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Beyond cell-cell adhesion

Emerging roles of the tight junction scaffold ZO-2

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Zonula occludens proteins (ZO-1, ZO-2, ZO-3), which belong to the family of membrane-associated guanylate kinase (MAGUK) homologs, serve as molecular hubs for the assembly of multi-protein networks at the cytoplasmic surface of intercellular contacts in epithelial and endothelial cells. These multi-PDZ proteins exert crucial functions in the structural organization of intercellular contacts and in transducing intracellular signals from the plasma membrane to the nucleus. The junctional MAGUK protein ZO-2 not only associates with the C-terminal PDZ-binding motif of various transmembrane junctional proteins but also transiently targets to the nucleus and interacts with a number of nuclear proteins, thereby modulating gene expression and cell proliferation. Recent evidence suggests that ZO-2 is also involved in stress response and cytoprotective mechanisms, which further highlights the multi-faceted nature of this PDZ domain-containing protein.

This review focuses on ZO-2 acting as a molecular scaffold at the cytoplasmic aspect of tight junctions and within the nucleus and discusses additional aspects of its cellular activities. The multitude of proteins interacting with ZO-2 and the heterogeneity of proteins either influencing or being influenced by ZO-2 suggests an exceptional functional capacity of this protein far beyond merely serving as a structural component of cellular junctions.

Introduction

Direct interactions of neighboring cells are conferred by several types of cellular junctions. These can functionally be grouped into occluding (i.e., tight junctions), anchoring (i.e., adherens junctions, desmosomes and hemidesmosomes) and communicating junctions (i.e., gap junctions). Tight junctions (TJs) are characterized by dynamic and highly organized plasma membrane-bound structures, which seal the paracellular space in order to allow the establishment and maintenance of a distinct internal and external milieu in tissues and organs.[1-3] The formation of such "ins" and "outs" is imperative for proper development and tissue function. For instance, the tight intercellular bonding between trophectoderm epithelial cells is necessary to create a suitable internal milieu for the developing mammalian embryo.[4] Or, the restrictive intercellular contacts between capillary endothelial cells, forming the so called blood-brain barrier, enable a physiological functioning of the brain within a homeostatic environment and protect the vulnerable neural tissue from the uncontrolled entrance of substances emanating from the systemic circulation.[5-8] Next to regulating the paracellular flux of solutes and ions, tight junctions also create a "fence" in the plane of the plasma membrane, contributing to the establishment of cellular polarity.[9-12] Epithelial and endothelial tight junctions consist of several classes of transmembrane proteins locating to the apical aspect of the cell.[13] The extracellular portions of the transmembrane proteins form a more or less tight seal between opposing cells, connecting the plasma membranes in a zipper-like fashion. Within the cell a highly organized cytoplasmic "plaque" consisting of an array of cytosolic proteins assembles in close vicinity to these contact sites, providing mechanical linkage between the plasma membrane and the cytoskeleton. A large number of junctional proteins have been identified during the last decade (reviewed in 13-19) and soon it was realized that these complexes not only ensure the structural integrity of tight junctions,[20-23] but also coordinate and transduce the signals impinging on and emanating from the apical plasma membrane. Consequently, next to serving as physical barriers tight junctions also influence pivotal processes such as morphogenesis, gene expression, cytoskeletal dynamics and cell proliferation.[14,18,24-26]

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PDZ-Containing Scaffolding Proteins: The Molecular Basis for Junctional Plaque Assembly

The most prominent subgroup of scaffolding proteins localizing to the cytoplasmic face of the adhesion site is represented by the MAGUK (membrane-associated guanylate kinase) proteins,[27-29] which can be classified into seven subfamilies based on their modular structure and sequence similarity.[30] The modular nature of MAGUK proteins was early recognized and comprises one or more PDZ domains next to other protein-protein

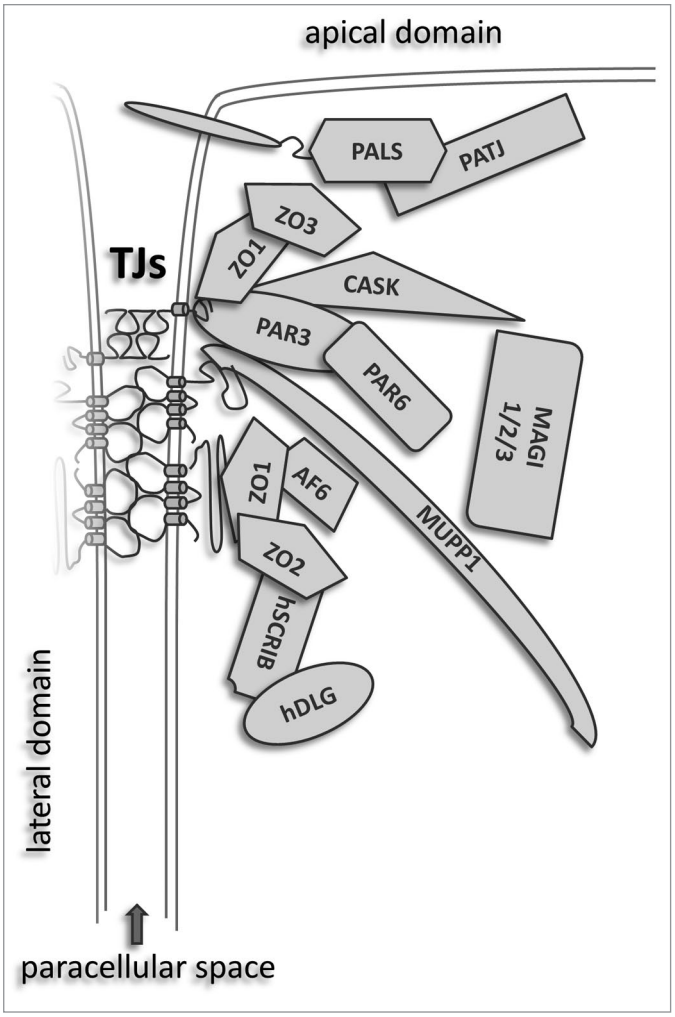

Figure 1. PDZ proteins as molecular base of tight junctional plaques. Two groups of proteins are involved in the establishment and maintenance of TJs: (1) Transmembrane proteins which bridge the intercellular space and create a paracellular seal and (2) peripheral proteins, constituting the cytoplasmic "plaque" of tight junctions interacting directly or indirectly with the transmembrane junctional components. The formation of these complexes largely relies on PDZ-PDZ interactions. Only cytosolic proteins harboring one or more PDZ domains are illustrated.

binding domains including SH3 (Src homology 3), WW, L27 (MAGUK LIN-2 + LIN-7), CaMK (calcium/calmodulin-dependent protein kinase) domains and a GUK (guanylate kinase) domain,[28] a region which lacks enzymatic activity due to a deletion in its ATP- and GMP-binding sites but appears to enable protein–protein binding.[31] The most intensely studied junctional MAGUKs include the zonula occludens proteins (ZO-1, ZO-2 and ZO-3).[32-35] Although originally described as TJ-specific proteins, ZO proteins also associate with other types of intercellular contacts, i.e., adherens and gap junctions (reviewed in 13, 14, 36, 37). Thus, ZO proteins appear to exert, at least in part, a basic and redundant role in establishing and/or maintaining intercellular adhesion and communication. Generally, ZO proteins serve as a multivalent binding platform for an ever growing list of junction-associated proteins. Next to the classical MAGUK domains, ZO proteins also contain a short binding region at the C-terminus (TEL), which represents an additional PDZ binding domain. Finally, a proline-rich region of varying length is present at the C-terminus of ZO-1 and ZO-2 and between the second and third PDZ domain of ZO-3 and has been shown to be targeted by actin-binding proteins and other cytoskeletal proteins.[38-40] In recent years, increasing interest has focused on the role of variable regions, numbered U (unique)1 to U6, which are localized between the core domains listed further above. The best studied variable region, termed HOOK domain (U5), is a basic hinge region between the SH3 and GUK domain which is involved in oligomerization and ligand binding of MAGUKs.[41] The U6 motif is unique to ZO proteins and appears to be critical for junction assembly. For instance, expression of a mutant ZO-1, lacking the U6 region, induces ectopic junctional strands consisting of occludin and claudins but lacking most of the cytoplasmic plaque proteins.[41]

Other junctional MAGUK proteins identified so far include MAGI-1, -2 and -3 (membrane-associated guanylate kinase with inverted orientation of protein–protein interaction domains-1, -2 and -3),[42-44] and the calcium/calmodulin-dependent serine protein kinase (CASK/LIN-2).[45] In addition, the human homolog of the Drosophila discs large tumor suppressor hDlg/SAP97 has been shown to localize to regions of cell-cell contact.[46,47] However the functional relevance of hDlg for TJ biology remains poorly characterized.

Next to the MAGUK proteins, several other proteins localizing to the junctional plaque harbor one or more PDZ domains. These protein-protein interaction modules, which often bind to short amino acid motifs at the C-termini of target proteins, are named after the first three proteins in which these domains have been identified: PSD-95 (post synaptic density protein-95), Dlg (the Drosophila discs large protein) and ZO-1 (zonula occludens-1).[48,49] At TJs, the large 13 PDZ domain-containing protein MUPP1 (multi PDZ domain protein-1)[50] and ZO proteins directly bind the cytoplasmic domains of the TJ-specific transmembrane proteins occludin and claudins.[51-53] In a similar manner, the Ig-like junction adhesion molecule 1 (JAM1) anchors Par-3,[54] and hence the Par6/aPKC (partitioning-defective protein-6/atypical protein kinase C) complex to the apical aspect of the plasma membrane.[55] PALS1 binds to a cytoplasmic portion of the transmembrane proteins CRB (crumbs)-1 and CRB-3, thereby targeting the evolutionary conserved polarity complex CRB1/3-PALS1-PATJ to the junction.[56] Further, the polarity protein Scribble, a large multi-domain protein involved in the maintenance of apical/basal polarity, migration and invasion,[57] was shown to associate with ZO-1 and has been demonstrated to be important for TJ assembly.[58] Finally, the Ras target AF-6/afadin[59] directly interacts with ZO-1 and localizes to TJs. Taken together, PDZ domain-mediated protein-protein interactions aid in the temporal and spatial assembly of multiprotein complexes at the cytoplasmic plaque and are pivotal for the functional and structural integrity of TJs (see **Fig. 1**).

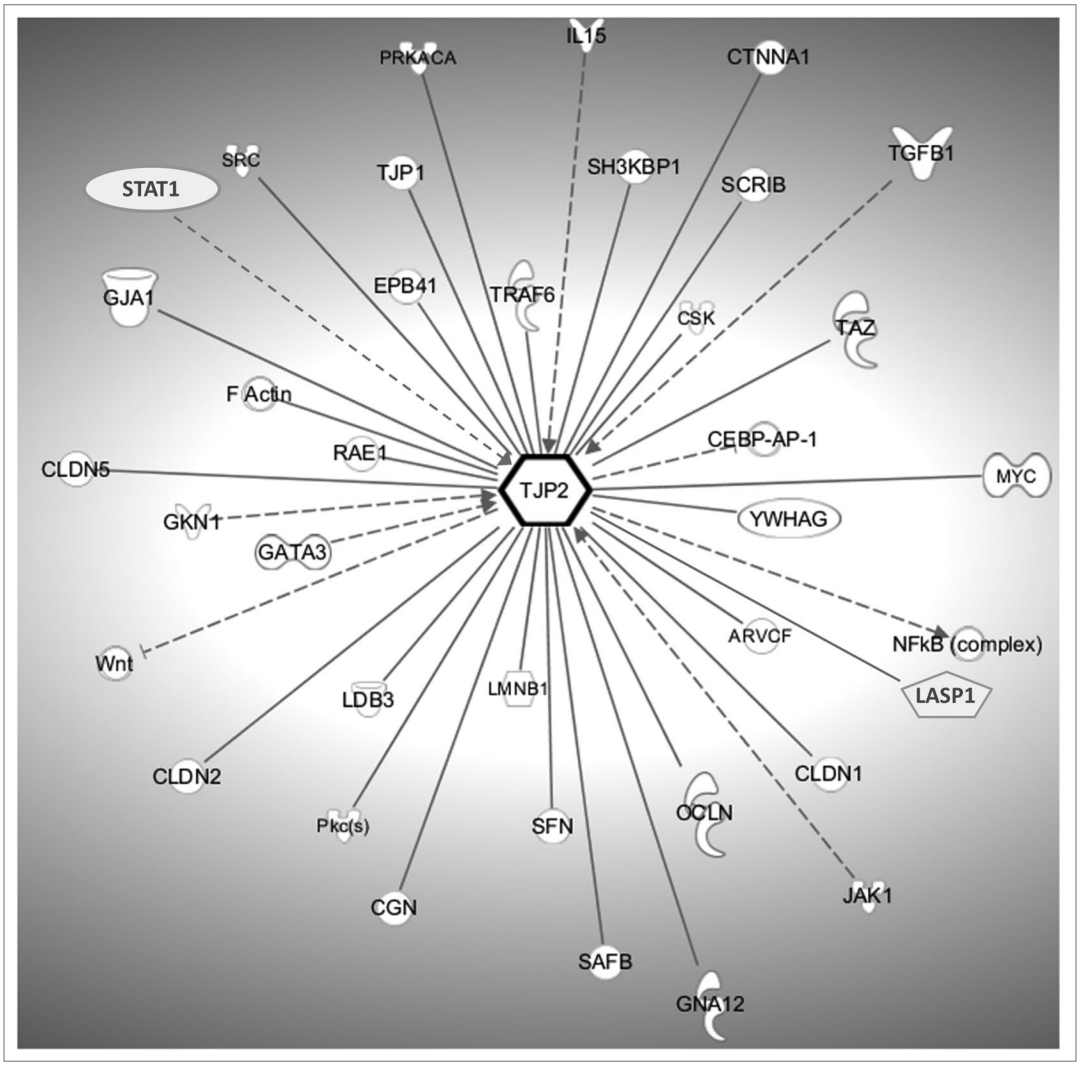

Figure 2. The ZO-2 (TJP2) interactome. Protein-protein interactions are symbolized by bold lines whereas outgoing dashed lines indicate that perturbations of ZO-2 expression affect the expression of the indicated proteins. Incoming dashed lines refer to proteins which impact upon the mRNA level of ZO-2. The graph was generated using the IPA software package (Ingenuity Systems) and gene symbols according to the H.G.N.C. nomenclature are shown.

Molecular Interactions of ZO-2 at the Junctional Site

Zonula occludens 2 (ZO-2) is a 160 kDa protein originally identified in a ZO-1 immunoprecipitate.[32] Proteins interacting with ZO-2 at cell-cell contact sites essentially can be subdivided into structural and non-structural proteins. **Figure 2** depicts a schematic diagram of the ZO-2 interactome. Some of the protein-protein interactions described for ZO-2 are redundant and have been shown for all ZO proteins. Such interactions include the binding of the first PDZ domain to the C-termini of claudins[52] or the homo- and hetero-dimerization of ZO-proteins via their second PDZ domain, which takes place by domain swapping of β1 and β2 strands.[60] These redundancies are not surprising as the ZO proteins share a high degree of homology among each other. Nevertheless, ZO proteins also fulfill a multitude of ZO-specific functions.

Transmembrane proteins interacting with ZO-2 include the tetra-span proteins claudins and occludin.[52,61] Claudin-1 to -8 interact via their C-terminal region with the first PDZ domain,[52] while connexins (Cx), including Cx-36 and Cx-43, were found to associate with PDZ-1 or PDZ-2, respectively.[62,63] Although the binding of occludin to a region at the SH3-hinge-GUK domain has only been demonstrated for ZO-1,[64] a similar interaction can be presumed for ZO-2, although this remains to be demonstrated.

The proline-rich C-terminal domain of ZO-2 has been shown to interact mainly with cytoskeleton-associated proteins, including protein 4.1R and F-actin.[38-40] Cingulin, a 140 kDa phosphoprotein and regulator of Rho-A signaling at TJs interacts directly with ZO-2 and provides a direct link to the actomyosin cytoskeleton.[65,66] Finally, data from a tandem proteomic approach suggests the direct or indirect interaction of ZO-2 with 14–3-3 binding proteins, which are known to be involved

in cytoskeletal regulation.[67] ZO-2, next to ZO-1,[58] also associates with the basolateral polarity protein Scribble (huScribble) via a C-terminal motif[57] and the ZO-2/Scribble complex appears to be involved in TJ assembly and function.[58] Finally, protein kinases, signaling molecules and other regulatory proteins including cytokines which directly or indirectly target ZO-2 complete the dynamic network of the ZO-2 scaffold. These include various isoforms of protein kinase C,[68-70] the tyrosine kinase c-Src and its negative regulator Csk (C-terminal Src kinase)[71] as well as the heterotrimeric G protein Galpha12,[72] which promotes Src phosphorylation of ZO-1 and ZO-2 resulting in disruption of TJs and an increase in paracellular permeability.[73] Interestingly, next to ZO-2 itself, several of the interacting proteins resemble "dual-residency" proteins, capable of shuttling between the cytoplasm and the nucleus. Therefore, ZO-2 serves as a molecular hub at the cytoplasmic aspect of TJs. In addition, the nuclear translocation of ZO-2 together with bound proteins substantially extends the physiological functions of this junctional MAGUK protein.

Nuclear ZO-2 and the Impact of ZO-2 on Transcription and Cell Proliferation

The presence of ZO-2 within the nucleus has been recognized more than a decade ago. All ZO proteins carry conserved nuclear localization and nuclear export sequences,[74] however only ZO-1 and ZO-2 have been shown to localize to cell nuclei of epithelial and endothelial cells.[75-79] In sparse cultures, ZO-1 and ZO-2 are present in cell nuclei but become redistributed to the plasma membrane as soon as cells reach confluence.[76,77] During mitosis and the concomitant disintegration of the nuclear membrane ZO-2 is evenly dispersed within the cytoplasm and during the late G1 phase ZO-2 accumulates in the nucleus. In quiescent cells ZO-2 is not present in the nucleus.[80] Further, it was demonstrated that ZO-2 preferentially targets the nuclei of epithelial cells during and upon chemical and heat stress.[79] Frequently, nuclear ZO-2 locates to nuclear speckles, which is dependent on the presence of an intact PDZ-1 domain[78] and potentially can be induced by the interaction with the heterogeneous nuclear ribonucleoprotein SAF-B/HET (scaffold attachment factor-B/HSP27 estrogen response element-TATA box-binding protein).[79] In addition, recruitment of ZO-2 to nuclear speckles requires binding to phosphatidylinositol 4,5-bisphosphate,[81] a phospholipid component of plasma membranes.

The notion that junctional MAGUKs fulfill functions next to their prime role in aiding in the establishment of cell-cell junctions is not without precedence. A first clue came from studies with the Drosophila tumor suppressor protein Dlg, a protein relevant for the formation of invertebrate septate junctions and neuronal synaptic junctions. Genetic studies in *Drospohila* revealed that mutations in *Dlg* resulted in tumorous overgrowth of imaginal discs.[82,83] Due to their high homology with Dlg it was speculated that the ZO family of MAGUK proteins, including ZO-2, are also involved in cell growth and proliferation. Indeed, several studies have demonstrated the interaction of ZO proteins with proteins involved in cell cycle progression and transcriptional regulation.[24,26,36] However, results from studies investigating the influence of ZO-2 on cellular proliferation remain controversial. Exogenous downregulation of ZO-2 resulted in functional perturbations of TJs in epithelial cells without altering cell proliferation or apoptosis rates.[84] Also, during mouse blastocyst formation repression of ZO-2 delayed the formation of the blastocoel cavity, without affecting cell proliferation.[4] In contrast, deletion of ZO-2 in mice is embryonic lethal shortly after implantation due to an arrest in early gastrulation. Interstingly, ZO-2 knockout embryos showed a decreased proliferation rate and an increase in apoptotic cells.[85] Finally, the nuclear accumulation of a ZO-2 variant tagged with exogenous SV40 nuclear localization signals led to increased cell proliferation of epithelial and endothelial cells.[86] In another study the overexpression of ZO-2 in epithelial cells resulted in binding to c-Myc triggering the downregulation of cyclin D1 and subsequent suppression of cell proliferation.[87] Later, *Lechuga S*, et al. provided evidence that the inhibitory effect of ZO-2 on cyclin D1 transcription is blocked by ZASP (ZO-2 associated speckle protein) through binding to the third PDZ domain of ZO-2.[88]

Modulation of cell proliferation is also facilitated by binding of ZO-2 to the transcriptional activator YAP2 (Yes kinase-associated protein 2), an effector of the Hippo signaling pathway which controls the regulation of proliferation and apoptosis during mammalian organogenesis.[89] Interaction with ZO-2, which can be abrogated by deletion of the 1st PDZ domain, enhances the nuclear localization and pro-apoptotic function of YAP.[90] Next to ZO-2, also ZO-1 has been identified as a binding partner of YAP-2, also known as TAZ (transcriptional coactivator with PDZ-binding motif).[91] ZO-2 was also found to interact with the cytoskeletal protein LASP-1 (LIM-and-SH3-domain-protein-1), usually present in focal contacts, where it regulates cytoskeletal dynamics and cell migration. Phosphorylation of LASP-1 by PKA (protein kinase A) induces nuclear targeting of the LASP-1/ZO-2 complex[92] and nuclear accumulation of LASP-1 is thought to be relevant during cancer progression.

Several proteins have been found to interact with ZO-2 during nuclear shuttling or within the nucleus itself. For example, the interaction of the armadillo-repeat protein ARVCF (armadillo repeat gene deleted in velocardiofacial syndrome) depends on an N-terminal PDZ domain of ZO-2,[93] a region which is also targeted by the non-receptor tyrosine kinase JAK1. Also, the transcription factors Jun, Fos and C/EBP were shown to associate with ZO-2 within the nucleus and at TJs in epithelial cells.[94] Next to directly associating with and/or influencing transcription factors, ZO-2 possibly impacts upon the transcription machinery via its association with the hnRNP SAF-B/HET.[79] SAF-B/HET is thought to serve as a molecular platform to assemble a transcription complex in the vicinity of actively transcribed genes,[95] a mechanism which appears to be highly conserved among several species.[96]

However, only few studies demonstrate a direct or indirect impact on gene transcription following the perturbation of ZO-2 levels. For instance, in vascular smooth muscle cells (VSMCS) of coronary arteries the expression of STAT1 (signal transducers and activators of transcription)-specific genes is upregulated in response to ZO-2 silencing.[97] Another study demonstrates the association of ZO-2 with the non-receptor tyrosine kinase JAK1 (Janus kinase 1) in VMSCs mediating specific homotypic

intercellular contacts.[98] Together, these observations suggest that ZO-2 is potentially involved in vascular remodeling and arteriogenesis. Overexpression of ZO-2 was also shown to increase β-catenin phosphorylation, thereby reducing β-catenin-mediated gene transcription of Wnt target genes.[99] In nasal epithelial cells, the experimentally induced upregulation of ZO-2 expression through activation of PKC signaling was shown to be inhibited by the transcriptional factor GATA-3.[70] Finally, in a human genome-wide siRNA screen ZO-2 has been identified as a novel NFκB activation pathway component.[100] However, for many of these observations the physiological ramifications remain poorly defined.

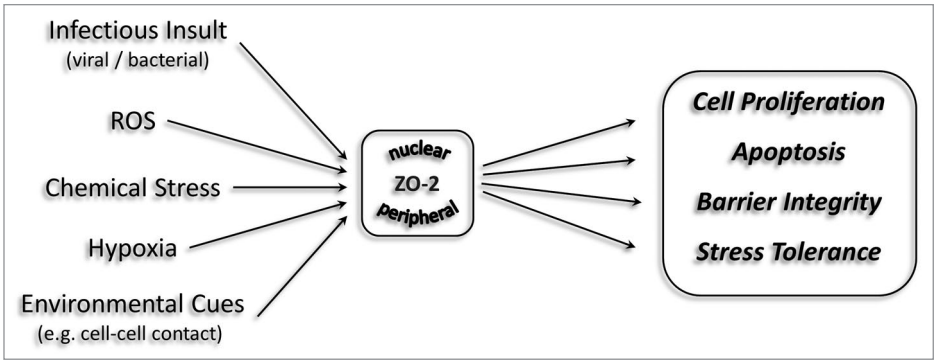

Figure 3. Functions of ZO-2 beyond cell-cell adhesion. The expression and intracellular distribution of the junctional MAGUK protein ZO-2 is influenced by various extrinsic and intrinsic cues, including cellular stress and cell-cell contact. In response ZO-2 affects diverse cellular processes, including cell proliferation, apoptosis, stress tolerance and barrier integrity by directly or indirectly influencing gene expression, ultimately feeding into various cell signaling pathways.

Taken together, one can postulate that not only peripheral, but also nuclear ZO-2 serves as a scaffold protein facilitating the transport of other proteins to the nucleus, aiding in the spatial and temporal assembly of nuclear "transcriptomes," thereby directly or indirectly influencing cell proliferation and/or gene transcription.

The Role of ZO-2 in Stress Response and Health and Disease

ZO-2 has also been associated with several human pathologies. Clinical studies revealed that, e.g., familial hypercholanemia or nonsyndromic progressive hearing loss are associated with mutations of the ZO-2 gene and/or a change in ZO-2 protein levels.[101,102] Due to the high degree of homology between the Drosophila tumor suppressor protein Dlg and ZO-1, together with the actions of ZO-2 on cell proliferation and gene transcription, it is also tempting to speculate that ZO-2 could act as a tumor suppressor. Indeed, in several tumors the mRNA levels of ZO-2 are reduced (reviewed in 103). However, most of these reports do not exclude that the reduction of ZO-2 and/or other junctional proteins is a consequence of the disease.

Recently, Bautista-Garcia et al. demonstrated a cytoprotective function of ZO-2. In a mouse model of adricmycin-induced kidney dysfunction overexpression of ZO-2 prevents podocyte injury by increasing phosphorylated β-catenin and decreasing the expression of Wnt/β-catenin downstream genes.[99] The interference of ZO-2 with the Wnt/β-catenin signaling pathway predicts an unforeseeable array of functions in biological processes where a fine-tuned balance between differentiation, cell growth and cell-cell adhesion is required. This includes the modulation of all types of epithelial-mesenchymal transition (EMT) underlying development, tissue regeneration and disease.[104]

ZO-2 is also potentially involved in cellular stress responses. For instance, upon chemical stress and heat shock, ZO-2 accumulates in the nucleus of epithelial cells.[79] Since nuclear ZO-2 associates directly with SAF-B/HET, a negative regulator of the heat shock protein 27 (Hsp27) transcription,[105] one could extrapolate that ZO-2 is involved in cytoprotection by modulating Hsp27 expression levels (**Fig. 3**). Further, in vitro studies have shown that cerebral endothelial cells, stably overexpressing nuclear ZO-2, show a moderate decrease in MMP9 (matrix metalloproteinase 9) mRNA levels.[106] The underlying mechanism explaining the modulation of MMP9 levels by ZO-2 remains to be determined. Nevertheless, it has been demonstrated several-fold that the downregulation of MMP9 exerts a protective effect on the endothelial barrier, particularly the blood-brain barrier, following ischemic damage.[107-111] Further, in human breast carcinoma cells MMP9 was shown to be suppressed by heme oxygenase 1 (HO-1), a target gene of the transcriptional repressor Bach1.[112,113] Interestingly, via a yeast based Two-hybrid assay, we identified Bach1 to interact directly with ZO-2 (unpublished data). It will be of particular interest to determine whether and how this interaction modulates HO-1 levels and potentially contributes to the cytoprotective action of HO-1.

As mentioned before, ZO-2 has also been shown to directly or indirectly act as a negative regulator of STAT-1 expression in VSMCs.[95] Interestingly, the JAK/STAT pathway mediates HIV-induced adhesion and transmigration of monocytes across the blood-brain barrier in vitro through increased expression of IL-6 and IL-8.[114] It will be interesting to determine whether or not ZO-2 suppresses STAT-1 expression in cerebral endothelial cells as well, thereby exerting a protective effect in HIV-induced neuroinflammation by decreasing the JAK/STAT-mediated leukocyte entry into the brain.

Many TJ proteins have been shown to be directly targeted by viruses with oncogenic and non-oncogenic potential, often resulting in a perturbation of the junctional barrier of their target cells.[115,116] As a result, the dissemination and transmission efficiency of the viruses is often increased.

Oxidative stress also alters ZO protein expression and localization in a number of pathologies, including hypoxia, bacterial and viral infections, inflammation and age-related diseases.[117] However, most of the studies have focused on ZO-1 and on increased permeability of epithelial and endothelial barriers and information concerning redundant and non-redundant

functions of ZO proteins upon oxidative stress is still missing. Of particular interest in this context is the role of nuclear ZO-2 for the cellular stress response.

In summary, TJ-associated proteins in general and ZO-2 in particular have been associated with a multitude of physiological and pathological conditions other than forming and maintaining the tight junction permeability barrier.

Summary

Historically, the multi PDZ domain MAGUK protein ZO-2 was believed to serve as a simple structural component of the "cytoplasmic plaque" of TJs. However, the recognition that ZO-2 transiently targets the nucleus of epithelial and endothelial cells has fuelled intense interest over the years and has led to the discovery of a myriad of functions extending beyond the assembly of TJs, including the modulation of gene transcription, cell growth and proliferation. ZO-1/2 protein expression and localization also has been shown to be altered during cellular stress responses (i.e., oxidative stress or hypoxia[117]) and various other pathologies. More recently, ZO-2 has further been shown to exert a cytoprotective effect by perturbing the Wnt/β-catenin pathway, preventing podocyte injury in a mouse model. Much remains to be learned and additional studies dissecting the molecular mechanism(s) underlying the proposed ZO-2-mediated cytoprotective response pathways are required, providing ample opportunities for future research.

Disclosure of Potential Conflicts of Interest

No potential conflict of interest was disclosed.

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