Transgelin-2 in immunity: Its implication in cell therapy

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Abstract
Transgelin-2 is a small 22-kDa actin-binding protein implicated in actin dynamics, which stabilizes actin structures and participates in actin-associated signaling pathways. Much curiosity regarding transgelin-2 has centered around its dysregulation in tumor development and associated diseases. However, recent studies have shed new light on the functions of transgelin-2, the only transgelin family member present in leukocytes, in the context of various immune responses. In this review, we outlined the biochemical properties of transgelin-2 and its physiological functions in T cells, B cells, and macrophages. Transgelin-2 regulates T cell activation by stabilizing the actin cytoskeleton at the immunological synapse. Transgelin-2 in B cells also participates in the stabilization of T cell–B cell conjugates. While transgelin-2 is expressed at trace levels in macrophages, its expression is highly upregulated upon lipopolysaccharide stimulation and plays an essential role in macrophage phagocytosis. Since transgelin-2 increases T cell adhesion to target cells via boosting the “inside-out” costimulatory activation of leukocyte function-associated antigen 1, transgelin-2 could be a suitable candidate to potenti ate the antitumor response of cytotoxic T cells by compensating for the lack of costimulation in tumor microenvironment. We discussed the feasibility of using native or engineered transgelin-2 as a synergistic molecule in cell-based immunotherapies, without inducing off-target disturbance in actin dynamics in other cells.

KEYWORDS
actin-binding protein, B lymphocytes, immunological synapse, immunotherapy, macrophages, T lymphocytes, transgelin-2

1 | INTRODUCTION

The actin cytoskeleton plays a crucial role for immune functions, orchestrating numerous cellular processes including cell proliferation and differentiation, apoptosis, migration, and cellular signaling.1–8 To accomplish these outcomes, the actin filaments are spatially and temporally regulated by actin-binding proteins (ABPs), which account for approximately 25% of the total cellular protein.9 Transgelin-2, a 22-kDa ABP, is encoded by the gene TAGLN2 and belongs to the transgelin superfamily of actin cross-linking/gelling proteins10 consisting of transgelin-1 (also known as smooth muscle protein 22α, SM22α), transgelin-2 (SM22β),11 and transgelin-3 (NP25).12 Because the first member of the transgelin family, transgelin-1, was first identified in 198713 and has been considered as a tumor suppressor,14 several studies on transgelin-2 have centered around its relevance with tumor development and allied diseases. However, its fundamental mechanisms and physiological significance are largely unknown. Notably, recent findings regarding transgelin-2, the only transgelin family member present in leukocytes,15 shed light on its biochemical properties and physiological roles in the immune system. In this review, we build a holistic picture of how transgelin-2 functions in cells of both innate and adaptive immune systems. We first provide the biochemical characteristics of transgelin-2 and its regulation in immune tissues and cells. We then review recently uncovered physiological functions of transgelin-2 in the immune system; this small ABP regulates cytoskeletal actin dynamics and stabilizes immune synapses that form when antigen-recognizing T cells meet antigen-presenting cells (APCs) or macrophages phagocytose infected bacteria.16–19 Several studies have suggested the feasibility of transgelin-2 as an endogenous factor to enhance T cell function, thereby boosting the antitumor response of...
cytotoxic T cells for immune cell therapy. Its oncogenic aspects are not addressed in detail in this paper but have been reviewed recently.20

2 | STRUCTURE

The human transgelin-2 is transcribed from the 7.4-kb TAGLN2 gene, which is located on chromosome 1q23.2 with 7 exons. Other isoforms, human transgelin-1 and transgelin-3, are encoded by distinct genes at a locus separate from transgelin-2; TAGLN1 and TAGLN3 are located on chromosome 11q23.3 and chromosome 3q13.2, respectively, each contains 5 exons. Therefore, the transcription of each gene is regulated by distinct noncoding promoter sequences. Each isoform performs unique biological roles and is expressed in different biological conditions. For example, transgelin-2, the only transgelin protein with an upstream promoter region containing a NF-κB consensus motif, is largely induced by the NF-κB pathway in macrophages, while the other two isoforms are not significantly influenced.17

Structurally, all three transgelsins contain a N-terminal single calponin homology (CH) domain, actin-binding motif (ABM), and C-terminal calponin-like repeat (CR, also named as C-terminal calponin-like module repeats, CLIK repeats) region (Fig. 1).14 The structure of the CH domain (residues 16–157) of human transgelin-2 has been determined to have a high similarity in tertiary structures to transgelin-1, although the N- and C-terminal structures remain inconclusive. The CH domain structures of all isoforms are globular and formed by 6 helices, which are conserved to some extent throughout the CH domains in other ABPs (reference was also obtained from RCSB Protein Data Bank).

3 | BIOCHEMICAL CHARACTERISTICS OF TRANSGELIN-2: ACTIN BINDING, BUNDLING, AND STABILIZATION

Transgelin-2, like other transgelsins, binds to both F-actin and G-actin through ABM, as determined by in vitro and in vivo observations with an ABM deletion mutant (ΔABM) in different contexts.15 In particular, the binding to G-actin is interesting as it implies that transgelin-2 has diverse roles in controlling actin structures and dynamics. For example, it may hinder or transform the binding sites for other accessory proteins, which results in the impediment of other ABP actions. For example, Na et al. reported that transgelin-2 competes with cofilin, an actin-severing and sequestering protein,15 due to the presence of an overlapping binding site at the actin subdomain1 (SD1), thereby, obstructing cofilin-mediated disassembly of actin filaments. In addition, actin side-binding proteins, such as EPLIN, have been known to inhibit the secondary activation of nucleation mediated by the Arp2/3 complex.19,22 As transgelin-2 also acts as a side-binding protein, it is plausible that transgelin-2 can compete with the Arp2/3 complex if the location of the transgelin-2 binding site in actin overlaps with the Arp2/3 actin-binding site.23

The transgelin family has been assumed to consist of actin-bundling and gelling proteins.24 However, the bundling activity was observed only at exceptionally high concentrations (16–24 μM), which corresponds to a ratio of transgelin-2 to actin of over 2:1. Additionally, since the working ratio of actin-bundling proteins, such as α-actinin, filamin, and fimbrin, to actin ranges from 1:2 to 1:20,25–28 transgelin-2 is not likely a direct actin-bundling protein. However, the strong localization in the cellular bundled actin structures, such as stress fibers or podosomes, similar to transgelin-114,15 suggests that transgelin-2 has an actin-bundling activity in vivo. However, how it promotes actin bundling in living cells remains unknown. One possibility is that transgelin-2 may not simply connect two actin filaments to form bundles as easily as observed for other actin-bundling proteins, but instead, it can be intercalated between two G-actin molecules since it is a G-actin-binding protein, thus, aiding in the formation of multimeric transgelin-2/actin structures. Because the affinity of transgelin-2 for F-actin is lower than that of other bundling proteins,15 this multimeric feature may suggest that it acts as a “molecular zipper or staple” for joining actin filaments into the bundles. The association of the N-terminus near the CH domain and the C-terminus CR region has been predicted as the mechanism of multimeric interactions of transgelin-2 at the site of actin polymerization.15 The property of transgelin-2 allowing it to be intercalated into the each G-actin can also influence the stability of F-actins.15 In cells, this property may result in the augmentation of F-actin contents at the distal-supramolecular activation cluster (d-SMAC) of the immunological synapse (IS) in T cells, localization at the filopodia of B cells during B–T conjugation, and ruffles and phagocytic cups in macrophages.2,15,17,19

4 | EXPRESSION AND LOCALIZATION OF TRANSGELIN-2 IN IMMUNE CELLS

4.1 | Expression and localization in various cell types

Transgelin-2 has been reported to be widely expressed in various cell types, from smooth muscle cells (SMCs) to non-SMCs, whereas
4.2 | Regulation of transgelin-2 in immune cells

The regulation of transgelin-2 expression has not been sufficiently studied. However, some studies have suggested that transgelin-2 expression is controlled at the transcriptional, translational, and post-translational levels in response to the various intercellular events. For instance, transgelin-2 expression is linked to the NF-κB pathway in macrophages. Kim et al. reported that transgelin-2 is selectively induced in LPS-activated macrophages via the NF-κB pathway, whereas other transgelin family members are not likely controlled by external signals, such as LPS. NFAT, a down-stream transcription factor of calcium signaling, seems to insignificantly contribute to its induction. In primary B cells, at the germinal center (GC), the TAGLN2 mRNA level increased approximately 3-fold after BCR stimulation. Consistent with this, in conventional B-2 cells, which histologically correspond to primary B cells, the TAGLN2 mRNA level was upregulated by 3-fold in response to either anti-Ig or LPS. Moreover, as mentioned above, Francès et al. reported that transgelin-2 levels differ at the transcriptional and translational (3-fold and 60-fold difference, respectively) level even in the same samples. Thus, a more accurate proteomic analysis would be needed to understand whether or how transgelin-2 expression is further controlled after transcription. Moreover, peritoneal B-1 cells, which also express TAGLN2 mRNA 3-fold higher than that in B-2 cells, showed upregulated levels of NF-κB, PKC, and phosphorylated p-ERK, the main players in the PI3K/Akt and Ras-ERK signaling pathways. Furthermore, TGF-β stimulation resulted in a 1.47-fold upregulation of transgelin-2 expression in a Smad4-dependent manner. This observation correlated with those in previous reports indicating that TGF-β regulated transgelin-1 expression.

5 | FUNCTIONS IN VARIOUS IMMUNE CELLS

5.1 | T Lymphocytes

In adaptive immunity, activated T lymphocytes play crucial roles by secreting cytokines or directly killing pathogen-infected cells or cancerous cells. For the full activation, spatial and temporal regulation of actin dynamics is crucial at the IS between T cells and APC. Transgelin-2 is essential for T cell effector functions; it stabilizes cortical F-actin cytoskeleton, regulates interactions between actin and other signaling proteins, and enhances LFA-1 integrin affinity and avidity, thereby maintaining the IS. Upon TCR stimulation, it localizes at the d-SMAC along with the F-actin in the IS. It controls the F-actin content, presumably attenuating the spontaneous or cofilin-mediated dissociation of F-actin at the IS. Interestingly, both transgelin-2 and cofilin share the same actin subunit, the SD1 site (also our unpublished results). However, it is striking to note that cofilin and transgelin-2 can potentially function together by occupying distinct locations in the IS rather than competing with each other. Cofilin mainly localizes to the upper region of d-SMAC and generates a large pool of actin monomers by severing and sequestering F-actin at the end of the actin flow, whereas transgelin-2 is rather enriched at the
B Lymphocytes

5.2 | B Lymphocytes

In B lymphocytes, transgelin-2 appears to be less crucial with respect to B-cell activation compared to its essential role in T-cell activation. In response to an antigen bound to BCR, the timing of the actin cytoskeletal reorganization corresponds to both the initiation and maintenance of B-cell stimulation.59–61 Initially, the induction of transgelin-2 as well as its colocalization with the F-actin ring to the periphery of BCR clusters after BCR stimulation implied a positive role for B-cell activation.31 Consistent with this, after antigen-driven B-cell stimulation, upregulation of the expression of some proteins, including the chemokine receptor 6 (CCR6) and Abl-interactor 2 (ABI2), was retarded in transgelin-2-deficient B cells compared to that in wild-type cells,31 and phosphorylation of PLCγ2, an early player in the BCR-signaling cascade, was diminished,31 indicating that transgelin-2 might affect B-cell activation. However, the influence of transgelin-2 in B-cell activation might not be as essential as that in T cells, since PI3K, ERK, and Akt, downstream proteins of phosphorylated PLCγ2, were not affected, and neither of surface molecules such as CXCR5 and BCR was affected.31 Consistent with these results, Na et al. demonstrated that knockout of TAGLN2 had little effect on B-cell functions, as determined by a lack of significant changes in the expression of CD69, MHC class II, CD80, and CD86, all of which are markers of B-cell activation.19 Interestingly, although transgelin-2 shows little influence on B-cell activation, it may be an important regulator for controlling B-cell-mediated T-cell activation. During IS formation, transgelin-2 accumulated at the F-actin-rich filopodia of B cells. It stabilizes T–B conjugates partly by enhancing its adhesion to T cells, which consequently induces T-cell activation.19 In a reverse manner, even though transgelin-2 in B cells has a minor function in B-cell activation, it is still important for B cells as transgelin-2 in T cells facilitates T-cell activation that subsequently activates B cells.15

5.3 | Macrophages

Macrophages serve several essential roles at the initial host defense; they produce inflammatory cytokines and destroy pathogens by phagocytosis, which blocks early dissemination of pathogens.52 Upon TLR-mediated activation, highly induced levels of transgelin-2 in macrophages contribute to the receptor-mediated (FcγR- or CR-mediated) phagocytosis as well as the release of inflammatory cytokines.17 Transgelin-2 enriched in the actin-rich membrane apical region facilitates fMLP-induced actin polymerization and subsequent ruffles and phagocytic cup formation, which are important structures for the phagocytosis of bacteria. In conjunction with the actin remodeling, transgelin-2 is linked to the PI3K/AKT- and ERK-signaling pathways, a well-known actin-linked signaling axis in receptor-mediated activation.63,64 Interestingly, transgelin-2 deficiency significantly retarded the fMLP-induced activation of PI3K, AKT, and ERK, demonstrating an involvement for fMLP-mediated actin reorganization65 in activated macrophages. As a consequence, large-scale transgelin-2 induction can explain the elevated phagocytic activity of activated macrophage. Furthermore, TAGLN2 knockout mice showed higher plasma levels of inflammatory cytokines secreted by macrophages: TNF-α, IL-6, IL-1β, and IL-12, as well as defective bacterial clearance due to damaged phagocytic function, therefore demonstrating the comprehensive influence of transgelin-2 in macrophages.17 As a consequence, TAGLN2 knockout mice showed highly increased susceptibility to bacterial infection.17

6 | TRANSGELIN-2 AS A T CELL BOOSTER FOR IMMUNOTHERAPY

For the management of cancer, cancer immunotherapy exploits the patients’ tumor-specific immunity by several strategies originating from studies on endogenous immune surveillance. Along with immune checkpoint blockades such as anticytotoxic T lymphocyte-associated protein 4-B7-1, B7-2, and antiprogrammed cell death protein 1 (PD1)-PD-L1 axis, one emerging immunotherapeutic regime is an adoptive cellular therapy (ACT) with reactivated tumor-infiltrated lymphocytes (TILs) and chimeric antigen receptor (CAR)-transformed T or NK cells.66,67 However, even though genetic engineering has been broadening the application of ACT, the immunosuppressive tumor microenvironment extensively limits the efficacy of regimes; a lack of costimulatory signals and the presence of inhibitory signals such as PD-L1 in tumor microenvironments inhibit the activation of immune cells.66 One possible strategy to overcome this insufficient costimulation at TILs or CAR-engineered T and NK cells could be the
stabilization of the cytotoxic IS between killer T cells and tumor target cells. Transgelin-2 is a good candidate for this approach, particularly via actin engineering at the T-cell side; upon TCR activation, it potentiates cytotoxic T cell functions through "inside-out" costimulatory LFA-1 activation via Rap1 and F-actin stabilization at the IS.\textsuperscript{15} Its significance is further supported by the fact that CD8\textsuperscript{+} T-cell costimulation requires only high affinity (transgelin-2-Rap1-activated) LFA-1, whereas CD4\textsuperscript{+} T-cell costimulation depends on both high and low affinity LFA-1.\textsuperscript{56} Recently, our group has observed that retroviral transduction of transgelin-2 in adoptively transferred CTLs largely enhanced its antitumor activity in an LFA-1/ICAM-1-dependent manner, targeting ICAM-1-expressed tumor tissues, both in vitro and in vivo (unpublished results). Moreover, the internalization of recombinant transgelin-2 fused with a protein transduction domain showed similar efficacy to viral transduction of transgelin-2 in the same study, thereby indicating the feasibility of recombinant transgelin-2 peptide as an active adjuvant in cell-based immunotherapies, including tumor-specific TILs or CAR-engineered killer cells.

7 | CONCLUDING REMARKS

The mechanisms underlying actin dynamics in a variety of immunological processes are quite sophisticated, involving the ABPs and interlaced signaling pathways. Transgelin-2 is actively involved in the actin cytoskeletal rearrangements and its expression seems to be up- or downregulated in different conditions, including BCR/TCR/TLR stimulation. Although transgelin-2 has been mainly studied within T cells,
B cells, and macrophages, there have been other immune cell types that have been reported to express transgelin-2, such as dendritic cells (DCs). A proteomic analysis of differentially matured DCs demonstrated that transgelin-2 expression was highly upregulated in some DC subpopulations. Moreover, it may be also worth mentioning that the DC cytoskeleton promotes T-cell adhesion and activation via ICAM-1 avidity alteration. In this regard, the function of transgelin-2 in controlling the actin cytoskeleton in B cells, another APC, implies an important role of transgelin-2 in DCs as well. Currently, our group is in the process of investigating how transgelin-2 functions in DCs. Figure 2 summarizes the known and potential functions of transgelin-2 in various immune cells.

The regulation of the actin cytoskeleton is critical both in cancer and CTL functions in immune surveillance, as it controls fundamental tumor-related processes including cell migration (cancer metastasis) and regulates IS formation, respectively. While microtubule, another essential cytoskeletal component, has been largely studied and established as a target for antitumor drugs and chemotherapeutic agents, actin-targeting approaches have yet to gain approval for clinical use, presumably due to the lack of knowledge in targeting tumor-specific pathways and concomitant off-target effects. However, transgelin-2 overexpression in ACT does not affect the actin cytoskeleton and cellular processes in other tissues or cells, as transgelin-2 or its engineered constructs can be transduced or treated ex vivo. The deleterious impact of transgelin-2-overexpressing cytotoxic T cells is not expected because of its endogenous nature in T cells, which has not been reported thus far. Notably, transgelin-2 has been suggested as a promising antitumor drug target in a recent study; its agonist, TSG12, relaxes both human and mice airway smooth muscle cells and reduces pulmonary resistance without detectable toxicity or desensitization. Taken together, transgelin-2-mediated actin and LFA-1-ICAM-1 axis concurrent enhancement may be a safe and potential supplementary regime for conventional cell-mediated cancer immunotherapies. In conclusion, recent studies have shown that transgelin-2 is an important immune regulator in the context of immune cell–cell interaction. Based on its role in CTL activation, an immunotherapeutic regime using transgelin-2 as a synergist of ACT is currently under investigation, and further engineering of transgelin-2 would facilitate translation of this approach from bench to bedside.

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AUTHORSHIP

S.J. and H.R.K. wrote the review. Y.M. created the figures. C.D.J. wrote and finalized the review.

DISCLOSURE

The authors declare no competing financial interests.

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