The Role of Podoplanin in the Immune System and Inflammation

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Abstract: Podoplanin is a small cell-surface mucin-like glycoprotein that participates in multiple physiological and pathological processes. Podoplanin exerts an important function in the immune response and is upregulated in fibroblasts, macrophages, T helper cells, and epithelial cells during inflammation. Herein, we summarize the latest knowledge on the functional expression of podoplanin in the immune system and review the contribution of podoplanin to several inflammatory diseases. Furthermore, we discuss podoplanin as a novel therapeutic target for various inflammatory diseases.

Keywords: podoplanin, immune system, inflammation

Introduction

The immune system and inflammation are essential for clearing pathogens and damaged cells, as well as tissue repair. Acute inflammation is a protective reaction that is beneficial to the organism. However, consistent and uncontrolled immune response and inflammation underly various degenerative diseases. Clinical treatments of these diseases lack biological agents to modify specific inflammatory and effector pathways, which is a promising therapeutic strategy. Podoplanin (PDPN) is a small cell-surface mucin-like glycoprotein, which is widely expressed in different tissues and cell types, such as glomerular podocytes (hence its name), type I alveolar cells, mesothelial cells, and different types of fibroblasts. Podoplanin is involved in multiple physiological and pathological processes, such as embryonic development, immune response, and cancer. Recent evidence indicates that podoplanin expression in immune cells participates in regulation of inflammation during different inflammation-related diseases. Interaction between podoplanin and its protein partners is the mechanism of regulating immune response and mediating inflammatory diseases, which is critical for the clinical treatment of inflammatory diseases.

Podoplanin

Podoplanin is a type I transmembrane sialomucin-like glycoprotein, with a heavily O-glycosylated extracellular domain and a cytoplasmic tail consisting of 9 amino acids. The structure of podoplanin lacks obvious enzymatic motifs and hence, it most likely exerts its cellular functions through protein-protein interactions. Among the many protein ligands of podoplanin, C-type lectin-like receptor 2 (CLEC-2), ezrin, and moesin are studied comprehensively.

CLEC-2 belongs to the family of the non-classical C-type lectins, expressed on dendritic cells, neutrophils, and platelets and to date, podoplanin is the only known endogenous ligand for CLEC-2. The interaction between platelet CLEC-2 and podoplanin is the key for platelet activation and its multiple roles besides hemostasis. The combination of CLEC-2 with the platelet aggregation-stimulating domains in the extracellular domain of podoplanin induces platelet activation through the Src, Syk and SLP-76 kinase pathway. Furthermore, the combination with CLEC-2 is also one
of the important ways for podoplanin to play an inflammatory regulatory role, which we elaborate in detail in the following sections.

Ezrin and moesin, which belong to the ERM (ezrin, radixin, moesin) protein family, can bind to the cytoplasmic domain of podoplanin, involved in cell polarity, adhesion, and migration. The interaction with ERM proteins is crucial for the modulation of small Rho GTPases and podoplanin-mediated rearrangement of the actin cytoskeleton, participating in many physiologic and pathologic processes, such as embryonic development, immune response, and epithelial-mesenchymal transition (EMT).

The main protein partners of podoplanin are presented in Table 1.

### Podoplanin Expression in the Innate and Adaptive Immune Systems

Inflammation underlies many chronic and degenerative disease, triggered by noxious stimuli, such as infection and tissue injury. Generally, a controlled inflammatory response is beneficial, but it can become detrimental if dysregulated. The acute inflammatory response induced by infection or tissue damage is triggered by the innate immune system, in which tissue-resident macrophages and mast cells mediate the initial recognition of stimuli and, subsequently, lead to the production of inflammatory mediators that elicit the exudate of plasma protein and leukocytes (mainly neutrophils). When acute inflammation eliminates harmful stimuli, it enters a resolution and repair phase mediated by tissue-resident and recruited macrophages, which is the main source of growth factors and cytokines that modulate tissue repair. Moreover, the adaptive immune system also plays a critical role in resisting pathogen invasion or insult. The adaptive immune response originates in secondary lymphoid organs (lymph nodes and spleen), generally under innate immune system signals, which are provided either by circulating pathogens directly or indirectly by antigen-presenting cells (APCs) migrating to the secondary lymphoid organs. Then lymphocytes including T and B lymphocytes emigrating from the spleen and lymph nodes travel to many sites in the body to exert effector functions. However, the persistence of pathogens or failure to resolve inflammation may lead to chronic inflammation. Inappropriate adaptive immune response can lead to development of autoimmune diseases, such as rheumatoid arthritis, psoriasis, and multiple sclerosis. Furthermore, lymphangiogenesis is also associated with inflammation. The lymphatic system plays a crucial role in immune defense against infection by transporting immune cells from peripheral tissues to lymph nodes, especially in the rapid activation of adaptive immunity during inflammatory response.

### Table 1 The Main Protein Partners of Podoplanin

| Ligands  | Binding sites with Podoplanin | Functions                                                                 | References       |
|----------|-------------------------------|---------------------------------------------------------------------------|------------------|
| CLEC-2   | Extracellular Domain           | Platelet activation Thrombosis Blood vascular integrity Lymphangiogenesis Immune response Cancer invasion and metastasis | [2,4,16–18]     |
| CCL21    | Extracellular Domain           | Immune response Development of nature Treg cells Tumor immune escape       | [2,19,20]       |
| Galectin-8 | Extracellular Domain               | Lymphangiogenesis                                                        | [21]             |
| CD9      | Transmembrane Domain           | Inhibition of podoplanin-CLEC-2 interaction                               | [22]             |
| CD44     | Transmembrane Domain           | Modulation of cell migration                                              | [23]             |
| ERM      | Cytoplasmic Tail               | Embryonic development Immune response Cancer invasion and metastasis Epithelial-mesenchymal transition | [13–15]         |
It has been well documented that podoplanin expression exists in the innate and adaptive immune systems during inflammation. Podoplanin expression has been reported in CD4+ effector T cells and macrophages. In addition, podoplanin on lymphatic endothelial cells (LECs) and fibroblast-like reticular cells (FRCs) has attracted equal attention.

**Macrophages**

Macrophages are the most plastic cells of the hematopoietic system, found in all tissues and showing good functional diversity. Podoplanin expression exists in particular subsets of macrophages, and this glycoprotein was identified as a marker of a subset of highly phagocytic F4/80+ macrophages in the spleen and peritoneal cavity. Podoplanin is unable to be detected on bone marrow-derived macrophages (BMDMs) and tissue-resident macrophages. Rather, podoplanin expression was upregulated in BMDMs following inflammatory stimulation, such as lipopolysaccharide (LPS), Toll-like receptors agonists and tumor necrosis factor (TNF), which suggests that podoplanin is expressed on inflammatory but not tissue-resident macrophages and its expression is upregulated in response to Toll-like receptor (TLR) stimulation and some inflammatory cytokines.

Studies show that podoplanin expression functionally affects macrophages, including polarization and mobility. Depending on the microenvironment, macrophages can acquire distinct functional phenotypes during inflammation. Two well-established polarization phenotypes are usually called classical activated macrophages (M1 macrophages) and alternatively activated macrophages (M2 macrophages). Fei et al reported podoplanin expression was correlated with mice microglia (macrophage in the brain and spinal cord) activation and phenotypes during neuroinflammation after traumatic brain injury. With hemoglobin treatment as inflammatory stimuli in vitro, knockdown of podoplanin could decrease the proportion of M1-like microglia and increase the proportion of M2-like microglia with reduced secretion of IL-1β and TNF-α and increased secretion of IL-10 and TGF-β. This finding demonstrated that podoplanin could influence the inflammatory phenotype of macrophages.

Furthermore, podoplanin expression also influences the mobility of macrophages. Using a mice sepsis model of cecal ligation and puncture (CLP), Rayes et al demonstrated that podoplanin expression on hematopoietic cells played a role in regulating macrophage recruitment to the infected peritoneum, modulating bacterial load in the peritoneal cavity and limiting subsequent organ damage. Moreover, Bourne et al reported that crosslinking podoplanin using recombinant CLEC-2-Fc limited the inflammatory environment by reducing inflammatory macrophage accumulation in the inflamed tissue during murine peritonitis. Platelet CLEC-2 induces a loss of phosphorylation of the serine residues in the intracellular podoplanin tail, which is associated with a rapid translocation of podoplanin from intracellular stores to the surface of inflammatory macrophages. Additionally, the interaction between podoplanin and CLEC-2 induced the reorganisation of the actin cytoskeleton and increased podoplanin interaction with ERM proteins and CD44, promoting macrophage migration. Cheok et al also proposed that during *Helicobacter pylori* infection, podoplanin drives motility of active macrophages via regulating Filamin C, a member of actin-crosslinking protein family that stabilizes and links actin web to the cell membrane. They demonstrated that podoplanin may promote Filamin C transactivation through interacting with the ERM complex and activating Rho GTPase signaling pathway, but further investigation is required to confirm this notion.

**CD4+ Effector T Cells**

Podoplanin is preferentially expressed on differentiated Th17 cells, rather than on other effector T cell subsets. Interleukin 17-producing helper T (Th17) cells play pathogenic roles in chronic inflammatory and autoimmune diseases, characterized by the production of IL-17A and IL-17F. Podoplanin expression has been confirmed on Th17 cells in the inflamed tissues of mice models of spontaneous SKG arthritis, autoimmune encephalomyelitis, and inflammatory bowel disease. And in vitro, a subset of naive CD4+ T cells expressed significant levels of podoplanin under Th17-polarizing conditions. By immunohistochemical analysis of inflamed synovium in the mice SKG arthritic model, notable numbers of podoplanin-expressing Th17 cells were found to infiltrate these tissues and these podoplanin-positive cells produce IL-17A with destruction of cartilage and bone. However, Nylander et al found that unlike in mice, human podoplanin+ T cells induced under classic Th17-polarizing conditions express transcription factors associated with Th17 cells but do not reflect IL-17 secretion characteristics. In contrast, by qPCR quantitative analysis, the mRNA expression profile of podoplanin+ Th17 cells is consistent with that of nonpathogenic Th17 cells and may be more regulatory.
express higher levels of nonpathogenic Th17 cells genes, including \textit{IL10}, \textit{IL9}, \textit{Ilkzf3}, \textit{Ahr}, and \textit{IL1rn}, and several of these genes are involved in the regulation of IL-10. Additionally, the differentiation of Th17 cells is promoted toward a pathogenic phenotype under a pro-inflammatory condition, such as high salt concentration, with the reduced podoplanin expression and increased IL-17 production. These results were contrary to those reported in mice, suggesting that human podoplanin-positive Th17 cells had a protective effect on inflammation, rather than promoting it.

In order to maintain peripheral and tissue tolerance, self-reactive T effector cells that escape negative selection in the thymus are actively controlled in the periphery by expression of inhibitory cell surface receptors, such as cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1). Podoplanin is a novel co-inhibitory receptor on effector T cells. In contrast to PD-1 and CTLA-4, podoplanin does not have an immunoreceptor tyrosine-based inhibitory motif (ITAM) in its short cytoplasmic tail, which is required for the former to modulate TCR signaling. The TCR signaling is essential for T-cell activation and therefore, podoplanin may not directly interfere with this process. On the other hand, cytokine IL-7 permits long-term survival of memory-precursor \textit{CD4$^+$} T cells after acute activation signals fade. Peters et al used global and T-cell-specific \textit{Pdpn}-deficient mice to demonstrate that podoplanin inhibits T cell responses by reducing responsiveness to IL-7 survival signal. However, the role of podoplanin in Th17 cells is far from clear. Nylander et al reported that ligation of podoplanin by its ligand CLEC-2 ameliorates the Th17 inflammatory response. As podoplanin does not possess an ITAM domain on its cytoplasmic tail to mediate intracellular signaling, it is unknown if there are other intracellular pathways that play a role in intracellular signaling in \textit{CD4$^+$} T cells in response to ligation of podoplanin by CLEC-2, and it is possible that podoplanin may be involved in multiple parallel downstream mechanisms resulting in Th17 regulation.

**Lymphatic Endothelial Cells (LECs) and Fibroblast-Like Reticular Cells (FRCs)**

LECs and FRCs are essential for the migration of antigen-presenting dendritic cells (DCs) from periphery to regional lymph nodes, which initiates adaptive immunity and tolerance. In this process, tissue-resident DCs enter the blind-ended afferent lymphatic vessels, moving along the lymphatic endothelium to reach lymph nodes. Subsequently, DCs crawl along the collagen-based reticular network formed by FRCs to present antigen to effector T cells. Podoplanin is expressed on both LECs and FRCs and participates in the intravasation of DCs into afferent lymphatic vessels and DC migration to and within lymph nodes by several mechanisms. First, podoplanin on LECs immobilizes the chemokine CCL21 in the lymphatic endothelium and upregulates the expression of the chemokine receptor CCR7 on DCs, which can bind CCL21 to promote DC adhesion to the endothelium and transmigration into the lumen of the vessel. Second, podoplanin on LECs and FRCs, which link frameworks that support migratory DCs from tissues to lymph nodes, can interact with CLEC-2 on DCs, coordinately stimulating Rac1 and reducing RhoA GTPase activity via a signaling pathway downstream of CLEC-2 similar to that of platelet activation. This process leads to changes in the dynamics of the actin cytoskeleton, resulting in DC spreading along stromal cell scaffolds and migration.

Furthermore, podoplanin appears to functionally affect LECs and FRCs. Previous research revealed that platelets inhibit LEC proliferation and migration through the CLEC-2-podoplanin interaction, in which BMP-9, a member of the bone morphogenetic protein (BMP) subfamily of TGF-β growth factors, plays a crucial role. Knockdown of podoplanin in human LEC inhibits polarization and migration mediated by upregulation of Cdc42 and downregulation of RhoA GTPase activity. Additionally, Kasinath et al studied the role of podoplanin-positive FRCs in nephrotoxic serum nephritis (NTN), a classic experimental anti–glomerular basement membrane antibody-mediated model of crescentic glomerulonephritis. Neutralization of podoplanin by an anti-podoplanin antibody inhibited the constitutive extracellular matrix fiber-secreting properties of FRCs, resulting in a disorganized fiber network and reduced expansion of lymphatic vasculature, which prevents the activation of \textit{CD4$^+$} T cells. Astarita et al demonstrated that podoplanin appears to affect physical elasticity of lymph nodes by regulating FRCs function in the reticular network. Under resting conditions, when FRCs are unlikely to encounter mature DCs expressing CLEC-2, podoplanin induces actomyosin contractility in FRCs via activation of RhoA/C and downstream Rho-associated protein kinase (ROCK). During inflammation, CLEC-2 on mature DCs rapidly uncouples podoplanin from RhoA/C activation, relaxing the actomyosin cytoskeleton and permitting FRC stretching. Podoplanin-CLEC-2 interaction allows FRC network stretching and lymph node expansion, which is a critical hallmark in adaptive immunity.
Podoplanin in Tissue and Organ Injury

The secondary inflammation after tissue injury is correlated with the expression of podoplanin. Kolar et al found that podoplanin was upregulated in reactive astrocytes in tumor and non-tumor brain injury models.\(^57\) Moreover, Song et al found upregulation of podoplanin in neurons rather than astrocytes involved in neuronal apoptosis in a LPS-induced neuron inflammatory model.\(^58\) These differences could be explained by the different models used in the two studies but still fail to further reveal the role of podoplanin in neuroinflammation. Using a mouse traumatic brain injury model, Fei et al confirmed the upregulated podoplanin on microglia rather than neurons or activated astrocytes in vivo, and in vitro, podoplanin in primary microglia was substantially elevated by inflammatory stimuli, such as ATP, LPS, H₂O₂, and hemoglobin (Hb).\(^35\) Interestingly, as we referred before, knockdown of podoplanin in primary microglia prevented the induction of the M1 phenotype and elevated the proportion of M2 phenotype cells after stimuli of Hb, with the reduced secretion of IL-1β and TNF-α and increased secretion of IL-10 and TGF-β, which suggests podoplanin might act as an inflammation sensor in microglia.\(^35\)

Growing evidence shows that LPS could induce upregulation of podoplanin on inflammatory macrophages and podoplanin-positive inflammatory macrophages play a key role in regulating inflammation via directly contacting platelets. Lax et al reported the podoplanin-CLEC-2 interaction protects against lung injury in a mouse model of LPS-induced acute respiratory distress syndrome. They reported a decline in arterial oxygen saturation and an augmentation of proinflammatory cytokines in bronchoalveolar lavage (BAL) in response to IT-LPS in hematopoietic-specific podoplanin-deficient mice, which indicates that podoplanin expression on inflammatory alveolar macrophages (iAM) prevents exaggerated lung inflammation.\(^59\) Further, Lax et al speculated that in alveolar space, CLEC-2 expressed on platelets interacts with podoplanin on inflammatory alveolar macrophages (iAM) to regulate matrix metalloproteinase (MMP)-12 release, which can cleave and inactivate CXC chemokines, resulting in “off” signals during acute lung inflammation and limiting lung injury.\(^59,60\) Similarly, using two mouse models of sepsis—intraperitoneal lipopolysaccharide and cecal ligation and puncture, Rayes et al demonstrated a protective role for podoplanin-CLEC-2 interaction in regulating the inflammatory reaction and preserving organ function in sepsis.\(^36\) In vitro, expression of podoplanin on inflammatory macrophages regulates the expression of TNF-α, with disruption of the podoplanin-CLEC-2 interaction by anti-podoplanin antibody in vivo altering cytokine and chemokine expression by inflammatory macrophages, including CXCL-1, CCL-2, and IL-6.\(^36\) These studies suggest that podoplanin on inflammatory macrophages appears to exert a protective or regulatory role in inflammation against pathogen insult. The upregulation of podoplanin on macrophages is common in several models of LPS-induced tissue injury. However, the intracellular pathway of podoplanin upregulation remains unclear and further studies are necessary to reveal the downstream mechanism of podoplanin affecting macrophage function.

Ischemia-reperfusion injury (IRI) contributes to a wide range of pathologies, such as myocardial infarction, ischemic stroke, and acute kidney injury, and it is also a major challenge during organ transplantation and cardiothoracic, vascular, and general surgery.\(^61\) Studies have shown the upregulation of podoplanin expression after ischemia in various tissues. Meng et al reported the role of the podoplanin-CLEC-2 axis in promoting the inflammatory response after ischemic stroke in mice via a mouse middle cerebral artery occlusion (MCAO) model.\(^62\) Podoplanin on both neurons and microglia was notably upregulated after ischemia-reperfusion and anti-podoplanin antibody pretreatment notably attenuated neurological deficits and decreased infarct volume, significantly decreasing the expression of IL-1β and IL-1β.\(^62\) Besides, Meng et al speculated that the production of IL-18 and IL-1β is attributed to the activation of NLRP3 inflammasome via the podoplanin-CLEC-2 axis.\(^62\) In kidney, Kasinath et al recently found that the immunofluorescent signal of podoplanin fades in the glomerulus and intensifies in the tubulointerstitial compartment of the kidney shortly after ischemia-reperfusion injury, which is mediated by the podoplanin-positive podocytes and spindle-shaped cells.\(^63\) The podocytes may encapsulate podoplanin in extracellular vesicles and expel it into the urine immediately after IRI, while podoplanin-positive spindle-shaped cells, which morphologically resemble fibroblasts, may support the growing vasculature in the kidney during the repair phase after IRI.\(^63\) More importantly, podoplanin can be detected in the urine immediately after IRI and increases with the severity of ischemia, which suggests that the measurement of urine podoplanin represents a promising possible solution to the current important unmet clinical need for the expedient identification of renal IRI.

In addition, during tissue injury, monocytes-macrophages are able to functionally affect platelets through the podoplanin-CLEC-2 axis. In a mouse model of systemic Salmonella typhimurium infection, Hitchcock et al demonstrated that infection-induced IFN-γ release increases podoplanin expression on monocytes and Kupffer cells in the hepatic
Podoplanin in Chronic Inflammatory Autoimmune Diseases

Autoimmune diseases, such as multiple sclerosis (MS), rheumatoid arthritis (RA), and colitis, are characterized by the dysregulation of the immune system which finally results in the break of tolerance to self-antigen. Immunosuppressive agents tried in autoimmune disease patients nonspecifically suppress the immune response, but often cause various side effects. Utility of biological agents to modify specific inflammatory and effector pathways is a promising therapeutic strategy in treating autoimmune diseases. The agents of blocking TNF-α were approved firstly for therapeutic drugs. However serious side effects result in unsatisfactory long-term prognoses and confined availability. Therefore, it is urgent to explore new therapeutic targets and strategies for chronic inflammatory autoimmune diseases.

CD4+ T helper cells play pivotal roles in the tissue destruction of many inflammatory autoimmune diseases, such as MS, RA, systemic sclerosis, and inflammatory bowel diseases. Autoimmune diseases are driven by self-reactive T helper Th1 and Th17 cells, and the latter can be heterogeneous and differentiate into two functional subtypes depending on the environmental stimuli. During inflammatory autoimmune diseases, Th17 cells can be highly proinflammatory, which induces irreversible tissue damage. Commonly, an association is made between Th17 cells and the secretion of IL-17, which is a pro-inflammatory cytokine involved in several chronic inflammatory diseases. A recent study indicates that interaction among activated lymphocytes and RA synoviocytes is critical for a high IL-17 secretion depending on the co-culture experiments with phytohemagglutinin-activated peripheral blood mononuclear cells (PBMCs) and synoviocytes isolated from patients with RA. However, both Th17 cells and synoviocytes express podoplanin with the respective involvement in IL-17 secretion. As we mentioned before, podoplanin can negatively regulate CD4+ effector T cell functions through podoplanin-CLEC-2 interaction and a high podoplanin expression was found on nonpathogenic Th17 lymphocytes. Hence, podoplanin displays two divergent functions which may depend on different ligands. Ligands such as CLEC-2 may mediate Th17 cell inhibition while another ligand, perhaps unknown, could promote inflammation by stimulating pro-inflammatory cytokine production.

The ectopic lymphoid follicle-like structure, characterized by the compartmentation of T and B cells and the presence of lymphatic vessels and high endothelial venules (HEVs), is a key factor in the pathogenesis of autoimmune diseases. The presence of ectopic lymphoid follicle-like structures is associated with the expression of podoplanin. In experimental autoimmune encephalomyelitis (EAE), the animal model of MS, development of ectopic lymphoid follicles was partly dependent on IL-17 and podoplanin, which was expressed on Th17 cells. Anti-podoplanin polyclonal antibody treatment reduced the number of ectopic lymphoid follicles. However, whether the blocking of podoplanin on Th17 cells or on other cell types including macrophages, stromal, and parenchymal cells leads to the reduction in ectopic lymphoid follicles remains to be determined. Moreover, in both clinical and experimental RA, podoplanin-expressing Th17 cells are associated with the formation of synovial ectopic lymphoid follicles and IL-27 inhibited the differentiation of podoplanin-expressing Th17 cells, negatively regulating ectopic lymphoid follicles development. Besides Th17 cells, expression of podoplanin in synoviocytes is also associated with ectopic lymphoid follicles and inflammation. Activated fibroblast-like synoviocytes (FLSs) in RA are key mediators of synovial tissue transformation and joint destruction. These aggressive cells share many characteristics with tumor cells, such as upregulated expression of proto-oncogenes and promigratory adhesion molecules, increased production of proinflammatory cytokines and matrix-degrading enzymes, as well as increased resistance to apoptosis. This is reminiscent of podoplanin upregulated in the invasive front of several human cancers, which is associated with epithelial-mesenchymal transition, cell migration and increased tissue invasion. In fact, podoplanin is highly expressed in FLSs of the invading synovial tissue in RA and pro-inflammatory mediators increased the podoplanin expression in cultured RA-FLS. Podoplanin-positive human synovial fibroblasts also exhibit characteristics of highly invasive myofibroblasts. In addition, in a severe combined immunodeficiency mouse model of RA, podoplanin-expressing synovial fibroblasts are associated with early
fibroblast migration and cartilage erosion.\textsuperscript{83} These results together indicate that podoplanin-expressing synoviocytes play a critical role in joint destruction.

### Podoplanin in Inflammatory Lymphangiogenesis

Lymphatic vessels play a critical role in fluid balance, nutrient absorption, and immune surveillance. Lymphangiogenesis is actively involved in a number of pathological processes including tissue inflammation and tumor dissemination.\textsuperscript{84} The key regulatory signaling axis that induces lymphangiogenesis is vascular endothelial growth factor receptor-3 (VEGFR-3) and its ligand, VEGF-C.\textsuperscript{85} Improved knowledge of the molecular mechanisms controlling lymphangiogenesis is attributed to progress in the identification of regulatory molecules and markers specific to the lymphatic endothelium. Physiologically, podoplanin expressed by LECs promotes blood-lymph separation and mice lacking podoplanin have leaky lymphatic vessels and congenital lymphedema.\textsuperscript{86,87} It has been reported that podoplanin is expressed in two lymphatic endothelial sublineages in human skin, which were defined by their cell surface densities of podoplanin and were designated LEC podo-low and LEC podo-high. LEC podo-low exists in precollector lymphatic vessels that secrete CCL27 and attract inflammatory CCR10-positive T lymphocytes, whereas LEC podo-high is restricted to initial lymphatic vessels, which produce CCL21 and attract CCR7-positive dendritic cells and regulatory T cells (Tregs).\textsuperscript{88} The differential podoplanin expression in both lymphatic endothelial sublineages appears to be negatively regulated by Notch signaling.\textsuperscript{89}

Galectin-8 is a tandem-repeat type member of the galectin family and in vitro studies have shown that galectin-8 binds to podoplanin and that the lectin promotes adhesion and haptotaxis of LECs.\textsuperscript{90} A recent work showed that podoplanin is a key player in VEGF-C-induced lymphangiogenesis. Chen et al found the upregulated galectin-8 expression in the inflamed human and mice corneas working as a key medium for VEGF-C signal transduction and an effective lymphangiogenesis factor in vivo through a mechanism involving the interaction with podoplanin and integrin.\textsuperscript{21} They demonstrated that galectin-8 has a unique dual-faceted mechanism of action to promote lymphangiogenesis, where galectin-8-mediated interactions between lymphangiogenic integrins (α1β1/α5β1) and podoplanin are sufficient to activate the integrins and trigger the process of lymphangiogenesis without the involvement of VEGFR-3, but in the presence of VEGF-C/VEGFR-3, podoplanin-galectin-8-integrin interactions substantially increase the magnitude of the lymphangiogenic pathway by potentiating VEGF-C/VEGFR-3 signaling.\textsuperscript{21}

Additionally, a previous study found that human CD34\textsuperscript{+} cells derived from fetal liver expressed podoplanin and VEGFR-3, which constitute a phenotypically and functionally distinct population of endothelial stem and precursor cells that may play a role in postnatal lymphangiogenesis.\textsuperscript{91} Lee et al also reported a novel type of bone-marrow-derived podoplanin-positive cells, which function as lymphatic endothelial progenitor cells and participate in postnatal lymphatic neovascularization through both vasculogenesis and lymphangiogenesis.\textsuperscript{92} Subsequent research found that induced by inflammatory stimuli including fibronectin, VEGF-C, TNF-α, LPS, or IL-3 in vitro, monocytes can transdifferentiate into lymphatic endothelial cells, expressing podoplanin and other lymphatic endothelial markers.\textsuperscript{93} Moreover, Maruyama et al reported that the CD11b\textsuperscript{+} and F4/80\textsuperscript{+} macrophages of mice, which express podoplanin, LYVE-1 and VEGFR-3 lymphatic markers, incorporate into lymphatic vessels in the inflamed cornea, playing a critical role in inflammatory lymphangiogenesis.\textsuperscript{94,95} Similar to corneal inflammation, the same researchers also found that lymphatic vessels that form during wound repair in diabetic mice are comprised largely of F4/80\textsuperscript{+} macrophages cells, which express LYVE-1 and podoplanin.\textsuperscript{96} These studies together indicate that podoplanin-positive cells from circulation and bone marrow function as progenitors of LECs, which are essential for lymphatic neovascularization under pathological conditions. On the other hand, Cimini et al firstly described a heterogeneous podoplanin-expressing cardiac interstitial cells population associated with inflammatory responses, fibrogenesis, and lymphangiogenesis after myocardial infarction.\textsuperscript{97} In fact, these podoplanin-expressing cells also contain a population with progenitor capabilities and distinctly display epitopes of fibrogenic and endothelial commitment, suggesting an alternative ability to lymphangiogenesis and pro-fibrosis.\textsuperscript{97,98}

The main inflammatory diseases podoplanin is involved in are summarized in Figure 1.

### Podoplanin as a Potential Therapeutic Target in Inflammatory Disease

Previous studies showed that CAR-T cells, antibodies and lectins that target podoplanin can inhibit the growth and progression of several cancers in animal models, such as mesothelioma, glioma, and squamous cell carcinoma.\textsuperscript{99–102} In view of the critical role of podoplanin in the immune system and inflammatory disease, targeted podoplanin to regulate
inflammation also represents a novel therapeutic strategy. The majority of podoplanin structure consists of a highly glycosylated extracellular domain that impacts podoplanin signaling and can be targeted by antibodies and lectins. Firstly, Galectins can bind podoplanin and the interaction between podoplanin and Galectin-8 is involved in pathological lymphangiogenesis. Hence, using plant lectins to interfere with the interaction between galectins and podoplanin may impede activation of downstream signaling pathways. The extracellular domain of podoplanin contains oligosaccharides, which are modified by the addition of sialic acid. Notably, MASL can preserve the structure and function of cartilage under osteoarthritis insults by interfering with the function of α-2,3-sialylated transmembrane receptors podoplanin. On the other hand, antibodies can be utilized to disrupt podoplanin-CLEC-2 interaction. Treatment with podoplanin-neutralizing antibody inhibits the interaction between podoplanin and CLEC-2 expressing immune cells in the heart, which can enhance the cardiac performance, regeneration, and angiogenesis after MI. Moreover, pharmacologic inhibition of the podoplanin-CLEC-2 axis by the anti-podoplanin antibody mAb 8.1.1 regulates the inflammatory reaction and immune cell infiltration during sepsis without inducing bleeding in the peritoneal cavity.

These observations together suggest podoplanin as a novel anti-inflammatory target regulating immune cell recruitment and activation.

**Conclusion and Outlook**

Researchers have studied podoplanin for over 30 years. In this review, we elaborate the podoplanin expression in immune system and the regulatory role of podoplanin in inflammation. However, the pathological role of the glycoprotein in inflammation is far from elucidated. It remains to be established which is the additional ligand of podoplanin and the identification of novel ligands is beneficial to better explain the mechanism of podoplanin in inflammation immune cell recruitment, polarization and activation. In addition, the upregulation of podoplanin in inflamed tissue is common in several models of inflammatory tissue injury, but the intracellular pathway of podoplanin upregulation remains unclear. The function of podoplanin in immune response remains controversial and further studies should put more effort in revealing the function of podoplanin in macrophages polarization, regulation of effector T cells and the interaction
between lymphocytes and mesenchymal cells. Also, the involvement of podoplanin in lymphangiogenesis deserves more in-depth research. These will notably improve our knowledge on the function of podoplanin in immunity and inflammation and lay the foundation for developing new therapeutic strategies.

**Abbreviations**

PDPN, podoplanin; CLEC-2, C-type lectin-like receptor 2; EMT, epithelial-mesenchymal transition; APC, antigen-presenting cell; LEC, lymphatic endothelial cell; FRC, fibroblast-like reticular cell; BMDM, bone marrow-derived macrophage; LPS, lipopolysaccharide; TNF, tumor necrosis factor; TLR, Toll-like receptor; CLP, cecal ligation and puncture; Th17 cell, interleukin 17-producing helper T cell; ITAM, immunoreceptor tyrosine-based inhibitory motif; DC, dendritic cell; BMP, bone morphogenetic protein; NTN, nephrotoxic serum nephritis; Hb, hemoglobin; BAL, bronchoalveolar lavage; iAM, inflammatory alveolar macrophage; MMP, matrix metalloproteinase; IRI, ischemia-reperfusion injury; MCAO, middle cerebral artery occlusion; MS, multiple sclerosis; RA, rheumatoid arthritis; PBMC, peripheral blood mononuclear cell; HEV, high endothelial venules; EAE, experimental autoimmune encephalomyelitis; FLS, fibroblast-like synoviocyte; VEGFR, vascular endothelial growth factor receptor; Treg, regulatory T cell.

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