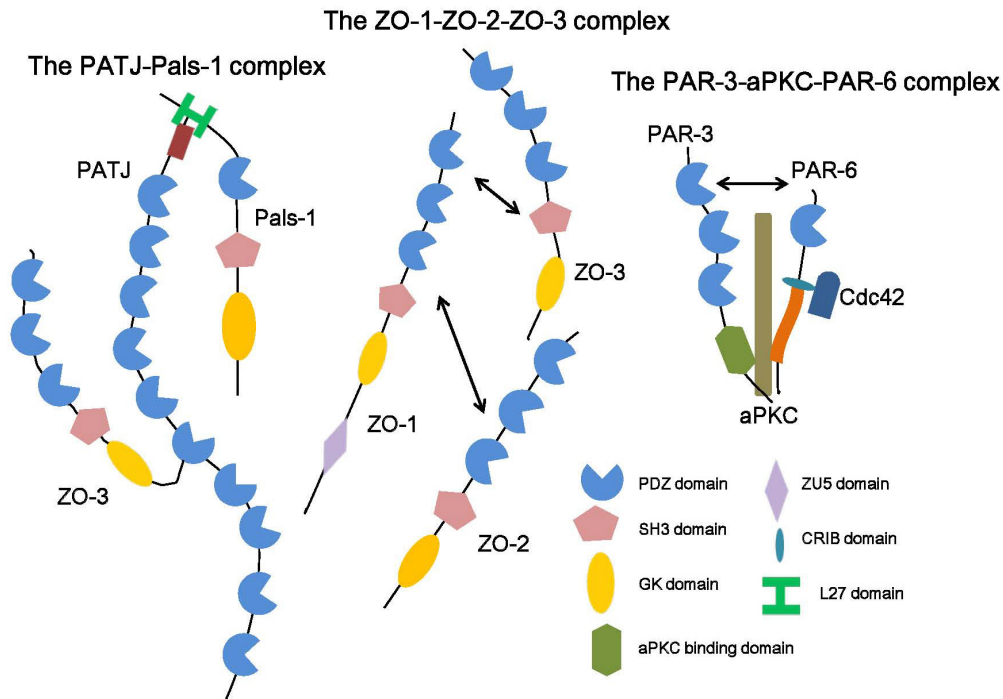


Fig. 3. Major multi-protein complexes at tight junctions. PATJ's N-terminal MAGUK recruitment domain interacts with Pals-1's L27N domain. ZO-2 and ZO-3 associate with ZO-1. Three ZOs can also bind to cell's membrane directly. PAR-3-aPKC-PAR-6 complex is involved in cell polarization. The activation of Cdc42 induces signal transduction through aPKC. PAR-3 binds to JAMs through first PDZ domain. This interaction anchors the complex at specific site.

to build larger protein complexes at the plasma membrane [23]. MUPP1 was originally identified as a protein that can bind to serotonin 5-hydroxytryptamine type 2 receptor (5HT-2A) in the brain [94]. Many other interacting proteins have been found through the studies, such as Pleckstrin homology (PH) domain-containing family A member 1 (PLEKHA1) [50], SynGAP [53], C-Kit [64], transmembrane proteoglycan NG2 [6], and claudin-5 in Schmitt-Lanterman incisure of myelinating Schwann cell (Fig. 1) [77]. Claudin-1 and JAM1, which form tight junction, interact with PDZ10 and PDZ3 of MUPP1 respectively [1, 35]. Olfactory receptors in the olfactory nerve bind to PDZ1 and PDZ2 of MUPP1 [15]. Many proteins and molecules that interact with MUPP1 have been discovered, but considering the number of PDZ domains, it is thought to have more binding partners. In mutation of MUPP1, it can cause severe congenital hydrocephalus, and can influence in alcohol withdrawal [3, 69]. These clinical symptoms are all related to the nervous system, so it is thought that MUPP1 plays crucial role in the nervous system.

**PATJ**

PATJ is a paralogue of MUPP1; it has 10 PDZ domains

and an L27 domain (Fig. 2) [83]. Like MUPP1, it is localized at tight junctions of epithelial cells [58, 83]. MUPP1 and PATJ have similar domain in common and both bind to claudin-1 [35, 58, 82]. In recent study, over-expression of MUPP1 reduces endogenous PATJ from tight junctions, and over-expression of PATJ does the opposite, respectively. This result can speculate that PATJ and MUPP1 have some overlapping molecular mechanisms [1]. PATJ binds to tight junctions that directly interact with claudin-1, and interacts with occludin through ZO-3 [67, 82]. Change in the expression of PATJ disrupts the tight junction-specific localization of ZO-1, ZO-3, and occludin, signifying that PATJ plays a role in stabilization of tight junctions [58, 68]. PATJ also affects Crumbs (CRB) complexes through Pals-1, which means that PATJ makes the link between the lateral and apical part of tight junction [68, 82].

**PAR-3**

PAR-3-PAR-6-aPKC (atypical protein kinase C) complex is composed of 3 proteins and plays a key role in regulation of cellular polarity in cell junction (Fig. 3). This protein complex has been highly conserved throughout biologic evolution process [52, 76]. PAR-3, an important part of this protein

complex, is associated with JAM-A at tight junctions. This protein interacts not only with JAMs, but also with other proteins, such as LIM-kinase 2 (LIMK2), T lymphoma invasion and metastasis 1 (Tiam1) [11, 12]. The correlation is related to the phosphorylation of PAR-3, which is regulated by aPKC [73]. PAR-3 maintains stable status when it binds with JAM-A directly, which implies that both proteins distribute to connection between cells [4]. The PAR-3-PAR-6-aPKC complex takes an important role for membrane polarity in tight junctions [76]. It means that if there are mutations in all of the three components, the structure of tight junction will be altered [28, 73, 91, 104]. When PAR-3 was degraded at PAR-3-PAR-6-aPKC complex, there is retardation at early stage of apical membrane domain development and the structure of tight junction was changed. It suggests that PAR-3 mutation makes the apical membrane domain hard to localize at cell contact region [39]. Taken together with the fact that proteins such as JAM-A bind with PAR-3, it can be thought that not only PAR-3-PAR-6-aPKC complex but also partners of PAR-3 can take important parts in forming polarization. For example the signal transduction of this multi-protein complex is induced by E-cadherin mediated activation of Cdc42 or Rac1 [49, 75] which possibly activates aPKC through interaction between PAR-6 and Cdc42/Rac1 [104].

### MAGI2

Membrane associated guanylate kinase inverted 2 (MAGI2), also called synaptic scaffolding molecule (S-SCAM) is a scaffolding proteins at tight junctions. MAGI2 contain nine potential parts which play an important role in protein-to-protein interaction, including six PDZ domains, two WW domains and a guanylate kinase-like domain (Fig. 2) [38, 97]. MAGI is inverted form of MAGUK family, which is widespread both synapses and epithelial cells, however, MAGI2 is specific in human neuronal system and interacts with AMPA receptors (AMPA) at excitatory synapses [13]. It interacts with the C-terminus of AMPAR regulating proteins (TARPs) such as stargazin in brain and maintains the synaptic plasticity by trafficking of the ionotropic glutamate receptors and regulating the functions of AMPAR [14]. These molecules of great capacity interact with phosphatase and tensin homolog (PTEN) [99], dendrite arborization and synapse maturation 1 (Dasm1) [87], hyperpolarization-activated cation channels [44],  $\beta$ -1 adrenergic receptors [101] and even NMDA receptors as well [9]. Since AMPARs mediate the

fast signal transmission in human central nervous system, MAGI2 is concerned to be essential in memory and learning. Recently report, MAGI2 gene plays a vital role in survival of neonatal mice because it contribute to the completely development of podocyte morphology [40]. MAGI2 is significant to maintain the slit diaphragm of glomerular filtration barrier and its absence could cause a critical problem like anuria [40]. MAGI2 is contributed some severe diseases to attack human's bodies. It is getting increased the risk of schizophrenia in the MAGI2 gene knock-out mice individuals because the cognitive functions and MAGI2 gene are conducted elaborately [63]. Another present study showed that mRNA of MAGI2 gene which is expressed by which binding with phosphatase and tensin homolog (PTEN), a tumor suppressor is statistically meaningful down-regulated in the prostate cancer cell line [99]. This means that it will be easy to detect prostate cancer earlier if we would develop some procedure related MAGI2 gene. In addition, this interaction also contributes to the lung adenocarcinoma depending on the epithelial mesenchymal transition (EMT) [51]. The up-to-date study mentioned the MAGI2 targeting microRNA could inhibit the EMT action and drug resistance making PTEN portions unstable, so that it would apply to the new therapeutic methods of advanced lung cancer.

### AF-6

AF-6 is a multidomain protein that scaffold between cell membrane proteins and actin of cytoskeleton. AF-6 contains N-terminal region which has two Ras-binding domains, C-terminal region and a PDZ domain (Fig. 2) [10]. AF-6 is expressed in the brain. AF-6 plays essential role in plasticity of dendritic spine [36] and the maintenance of adherens junction in the midbrain [102]. AF-6 links JAM-A with PDZ-mediated interaction [18]. And, it is also associated with ZO-1 [8, 59]. The connection between AF-6 and ZO-1 is mediated by competitive binding reaction of Ras and Rap-1 (small GTPases) at the same binding site of AF-6 [103]. According to previous studies, ZO-1 plays a role as a linker between AF-6 and JAM-A [26], and their association is apparent at early stage of contact formation of cell rather than at advanced stage with clearly polarized cells of well developed tight junctions [18]. When microinjected into epithelial cells, JAM-A is detected where AF-6 is presented. This result suggests that there is no clear functional relationship between JAM-A and AF-6, but they may work together at cell

contact sites [18]. On the other hand, JAM-A is not always found at where ZO-1 is abundant. Therefore, it can be thought that ZO-1 and AF-6 plays a different role for localization of JAM-A [18]. AF-6 is also associated with MUPP1. In neuronal tissue, especially in the brain, AF-6 and MUPP1 are detected together using immunofluorescence assay [59]. This result suggests that there is a relationship between AF-6, MUPP1, and gap junction protein Cx36. Cx36 forms electrical synapses which regulate inhibition and experience-dependent plasticity through  $\gamma$ -aminobutyric acid (GABA) release [79].

### CASK

Calcium/calmodulin-dependent serine protein kinase (CASK) is a peripheral plasma membrane protein, also known as a homolog of LIN2. It is expressed by far the greatest in brain relative to kidney, lung and liver [89]; microscopically in nucleus, cytoplasm and cell membrane [29]. CASK is widely found in tight junctions and belongs to the MAGUK family like ZO-1 and Pals-1, which takes part in forming intercellular junctions [54, 85]. Several domains are found in this protein; 1 guanylate kinase like domain, 2 L27 domains, 1 PDZ domain and 1 SH3 domain (Fig. 2). The multiple domains in CASK are able to interact with numerous proteins. For instance, Two L27 domains interact with DLG1 and LIN7 respectively [85], and the protein kinase domain with FER-CIP4 homology (FCH) domain and double SH3 domains containing proteins 2 (FCHSD2). CASK plays an important role in neural development through interaction with transcription factor T-box brain 1 (TBR1) [54], afterwards stabilizing the integrity of synapses of the brain [29].

### Summary and perspective

Several autotypic junction proteins contribute to autotypic tight junction formation. Autotypic junction proteins which contain PDZ domains play an important role in conducting intracellular signals. Intrinsic interactions between specific proteins are tightly regulated in human tissue, as seen in strong conservation throughout evolution. For instance, PAR3-aPKC-PAR6 complex which is essential for cell polarization has been found from *Drosophila sp.* to vertebrates [52, 76]. ZO-1 works with JAMs in intercellular contact sites to recruit and form the basis of tight junction. ZO-1 promotes aggregation of JAMs to form large molecular complexes. AF-6 is one good partner for ZO-1, as the connection between AF-6 and JAM-A is facilitated by ZO-1 [26]. ZO-3,

on the other hand, binds to other PDZ domain-containing proteins such as MUPP1 and PATJ [77]. MUPP1 is able to interact with numerous proteins like ZO-1 on account of its multiple PDZ domains [23]. PATJ is detected in paranodal loops whereas MUPP1 is found in mesaxons and Schmidt-Lanterman incisures. ZO-1 is seen in paranodal areas, Schmidt-Lanterman incisures and mesaxons but not in node of Ranvier [2]. It is not so difficult to speculate that various types of proteins are fulfilling unique functions according to their distribution.

An interesting challenge has emerged to elucidate clear physiological functions of these versatile proteins at autotypic junctions. Thus, future studies of the molecular basis and distribution for autotypic junction proteins will extend our understanding of the intracellular signal transduction, cell polarization, and autotypic tight junctions in myelinating Schwann cells and the consequences of defects in those processes for neurodegenerative diseases and potentially other age related diseases.

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**초록 : 수초화 슈반세포 autotypic 세포연접의 PDZ 도메인 보유 단백질**

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자가밀착연접 단백질들은 세포, 특히 수초화된 신경교세포막의 층상구조 사이에 존재하는 밀착연접에 존재한다. 그들 중 일부는 다른 단백질의 C-말단의 PDZ 결합 모티프에 붙는 postsynaptic density-95/Disks large/Zonula occludens-1 (PDZ) 도메인을 가진다. PDZ domain은 박테리아, 식물, 세균, 후생동물, *Drosophila*에 존재하여 거대한 단백질복합체를 형성할 수 있게 해준다. 이러한 단백질복합체들은 세포 내 신호전달, 단백질 표적화, 그리고 세포막 극화 작용을 한다. ZO-1, ZO-2, AF-6, PATJ, MUPP1, PAR-3는 자가밀착연접에 존재한다고 확인되었다. PAR-3는 atypical protein kinase C와 PAR-6와 반응하여 세포의 극성 형성에 중요한 역할을 하는 3차원 단백질복합체를 형성하는데 이는 *Caenorhabditis elegans*와 *Drosophila* 종에서 척추동물에까지 보존되었다. MAGI2는 흥분성 시냅스에서  $\alpha$ -amino-3-hydroxyl-5-methyl-4-isoxazole propionate (AMPA) 수용체와 반응한다. PATJ는 claudin-1과 함께 마디걸 루프에서 발견되는 반면, MUPP1은 claudin-5와 함께 축삭사이막과 Schmidt-Lanterman 절흔에서 찾을 수 있다. ZO-1, ZO-2 그리고 PAR-3의 경우에는 세 장소 모두에서 발견된다. PDZ 도메인을 보유한 단백질들의 서로 다른 분포는 자가밀착연접의 발생에 영향을 준다. 이 총설에서는 수초화된 슈반 세포의 자가밀착연접에 존재하는 PDZ 도메인을 가진 단백질들과 그들의 기능을 알아볼 것이다.