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Extracellular matrix molecules associated with lymphatic vessels in health and disease

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Summary. Lymphatic vessels (LyVs), responsible for fluid, solute, and immune cell homeostasis in the body, are closely associated with the adjacent extracellular matrix (ECM) molecules whose structural and functional impact on LyVs is currently more appreciated, albeit not entirely elucidated. These molecules, serving as a platform for various connective tissue cell activities and affecting LyV biology should be considered also as an integral part of the lymphatic system. Any alterations and changes in ECM molecules over the course of disease impair the function and structure of the LyV network. Remodeling of LyV cells, which are components of lymphatic vessel walls, also triggers alterations in ECM molecules and interstitial tissue composition. Therefore, in this review we aimed to present the current knowledge on ECM in tissues and particularly on molecules surrounding lymphatics in normal conditions and in disease.

Key words: Collagens, Elastin, Glycosaminoglycans, Hyaluronan, Basement membrane, Anchoring filaments, Primary valve, Lymph formation, Lymph propulsion

Introduction

The LyV network is present in almost all organs in the body, and it plays a crucial role in fluid and solute homeostasis and immune cell surveillance (Vuorio et al., 2017; Breslin et al., 2018; Brakenhielm and Alitalo, 2019; Oliver et al., 2020). This network is associated with the adjacent ECM more closely than the blood vessel network. LyVs are simply "anchored" to the ECM molecules and rely functionally on these molecules.

The composition and three-dimensional structure of

Abbreviations. AnchF, anchoring filaments; AGE, advanced glycation end products; Angiopoietin 2, Ang 2, a growth factor belonging to the angiopoietin/Tie signaling pathway, one of the main pathways involved in angiogenesis, different from VEGF-dependent pathway; APCs, Antigen-presenting cells; BM, basement membrane; BEC(s), Blood endothelial cell(s); CRSBP-1, Cell-surface retention sequence-binding protein-1; DC(s), Dendritic cell(s); DDR1, Discoidin Domain Transmembrane receptor 1 – a receptor for collagens I, III, and IV; ECM, extracellular matrix; FGF, fibroblast growth factor; FBN(s), Fibrillin(s); FBLN(s), Fibulin(s); FMOD, Fibromodulin; FN, Fibronectin; Foxc2, a transcription factor that belongs to the forkhead family and is characterized by a distinct DNA-binding forkhead domain, crucial for lymphangiogenesis, especially lymphatic valve formation; GAG(s), glycosaminoglycan(s); Galectins, i.e., Gal-9, galectin-9; GATA2, or GATA-binding factor 2 is a transcription factor, i.e., a nuclear protein which regulates the expression of many genes that are critical for the embryonic development, self-renewal, maintenance, and functionality of blood-forming, lymphatic system-forming, and other tissue-forming stem cells; HA, hyaluronan, hyaluronic acid; HARE/Stabilin 2, Hyaluronan receptor for endocytosis; HSPG2 (=perlecan), Heparan sulfate proteoglycan 2; HTRA3, Htra serine peptidase 3; ICAM-1, Intercellular Adhesion Molecule 1; LEC(s), lymphatic endothelial cell(s); LOX, lysyl oxidase; LTBP, latent TGF-β binding protein(s); LyV(s), lymphatic vessel(s); *Lam(a4, a5, b1, b2, c)*, Laminin genes; Lyve-1, lymphatic vessel endothelial hyaluronan receptor-1; MMP(s), matrix metalloprotease(s); MCP1, monocyte chemotactic protein 1; MetS, metabolic syndrome; MW, molecular weight; MT1-MMP, membrane-type matrix metalloprotease; *Nid1*, nidogen 1 gene; OSS, oscillatory shear stress; Polydom, Svep, Sushi, von Willebrand factor type A, EGF and pentraxin domain-containing protein 1; RASA-1, RAS p21 protein activator 1; sGAG, sulfated GAG; SMC(s), smooth muscle cell(s); TEM, transmission electron microscopy, -ic; TNXB, tenascin XB; TNS1, Tensin 1, is located in cell adhesions and links the cytoskeleton with ECM proteins transmitting signals from tissue environment to intracellular compartment; Tie 2, Tie2 receptor, a tyrosine kinase receptor containing epidermal growth factor homology motifs, immunoglobulin-like loops, and fibronectin type III repeats, expressed in endothelial cells and hematopoietic cells; VEGF-C, vascular endothelial growth factor C; VEGFR-3, vascular endothelial growth factor receptor 3; VCAM-1, vascular cell adhesion molecule 1.

ECM influence LyV developmental biology and LyV function in normal conditions and in disease states such as benign and malignant tumors, infections, and non-infection-related diseases, including metabolic syndrome (MetS). MetS is a spectrum of clinical disorders with increasing prevalence world-wide and, therefore, is currently considered as a global non-infectious pandemic. There is a growing interest in LyVs, as this vascular network is is recognized as a player in disbalanced fluid, solutes and immune cell tissue homeostasis in the progression of various diseases, including MetS; however, the relationship between LyVs and the condition of the adjacent ECM has been so far poorly explored. Therefore, the topic of this review is to present the current knowledge on ECM in relation to LyVs in various tissues in normal conditions and in diseases.

Lymphatic vessels

The lymphatic vessel hierarchical system is composed of blind-ended initial capillaries, precollector vessels, collectors, and lymphatic trunks. Between precollectors/collectors and major lymphatic trunks there are lymph nodes that filter lymph and facilitate immune cell function. Initial capillaries absorb fluids and solutes from the interstitial tissue and serve as a way for transmigration of inflammatory/immune cells to the vessel lumina. Initial lymphatics, which are composed only of lymphatic endothelial cells (LECs) devoid of, or partially covered with, basement membrane (BM), are characterized by connections between adjacent individual LECs in the form of "button" junctions (Baluk et al., 2007). Between the adjacent "buttons," endothelial cells form flaps by overlapping or interdigitation. These opening flaps are called primary valves or microvalves, since they act as LyV absorbing units (Schmid-Schonbein, 1990; Trzewik et al., 2001; Azzali, 2007; Lynch et al., 2007). Capillaries coalesce to larger precollector/or collector vessels, which are covered by a discontinuous or continuous layer of smooth muscle cells (SMCs), thick continuous BMs, and are endowed with luminal valves (called also secondary valves) that prevent lymph backflow. The LECs of precollector/collector vessels have "zipper"-like (continuous) intercellular junctions (Baluk et al., 2007).

LyVs are "embedded" in the ECM, which, along with the interstitial fluid, constitute the LyV environment. Changes in composition and organization of all ECM components affect LyV development and function in normal conditions and in disease.

The LECs of initial capillaries are connected to the adjacent components of the ECM via unique structures called anchoring filaments (AnchFs), which are specific only to mature LECs of initial vessels (Leak and Burke, 1968; Leak et al., 1978; Ryan, 1989; Solito et al., 1997; Grimaldi et al., 2006).

The propulsion of chyle through lymphatic capillaries is believed to be stimulated by actively moving or contractile tissues, such as the myocardium and/or adjacent coronary vessels, the diaphragm, skeletal muscle, or lungs during respiratory movements. Moreover, ECM components may play a role in mediating these movements by transforming mechanical forces onto LyVs (Breslin, 2014; Oliver et al., 2020).

ECM components and their relationship with LyVs

The ECM provides a scaffolding that consists of multiple individual molecules whose interaction, 3-D architecture, and biomechanical properties are crucial for controlling a variety of cellular activities and properties, including cell differentiation, migration, proliferation, adhesive properties, intercellular junction integrity, intercellular exchange signals, shape changes, cell metabolic profiles (Zhang et al., 2005; Wick et al., 2007; Danussi et al., 2008; Koyama et al., 2008; Avraham et al., 2009; Cueni and Detmar, 2009; Kruegel and Miosge, 2010; Wiig et al., 2010; Bos et al., 2011; Cursiefen et al., 2011; Paupert et al., 2011; Danussi et al., 2012; Wiig and Swartz, 2012; Danussi et al., 2013; Lutter and Makinen, 2014; Wu et al., 2014; Jung et al., 2015; Mitsi et al., 2015; Greiwe et al., 2016; Frye et al., 2018; Kumaravel et al., 2020). There is a balanced communication loop between LyV walls and the ECM, which can be disrupted under specific conditions, e.g., inflammation, hypoxia, infections, obesity, hypertension, and other MetS-related symptoms.

The ECM forms a structural and mechanical environment that is particularly important for LyV activities and is composed mainly of fibrillar collagens, elastin fibers, glycosaminoglycans (GAGs, i.e., hyaluronan), proteoglycans, and such molecules as emilin, fibronectin (FN), fibrillins (FBNs), vitronectin, thrombospondin, or laminins (Ryan, 1989; Gerli et al., 1990, 1991; Oh et al., 1997; Sawa et al., 1998; Vainionpaa et al., 2007; Kruegel and Miosge, 2010; Ou et al., 2010; Wiig et al., 2010; Paupert et al., 2011; Wiig and Swartz, 2012; Lutter and Makinen, 2014; Jha et al., 2018; Janardhan et al., 2022; Wilting et al., 2022). Moreover, the ECM serves as a reservoir for growth factors, hormones, nutrients, electrolytes, metallopro-teases, waste metabolic products, secreted by LECs, blood vessel cells, epithelial cells, and other connective tissue cells, including mesenchymal cells (Wiig et al., 2010; Brakenhielm and Alitalo, 2019; Oliver et al., 2020). LECs interact with ECM components or immune cells via specific receptors, such as LYVE-1 and integrins (transmembrane linkers between extracellular ligands and cytoskeleton) (Teijeira et al., 2013; Jackson, 2019b; Stanly et al., 2020) (Fig. 1).

Collagens (I and III)

LyVs are surrounded by collagen fibers consisting mostly of collagen type I and III. Of interest, LyVs that accompany larger blood vessels (such as coronary arteries) are in fact embedded in the adventitia, a blood

vessel layer known to be rich in collagen fibers (Fig. 2). As LyVs are involved in cholesterol removal from the interstitium transporting it to the blood circulation (Lim et al., 2013), periadventitial LyV-mediated cholesterol transport has been suggested to reduce atherosclerosis by means of cholesterol uptake from arterial plaque-resident macrophages (Martel et al., 2013; Csányi and Singla, 2019). LECs are not directly involved in these types of collagen synthesis and deposition; however, they are active in collagen processing, fiber stability, and cross-linking, as has been recently demonstrated by *in vitro* human LEC cultures (Kalucka et al., 2020; Becker et al., 2021; Wilting and Becker, 2022). The expression of transcripts and some proteins associated with collagen processing is elevated in LECs cultured in hypoxic conditions which lead to lymphedema (Wilting and Becker, 2022). The relevant molecules include

procollagen-lysin 2-oxoglutarate 5-dioxygenase 2 (PLOD2) and prolyl 4-hydroxylase subunit alpha 1 (P4HA1), the enzymes which are responsible for hydroxylation of lysine and proline during collagen synthesis, respectively, lysyl oxidase (LOX), an enzyme involved in cross-linking of collagen molecules (Laczko and Csiszar, 2020), lysyl hydroxylase and trans-glutaminase (Wells, 2008), and other molecules involved in the regulation of the compactness, cross-linking, packing, assembly, and cohesion of collagen fiber bundles: fibromodulin (FMOD) and tenascin-XB (TNXB) (Svensson et al., 1999; Lethias et al., 2006; Egging et al., 2007; Mormone et al., 2012; Wilting et al., 2022). Moreover, LECs isolated from patients with skin lymphedema exhibit alterations in these transcripts and their relevant proteins when studied by *in situ* labeling of LyVs (Becker et al., 2021).
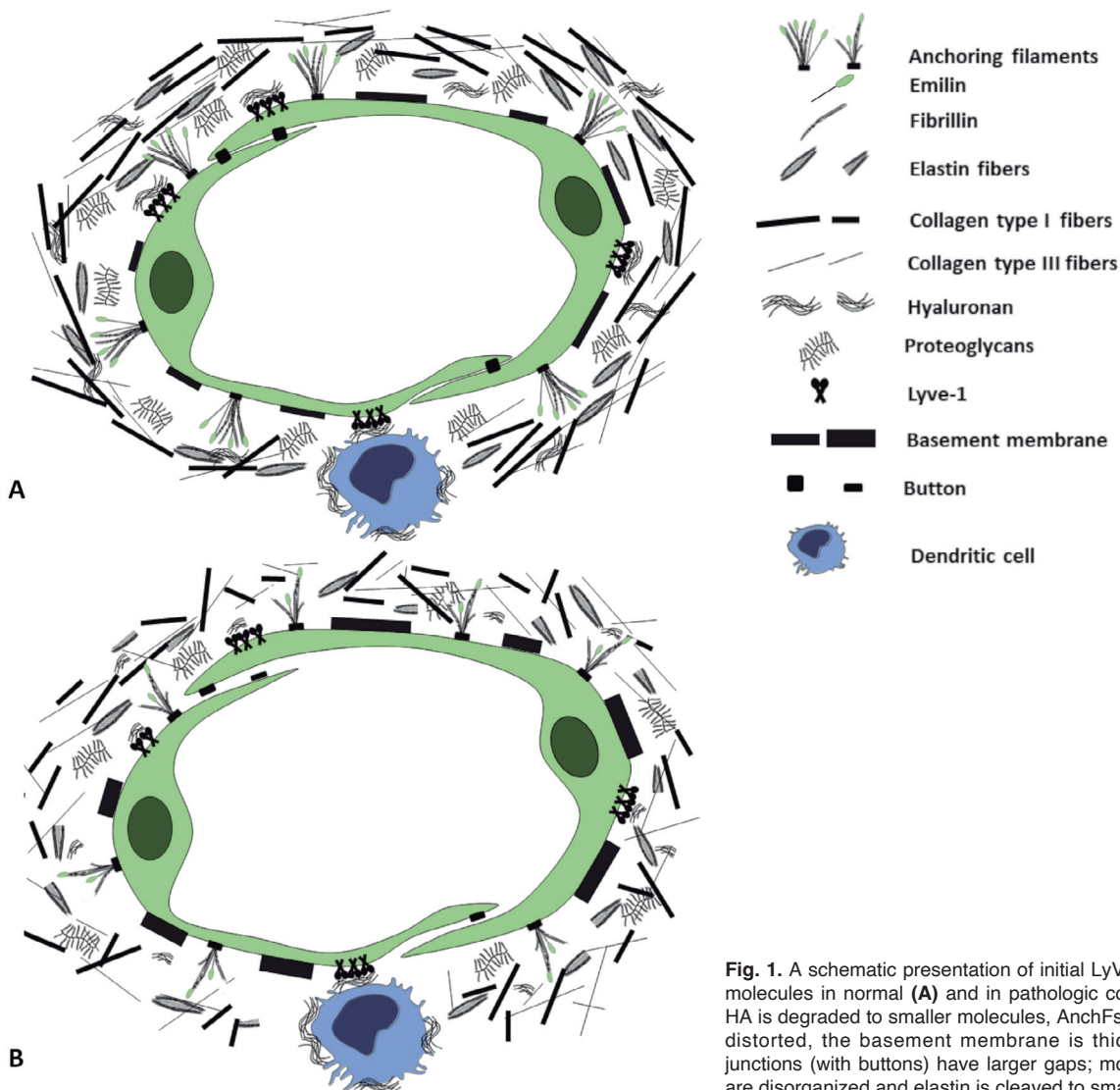

Fig. 1. A schematic presentation of initial LyVs and associated ECM molecules in normal **(A)** and in pathologic conditions **(B)**. Note that HA is degraded to smaller molecules, AnchFs are less abundant and distorted, the basement membrane is thicker, and intercellular junctions (with buttons) have larger gaps; moreover, collagen fibers are disorganized and elastin is cleaved to smaller molecules.

It is not clearly demonstrated whether collagen I and III bind directly to LECs. Discoidin domain transmembrane receptor 1 (DDR1), known to bind collagens I, III, and other types of collagens, such as BM collagen IV (Shrivastava et al., 1997; Vogel et al., 1997), is involved in the regulation of lymphangiogenesis, as demonstrated in an experimental model of corneal injury lymphangiogenesis. Interaction of collagen I with DDR1 is indispensable for lymphangiogenesis, whose inhibition is mediated by miR199a/b-5p (Oh et al., 2018). Moreover, the integrin α2 transcript product has been recently detected in a population of LECs within mouse lymph nodes (Fujimoto et al., 2020). Heterodimeric integrin α2/β1 binds collagen I and III to the cell membrane (Popova et al., 2007). Therefore, collagens I and III may play important roles in nodal LyV functions, apart from serving as a scaffolding for LyVs.

Matrix metalloproteinases (MMPs) are key regulators of ECM remodeling via their effect on ECM degradation. LECs produce MT1-MMP (Membrane-type matrix metalloproteinase 1), MMP-2 and MMP-9 (Nakamura et al., 2004; Bruyere et al., 2008). The relevant transcripts are upregulated when LECs are cultured under hypoxic conditions (Becker et al., 2021). These are MMP1, which cleaves helical domains of major types of collagens (Goldberg et al., 1986), and HtrA serine peptidase 3 (HTRA3), known to digest decorin and biglycan, molecules involved in collagen I fiber assembly (Schönherr et al., 1998; Glaza et al., 2015). Degradation of these glycoproteins, known to be tightly bound to collagens, and observed in lymphedema, elucidates abnormal organization, i.e., haphazardly oriented collagen fibers in this pathology (Karayi et al., 2020; Becker et al., 2021).

It has been demonstrated that a deficiency of MMP2, but not of MMP9, impairs LECs sprouting *in vitro* (Bruyere et al., 2008), which suggests that MMP2 plays a role in lymphangiogenesis. Moreover, MMP2 seems to be crucial and indispensable for LyV sprouting, migration, and branching, as demonstrated in various models of lymphangiogenesis. MMP-2 is involved in the "tunneling process" associated with new LyV formation. The tunneling process is intensive remodeling of the ECM consisting mostly of cross-linked collagen I, which facilitates the migration and alignment of endothelial cells into tubules by activating a mesenchymal-like LEC migration program (Detry et al., 2012).

Of interest, a sustained edema triggers fibrosis in the interstitium, which results in an increased tissue stiffness, as observed in skin lymphedema often associated with fatty tissue deposition (Zampell et al., 2012; Karayi et al., 2020), in the myocardium of heart failure patients (Laine and Allen, 1991; Solti et al., 1991, 1994; Desai et al., 2008), and in other diseases resulting from dysfunctional lymphatics, such as in patients with breast cancer (Coutts et al., 2016). Edema with inflammatory cell infiltration triggers fibroblast/myofibroblast activation and tissue fibrosis in a MetS cardiac environment associated with a moderate chronic inflammation (Brakenhielm et al., 2020).

Fibronectin

FN is a cell adhesion glycoprotein that surrounds cells and links cells with ECM molecules by binding with integrins α4β1 and α9β1. Although FN is distributed ubiquitously in the interstitial matrix, it is also characteristically concentrated immediately adjacent to BMs in many adult organs, as previously reported
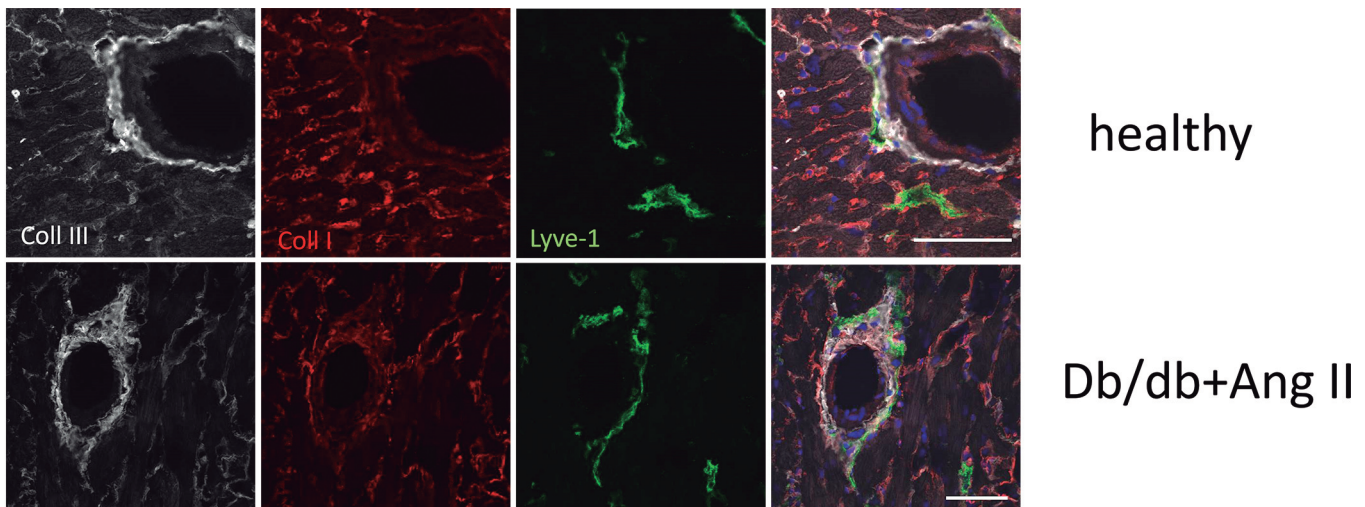

Fig. 2. Immunoconfocal images of collagen I (red) and collagen III (white) deposits adjoining LyVs (Lyve-1, green) that are embedded in the adventitia of coronary vessels of a healthy adult male mouse (upper panels) and of a mouse at the same age with MetS, i.e., db/db strain treated with angiotensin II (Ang II) (lower panels). Scale bars: 50 *μ*m.

(Linder et al., 1978; Couchman et al., 1979; Leppi et al., 1982; Gil and Martinez-Hernandez, 1984; Uscanga et al., 1984; Gardiner et al., 1986; Hynes, 1999), being also present in very close proximity to LyV BMs (Fig. 3). The mechanism of this spatial accumulation of FN at BMs has been recently explained as dependent on collagen IV and laminin interaction with crude FN (Domogatskaya et al., 2012; Fidler et al., 2018) and involving active binding to integrins that accumulate in focal adhesions; all these reciprocal molecular interactions can produce robust local FN fibrillogenesis in close vicinity of BMs (Lu et al., 2020).

FN in association with a cartilage oligomeric protein (=thrombospondin 5) are deposited around initial and collector vessels (Zolla et al., 2015). FN domain EIIIA is crucial primarily during embryogenesis, and its interaction with integrin α9 expressed on LECs regulates FN fibril assembly, which is essential for the formation of the ECM elastin core of valve leaflets (Bazigou et al., 2009). Of note, FN individual fibers promote sprout formation and migration during *in vitro* LEC culture, which indicates that FN fiber organization affects early stages of lymphangiogenesis (Mitsi et al., 2015). New LyV formation that occurs in tumor growth requires the α4β1 integrin known to bind FN. This integrin has an impact on LEC survival, proliferation, and migration (Garmy-Susini et al., 2010). As the FN-EIIIA domain has an affinity to wound fibroblasts, novel findings with the use of the F8-VEGF-C construct (directed to the EIIIA domain of FN) for delivering VEGF-C to diabetic

wounds indicated that promoting lymphangiogenesis accelerates also wound healing (Brunner et al., 2023). The role of FN in lymphangiogenesis has been confirmed under optimized conditions in an *in vitro* three-dimensional (3-D) collagen-based model that induced LEC invasion and recapitulated physiological formation of lumenated lymphatic capillaries. When added to this modified ECM, FN strongly enhances sprout length and density, and therefore stimulates lymphangiogenesis (Kumaravel et al., 2020).

FN has also an impact on lymphatic vessel barrier integrity. Application of organ-on-a-chip technology (LyV-on-chip containing collagen I and FN) allows the study of LEC biology. The use of this model has demonstrated that adding FN to the collagen I scaffolding improves the LyV barrier by tightening VE-cadherin intercellular junctions (Henderson et al., 2021). Deposited in the vicinity of LyVs, FN forms a connection between LECs and elastin fibers. In this way it presumably participates in the maintenance of the LyV wall barrier and VE-cadherin junctions.

Importantly, LECs grown on a soft matrix, which corresponds to the stiffness of embryonic tissue, exhibit increased GATA2 expression and GATA2-dependent upregulation of the genes involved in cell migration and lymphangiogenesis, including *Vegfr3*. In a stiff ECM (25kPa) there is intracellular actin stress fiber formation, cell spreading, and proliferation, whereas in a "soft" ECM (0.2 kPa) there is promotion of migratory cell activities involved in lymphangiogensis (Frye et al.,
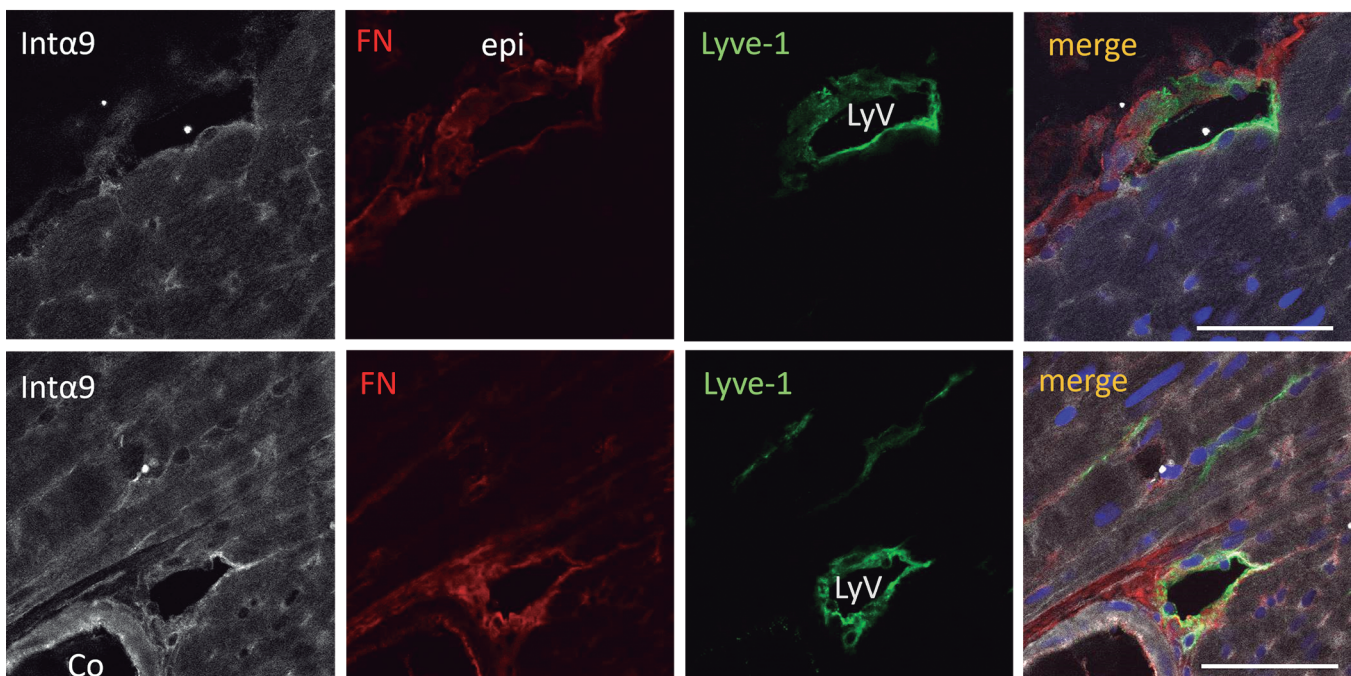

Fig. 3. Myocardial sections of an adult mouse immunolabelled to Lyve-1 (green), FN (red), and Integrin α9 (Intα9, white). There is faint FN and Intα9 immunostaining around subepicardial lymphatics (upper panels) whereas there are stronger immunostainings around lymphatics located pericoronary (lower panels); Co - coronary artery lumen; Epi - epicardium. Scale bars: 50 *µ*m.

2018). All these matrices contain FN fibers organized in various ways. Therefore, FN 3-D organization that mimics embryonic or adult tissue, seems to be crucial for LyV formation and LEC proliferation and survival. Of interest, YAP and TAZ, nuclear transcription factors, have been identified as molecular 'readers' of ECM elasticity and cell geometry, as evidenced on FN coated bioengineered hydrogels (Dupont et al., 2011). Sabine et al. identified the specific role for TAZ in controlling LEC response to oscillatory shear stress (OSS), which provides a stimulus for the initiation of LyV luminal valve formation (Sabine et al., 2012, 2015, 2016). The use of stiff matrix in *in vitro* culture mimics the presence of OSS. OSS also affects LyV wall integrity and lymphangiogenesis.

Tensin (TNS1)

TNS1 localizes to focal adhesions and links the ECM (mainly FN) with the actin filament system in the cytoplasm, which controls cell shape (Wang et al., 2022). TNS1, together with the adhesion complex proteins, acts as a mechanosensor to ECM signals. TNS1 is upregulated in LECs cultured under hypoxic conditions (Becker et al., 2021), which may indicate an intensified interaction between LECs and ECM in this environment.

Glycosaminoglycans, proteoglycans

Sulfated GAGs (sGAGs) and *non-sulfated* GAG (hyaluronan, HA) as negatively charged molecules have been proposed to have a central role in Na^+ homeostasis due to their ability to bind Na+, thus serving as a Na^+ reservoir and keeping the interstitial skin osmotic pressure unchanged (Titze and Machnik, 2010). Studies by Nijst et al. and Guyton et al. (Guyton et al., 1971; Nijst et al., 2018) suggested, that Na^+ can be buffered in the body in kidney-independent reservoirs, namely owing to these GAGs Na^+ absorbing properties. The standard was that Na^+ is able to hold water in the extracellular space acting as a principal extracellular regulator of tissue edema (Titze and Machnik, 2010). Moreover, HA and GAGs have water absorbing potential (Bayer, 2020). In salt overloading (i.e., high dietary salt intake) the binding of Na^+ to modified dermal GAGs renders again tissue osmotically inactive (Titze et al., 2003). This condition is termed "osmotically inactive Na^+ storage" (Titze et al., 2004, 2005, 2006; Schafflhuber et al., 2007; Ziomber et al., 2008). Currently, however, the assertion that GAGs are a Na^+ reservoir is being questioned by Towsen et al. (Thowsen et al., 2022b) who suggested another mechanism for skin Na^+ absorption: those authors proposed that Na^+ excess is absorbed by intracellular proteins. The role of tissue interstitium, known to have a high GAG content, remains to be explored as a potential target in the management of fluid volume disturbances.

Recently, immune cells of the skin interstitium, such as macrophages and dendritic cells (DCs), are believed to "sense" Na^+ interstitial tissue overload in a high-salt diet and respond by stimulating LyV growth and controlling blood pressure (Machnik et al., 2009; Wiig et al., 2013, 2018). Similar observations were reported for cardiac tissue of experimental animals on a high-salt diet (Yang et al., 2017). However, novel findings reported by Thowsen et al., based on genetically modified animal models with absent, reduced, or overexpressed skin lymphatics, revealed that dermal LyVs do not control blood pressure and electrolyte homeostasis in animals with hypertension and salt overload (Thowsen et al., 2022a). These studies suggest that the relationship between salt-overload-induced interstitial tissue pressure, immune cells, and lymphangiogenesis is not entirely clear, and needs to be interpreted more carefully.

Heparan sulfate proteoglygans (HSPGs) also serve as a reservoir for growth factors, including members of the FGF family, VEGFs, and others (Wiig et al., 2010; Karamanos et al., 2018). HSPG modulation by enzymatic processing facilitates the interaction between these growth factors and their receptors. Thus, HSPGs orchestrate growth factor availability and activity, two key important elements in organogenesis and morphogenesis (Patel et al., 2017), including LyV formation during development (Rutkowski et al., 2006; Wang et al., 2016), in normal adults and in tumor environment (Wiig et al., 2010; Yu et al., 2017).

Fibromodulin (FMOD), a 59-kD small leucine-rich proteoglycan (SLRP) that directly binds to ECM structural components, such as collagen and LOX, regulates collagen cross-linking, assembly, and fibril 3-D architecture via a multivalent interaction (Svensson et al., 1999; Mormone et al., 2012). FMOD involvement in collagen fibril assembly occurs prior to cross-linking and proceeds by LOX-FMOD-collagen complex formation. This FMOD-mediated collagen assembly results in well-organized collagen architecture (Zheng et al., 2023). Apart from interacting with collagen and LOX, as a multifunctional molecule, FMOD binds other cytokines and growth factors, such as FGF-2, IL-10, and MMP-13, and especially those belonging to the TGF-β superfamily (Svensson et al., 1999; Geng et al., 2006; Halasi et al., 2022; Zheng et al., 2023). Therefore, FMOD indirectly interacts with the corresponding signaling molecules involved in cell adhesion, spreading, proliferation, migration, invasion, differentiation, and metastasis. By forming a complex with TGFβs, FMOD has been supposed to eliminate TGFβs from tissue or to sequester their signal in the ECM, therefore reducing TGFβ's bioactivities (Zheng et al., 2023). Consequently, FMOD exhibits proangiogenic, anti-inflammatory, and antifibrogenic properties and plays essential roles in determining cell fate and maturation, progenitor cell recruitment, and tissue regeneration (Zheng et al., 2023). Recently, FMOD and its transcripts have been reported to be upregulated in LECs cultured under hypoxic conditions and in LECs derived from patients with skin

lymphedema (Becker et al., 2021; Wilting et al., 2022).

Hyaluronan and Lyve-1

Hyaluronan is a component of the ECM with a very high turnover rate and has the capacity to bind the lymphatic vessel endothelial cell receptor - Lyve-1. Originally found to be expressed on LECs (Banerji et al., 1999), Lyve-1 is involved in HA uptake from the tissue matrix and its transport to the lymphatic system (Banerji et al., 1999; Prevo et al., 2001). Lyve-1 also facilitates the transit of leukocytes and tumor cells through lymphatic vessel walls into LyV lumina (Jackson, 2019a) and is responsible for maintenance of vessel wall integrity (Jackson, 2004, 2009; Mäkinen et al., 2007; Johnson et al., 2017). Lyve-1 molecules contain a Link domain-containing hyaladherin, homologous to leukocyte hyaluronan receptor - CD44 (Aruffo et al., 1990; Ponta et al., 2003), with which it shares an approximately 46% amino acid sequence similarity, within the N-terminal ectodomain (Nightingale et al., 2009). Under inflammatory conditions Lyve-1 undergoes internalization into cells and degradation within lysosomes (Johnson et al., 2007). This may result in an impaired functional capacity of Lyve-1 in inflamed tissues and diminish the possibility of identifying LyVs in tissues with the use of immunostaining with anti-Lyve-1 antibodies.

The Lyve-1 molecule is also known as Cell-surface retention sequence binding protein (CRSBP1) (Hou et al., 2011). A CRSBP1-dependent mechanism (=Lyve-1-dependent mechanism) has been suggested to facilitate opening of VE-cadherin intercellular junctions, which allows the interstitial fluid with molecules to enter the LyV lumen (Hou et al., 2011). The mechanism of intercellular junction opening is triggered by CRSBP1 binding to various ligands (such as PDGF-BB, VEGF-A165, PDGF, VEGF) with the contribution of HA, which subsequently stimulates β-catenin and p120-catenin dissociation and VE-cadherin internalization. Moreover, CRSBP-1 ligands can stimulate LEC monolayer contraction, thus eliciting VE-cadherin intercellular junction openings (the "unbuttoning" of LEC junctions). This leads to increased permeability of LyV walls and increased interstitial-lymphatic transit (Hou et al., 2011, 2012).

After HA internalization into LyV lumina, the resulting HA levels in lymph are higher than in blood and vary between 0.2 and 50 mg/L with the highest levels in mesenteric lymphatics (Tengblad et al., 1986). In spite of a high turnover of HA in lymphatic vessels (Jackson et al., 2001), Lyve-1 is not essential for HA metabolism, contrary to what was previously suggested by Gale (Gale et al., 2007); in fact, Lyve-1-dependent degradation of HA is currently put into question (Nightingale et al., 2009, Leong et al., 2022). In fact, after internalization to the lymphatic system (Prevo et al., 2001), HA is transported with lymph to be further degraded/removed in the liver (Karamanos et al., 2018).

Hyaluronan is ubiquitously expressed in all tissues and forms a linear/unbranched polymer composed of repeating units of D-glucuronic acid and N-acetyl-D-glucosamine (Toole, 2004). The number of disaccharides in HA length may vary from 2,000 to up to 25,000. HA, in contrast to other GAG molecules, is synthesized by hyaluronan synthases (HAS1, HAS2, and HAS3), which are transmembrane enzymes resulting in HA extrusion through the plasma membrane onto the cell surface or into the ECM while it is being synthesized (Weigel et al., 1997; Dicker et al., 2014; Kobayashi et al., 2020). As HA mass decreases, the molecule undergoes a conformational change from a more compact random-coil to an extended and rigid rod-like form (Weigel and Baggenstoss, 2017) described by other authors as extended, relaxed, and condensed conformations (Dicker et al., 2014). HA exhibits differences in biological functions dependent on its molecular weight (MW), 3-D organization, and on its tissue density. For example, low-MW HA upregulates inflammation and angiogenesis, including cell activities such as proliferation, migration, and tube formation (Ponta et al., 2003; Slevin et al., 2007), regulates wound healing (Laurent and Fraser, 1992; Laurent et al., 1995; Lee and Spicer, 2000; Litwiniuk et al., 2016; Kang et al., 2019), and epithelial–mesenchymal transition during cancer and embryonic development, whereas high-MW HA hampers the inflammatory response, is anti-angiogenic, and immunosuppressive (Jackson, 2009). Of note, low-MW HA acting in concert with sphingosine-1-phosphate receptor and Lyve-1 (by triggering their co-localization on cell membrane) stimulates lymphangiogenesis (Yu et al., 2015). Wu et al. also reported that low-MW HA in association with Lyve-1 stimulates lymphangiogenesis *in vitro* (Wu et al., 2014). The low-MW HA/LYVE-1 complexes can also engage VEGF-C and FGF-2 in LEC proliferation and lymphangiogenesis (Bauer et al., 2018). HA is dynamically processed during tumor-associated lymphangiogenesis forming low-MW HA fragments, which impair vessel wall integrity (Du et al., 2022). Bronchoalveolar lavage fluid of patients with idiopathic pulmonary fibrosis contains high levels of low-MW HA, which stimulates abnormal pulmonary lymphangiogenesis contributing to adverse lung remodeling in this disease (El-Chemaly et al., 2009). Interestingly, by binding to low-MW HA, soluble Lyve-1 (which acts as a decoy receptor) inhibits angiogenic and lymphangiogenic activities (Carvalho et al., 2022).

Due to their capacity to bind cell transmembrane receptors and other active components of the ECM (such as VEGFs, hormones, TGF- β, and activated MMPs), HA and other GAG molecules serve as regulators of various cell functions involved in angiogenesis, fibrosis, wound healing, and cell differentiation and survival (Wiig et al., 2010; Jung et al., 2015; De Angelis et al., 2017; Jackson, 2019b; Hastings et al., 2019).

Hyaluronan can act as a chemical glue, allowing the formation of a stable ECM through the ability of several proteoglycans (such as aggrecan, versican, neurocan,

and brevican) to physically interact with HA via the Link domain/module (Kohda et al., 1996; Toole, 2004; Karamanos et al., 2018; Johnson and Jackson, 2021). Hyaluronan receptor for endocytosis (HARE/Stabilin 2), identified in liver sinusoidal endothelial cells (Zhou et al., 1999) and in LECs (Ouasti et al., 2012) can also bind HA (Weigel and Baggenstoss, 2017; Weigel, 2019). HARE is responsible for the uptake and turnover of about 30% of the total body HA (Jackson, 2004; Ouasti et al., 2012). The remaining HA is degraded by reactive oxygen/nitrogen species to shorter HA fragments and oligomers (Nastase et al., 2017; Carvalho et al., 2022).

Hyaluronan is abundantly present around LyVs (Wiig et al., 2010) and forms an immune-cell coating (as a component of immune cell glycocalyx) (Mummert et al., 2002; Dicker et al., 2014; Jackson, 2014); acting in concert with Lyve-1, HA facilitates immune cell transmigration into LyV lumina (Jackson, 2019a). In fact, cell transmigration (in detail described for DCs) is quite complex, and one recently elucidated mechanism involves HA binding to the CD44 cellular receptor, presented on DCs, and to Lyve-1, expressed on LECs (Jackson, 2019a,b; Johnson and Jackson, 2021; Ravaud et al., 2021). It has been shown that HA is crucial for immune cells to attach to LyVs and transmigrate into LyV lumina under normal conditions. Moreover, appropriate dimerization or "clustering" of Lyve-1 receptors, regulated by the submembranous actin cytoskeleton depolymerization within LECs, is required for efficient HA binding by LYVE-1. The capacity of DCs and macrophages to adhere to and transmigrate across the lymphatic endothelium depends on such LYVE-1 clustering and on HA-coating on the leukocyte surface (Stanly et al., 2020). Another mechanism of immune cell transmigration is activated in inflammation; it involves integrins and adhesive molecules such as ICAM and VCAM (Jackson, 2014; Ravaud et al., 2021). However, interaction of individual components may vary according to the nature of the inflammatory stimulus (Russo et al., 2013).

Due to its unique physical and mechanical characteristics, HA has high viscoelastic and water absorption properties, contributing to maintenance of tissue hydration, and exerting swelling pressure on tissues (as described above in the section on GAGs). When tissue pressure is high, HA shrinks, but when tissue pressure goes down, it returns to its original size. This property of HA molecules provides resilience and malleability to many tissues where HA is abundantly present (Toole, 2004) and is important for sustaining LyV wall elasticity.

Elastin and elastin-associated proteins

The *elastin fibers* deposited around initial LyVs, precollectors, and collectors, form a sleeve that ensures a low-resistance pathway for transcellular fluid and macromolecule transport across the wall of initials, and is able to "snap back" into its previous shape after compression (Ryan and De Berker, 1995). The LyVs that are constitutively surrounded by elastin fibers under normal conditions seem to be able to assume a "collapsed" configuration during the onset of inflammation, over the course of inflammation-associated diseases, and in tissue edema. In inflammatory tissue milieu elastin is degraded (by elastases derived mainly from granulocytes), and therefore LyVs lose their compliance, elasticity, and wall stiffness (Ryan, 2009).

The connection between elastin and initial lymphatics is presumed to be mediated by AnchFs and not by a direct binding of elastin to the LEC membrane. Nevertheless, some indirect connections between LECs and elastin have been defined between tropoelastin and galectin3, integrins αvβ3, α5 β5, and lactose insensitive receptor, all of which are known to be expressed in LECs (Tembely et al., 2022). Elastin, which has a long half-life of 70 years, is prone to degradation and modification in diseased tissues, over the course of such conditions as diabetes, obesity, inflammation, and also during ageing (Wahart et al., 2019) (Fig. 1); therefore, it has presumably a detrimental effect on LyV distensibility. Moreover, the significance of elastin for the strain of LyV collectors is also poorly understood. Functional studies suggest that increased pressure in the ECM produces a small increase in strain and causes a slight re-arrangement of the matrix in close proximity to LyVs (Arkill et al., 2010). It seems that sparse elastic network around LyV collectors rather relate to maintaining the organization of collagen network than supporting stress to collectors.

Elastic system fibers complement collagen fibrils. Elastin consists of oxytalan fibers, elaunin fibers, and elastic fibers that differ in their relative microfibril and elastin content (Inoué and Leblond, 1986; Gerli et al., 1990; Kielty et al., 2002; Sawada et al., 2006; Sugawara et al., 2010; Hann and Fautsch, 2011; Nakatomi et al., 2011; Charles-de-Sá et al., 2020). Microfibrils are heterogeneous in composition and contain a number of molecules, including FBNs, microfibril-associated glycoproteins, microfibril-associated proteins, fibulins (FLBNs), latent TGF-β binding proteins (LTBPs), proteoglycans, FN, and an amyloid P component (Kielty et al., 2002; Duca et al., 2016). Elastin, like collagens I and III, acts as a reservoir for growth factors and other molecules, such as versican, lumican, osteoglycin/mimecan, prolargin, FMOD (all of which belong to the SLRP family) (Schaefer and Iozzo, 2008), and galectins, including Gal-9, by binding to their glycan cores (Mithieux and Weiss, 2005; Itoh et al., 2017). SLRPs function as collagen cross-linkers and regulate collagen fiber diameter during collagen deposition (Chute et al., 2019). Elastin is significantly downregulated in LECs cultured under hypoxic conditions, whereas fibulin 5 (which controls the aggregation and positioning of elastic fibers and tropoelastin monomers) and LOX (which cross-links elastin and collagen) are upregulated (Becker 2021; Wilting et al., 2022).

Recent studies on lymph nodes demonstrate a specific role of the elastin surrounding LyVs in mediating the transport of antigens and antigen-presenting cells (APCs) (Lin et al., 2018).

At the electron microscopic level, elaunin fibers are composed of bundles of tubular microfibrils intermingled with elongated patches of dense amorphous material. Elaunin fibers are the only components of the elastic system fibers found around the seminiferous tubules and the secretory coil of human eccrine sweat glands. In addition, in the chordae tendineae (which extend from the papillary muscles to the edges of atrioventricular heart valve cusps), the elastic system fibers are represented exclusively by elaunin fibers. We cannot exclude that the fiber system found around LyVs in electron microscopy consists of elaunin.

FBLNs 4 and 5 are essential for elastin formation and assembly during extracellular deposition. FBLN-2 and -3 expression is increased in human pterygium at mRNA and protein levels (Perez-Rico et al., 2011) and these fibulins are deposited along lymphatic and blood vessels. Of note, FBLN 4 requires also Emilin-1 for fibril deposition in ECM of osteoblasts (Schiavinato et al., 2017). FBLN-5 transcription is upregulated in cultured LECs and in bovine aortic endothelial cells under hypoxic conditions. It is likely that FBLN-5 as a component of the BM is deposited around LyVs during lymphedema development (Becker et al., 2021).

Basement membrane (BM)

The BM is a specific form of cell-adherent extracellular matrix that serves as a supportive structure of the cytoplasmic membrane of various cell types, such as endothelial cells, pericytes, epithelial cells, and also cardiac myocytes, smooth and skeletal muscle cells, Schwann cells, and adipocytes. This thin-layered structure protects tissues from disruptive physical stresses and provides an interactive interface between cells and other ECM molecules, serves as a barrier regulating transport of various macromolecules, and as a platform for cell signaling that can mediate local and distant signals within and between cellular/ECM compartments (Timpl and Aumailley, 1989; Yurchenco, 2011). Such signals appear to be largely processed through integrins, CD44 molecules, growth factor interactions, thyrosine kinase receptors, and other transmembrane molecules, such as dystroglycan and DDR-1 (Yurchenco, 2011; Pozzi et al., 2017; Karamanos et al., 2022). Cell-surface integrins bind to ECM proteins containing peptide sequences with the arginine-glycine-aspartic acid (RGD) motif. This connection includes collagen, laminin and FN. Thus, there is bi-directional communication between the ECM and cells. The BM is a dynamic structure whose thickness and mechanical properties may be changed by the synthesis, degradation, or reorganization of its components in various pathologic conditions (Lu et al., 2011; Khalilgharibi and Mao, 2021).

The fundamental composition of the BM is highly conserved among species and tissues; it consists of collagen IV, laminins, perlecan, agrin, and nidogens/entactins (Baum and Bigler, 2016; Boland et al., 2021). Collagen IV and laminin are large molecules organized into a layer in which they are arranged with their long axes parallel to the base of the vascular endothelium (Yurchenco, 2011). Biochemical studies have revealed differences in the relative amounts of BM components, depending on type of tissue (vessels, such as capillaries, veins, arteries, lymphatics), location within the vascular tree, and disease status (Pozzi et al., 2017; Marchand et al., 2019; Becker et al., 2021; Nguyen et al., 2021; Janardhan et al., 2022; Wilting and Becker, 2022). Of note, these variations are reported also in the BMs associated with the lymphatic vascular plexus.

The BM is usually, but not consistently, present as a component of LyV coverage. Initial lymphatic capillaries
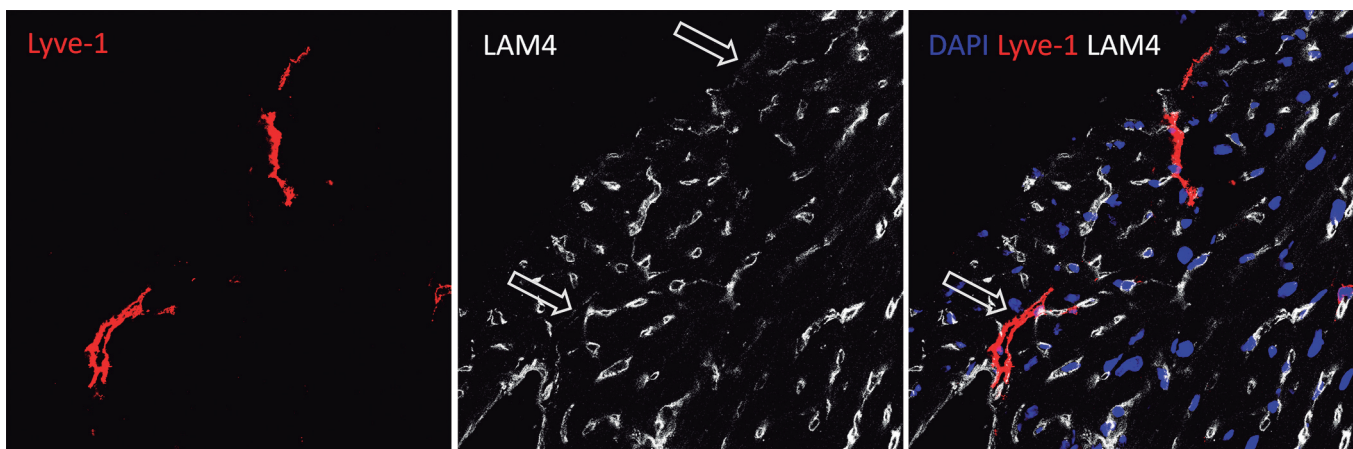

Fig. 4. Immunoconfocal images of a myocardial section of an adult male mouse stained with anti-Lyve-1 (red), anti-laminin 4 (LAM4, white) with nuclei stained with DAPI (blue); arrows point to a discontinuous BM associated with LyVs as evidenced by a faint anti-LAM4 staining. Scale bar: 50 *μ*m.

do not contain any BMs, or their BM is discontinuous (Fig. 4) (Vainionpaa et al., 2007; Pflicke and Sixt, 2009) and much thinner, compared with the thickness of blood capillary BMs, whereas precollectors and collectors are covered by a continuous BM. The BM of precollector and collector vessels supports LyV walls and its interaction with SMCs ensures LyV stability (Vainionpaa et al., 2007). LyVs seem to be exceptions in terms of the BM role in anchoring endothelial cells, since LECs in areas devoid of the BM are bound to the ECM by anchoring filaments (AnchFs).

One study by Plicke et al. revealed that the gaps of BM coating are sites of inflammatory cell transmigration across LyV walls into LyV lumina. The inflammatory cells more eagerly transmigrate across the walls of lymphatic initial capillaries than across the walls of collectors (Pflicke and Sixt, 2009). However, immune cell transmigration across collector walls has also been demonstrated as an alternative pathway. A recent study by Arasa et al. indicates that during inflammation, DCs can transmigrate across lymphatic collector vessel walls, known to be endowed with a thick BM, and this process requires the BM to be digested by activated MMPs and is highly CCR7- and VCAM-1-dependent (Arasa et al., 2021).

The lymphatic vessel BM is composed of laminin α4/5, β1/2, and γ1 chains, collagens IV and XVII, reelin, and nidogen 1. Laminins, collagens, and nidogen are produced by LECs. Nidogen, like perlecan (heparan sulfate proteoglycan 2, HSPG2), cross-links laminin and collagen layers (Vainionpaa et al., 2007; Pflicke and Sixt, 2009; Lutter et al., 2012). Accessory molecules of most BMs, including the BM of LyVs, are FN, collagen V, collagens VIII, and XVIII (Jackson, 2019b; Wilting et al., 2022). Single-Cell RNA Sequencing revealed that pulmonary LECs express *Col4a1*, *Col4a2*, *Lama4*, *Lama5*, *Lamb1*, *Lamb2*, *Lamc1*, *Lamc2*, and *Nid1* gene transcripts, whose products are constituents of BMs (Schupp et al., 2021; Sun et al., 2022). Whether and how these subtle differences in composition and the amount of these BM molecules reflect their functional impact on the LyV network is, nevertheless not entirely known. These transcripts, including *Hspg2*, are downregulated under the conditions of pathologic mitogen-activated protein kinase activation, causing lymphangiectasia and LyV leakage (Janardhan et al., 2022), which would suggest that major BM components (laminins, collagens, nidogens, and HSPG2) may have an impact on BM stability, which in turn affects LyV wall integrity. Nidogen1 and nidogen2 transcript content varies in capillary LECs, in comparison with collector LECs in the mouse ear. The expression of nidogen1 also changes in an inflammatory state, being high in capillary LECs during inflammation, absent in controls, and almost absent in collector LECs (Arasa et al., 2021). Based on these findings, we can speculate that BM "sealing" by high amounts of cross-linking nidogen is crucial in inflammatory states.

However, variations in BM thickness, which result from the higher turnover or excess synthesis/degradation of BM components and altered 3-D organization adjacent to LyVs reflect differences in the biophysical properties and metabolic demands of a given tissue. For example, the BM covering LyVs is thicker in motionless tissues, such as ear skin, and thinner in actively moving tissues, such as skeletal muscles, the diaphragm, heart, or lungs (Boucher et al., 1985). Another example of diverse 3-D organization of BMs was reported in cardiac LyVs of mongrel dogs, which exhibit various percentages of BM coverage depending on the anatomical location: LyVs of the subepicardial area are covered with BM in 18%, in the myocardial area - in 10%, and in the subendocardial area - in 33% (Boucher et al., 1985). These differences may reflect the myocardial compartment being the most demanding in terms of energy expenditure for contractile activity.

The BM is a structure which regulates the transport of solutes and cellular components under normal conditions, and it can act to facilitate permeability in an inflammatory environment or in various diseases. The thickness of the BMs associated with capillary walls is higher in disease states, such as obesity and type 2 diabetes, and similar to the thickness of the glomerular BMs (Karttunen et al., 1986). Moreover, the stiffness of BMs increases in certain diseases, including diabetes mellitus, and in ageing. BM stiffness depends on collagen IV and it increases with cross-linking of collagen IV (Khalilgharibi and Mao, 2021). In fact, advanced glycation end products (AGEs), which are produced in diabetes, stimulate collagen crosslinking and make BMs more rigid and less prone to degradation due to accumulation of AGE-collagen adducts. All these processes result in BM thickening and stiffening. Moreover, the thick BMs of human kidney glomeruli are characterized by additional accumulation of collagen IV and VI and decreased laminin and proteoglycan content in diabetic and aging individuals (Karttunen et al., 1986). All these changes in BM composition and thickening can affect BM plasticity, stiffness, and therefore its mechanical properties (Khalilgharibi and Mao, 2021).

Of note, some BM molecules, such as collagen IV or laminins affect cell shapes when studied *in vitro*, resulting in either longitudinal/polygonal or round cell shapes, as demonstrated by culture of podocytes on laminin types 511, 521, and collagen IV, respectively. The signaling for these distinct behaviors is mediated by BM- or integrin-associated adhesome which triggers different signaling pathways: protein kinase C for longitudinal, and Rac family Small GTP-ase 1 for round cell morphologies (Randles et al., 2020). It would be worth exploring whether this function of BM molecules is also related to LEC shape changes.

Another interesting finding is the impact of some ECM molecules, such as collagen I, Matrigel, and fibrin, on altering blood endothelial cell (BEC) phenotype

towards lymphatic-like when HUVECs are cultured *in vitro*, although the mechanism(s) were not elucidated (Cooley et al., 2010).

Collagen IV is a basic component of BMs and is constitutively present in the lamina densa of blood and lymphatic vessels. Collagen IV may undergo abnormal folding during its synthesis, which affects the BM integrity and proper angiogenic/lymphangiogenic function and vessel wall stability (Pöschl et al., 2004; Zhang et al., 2011; Marchand et al., 2019; Khalilgharibi and Mao, 2021). As has been demonstrated recently, proper collagen IV synthesis and its extracellular export is regulated by RASA-1, the gene that encodes a negative regulator of the Ras signaling pathway, which promotes cell growth, proliferation, and differentiation. Using different murine models of RASA-1-deficiency, (RASA-1-deficient mice, RASA-1-deficient ECs) it has been demonstrated that RASA-1 is crucial for EC survival and angiogenesis (Chen et al., 2019). Moreover, these models exhibit intracellular accumulation of collagen IV and malformed/shortened lymphatic valve formation. The underlying mechanism behind this process is misfolding of collagen IV protein in the rough endoplasmic reticulum and protein accumulation in this compartment (Chen et al., 2020).

Laminins bind to cellular receptors, including integrins (such as $\alpha1\beta1$, $\alpha2\beta1$, and $\alpha9\beta1$), alpha-dystroglycan, heparan sulfates, and sulfated glycolipids. Other binding molecules are perlecan and agrin (Hohenester and Yurchenco, 2013). Type IV collagens interact with the laminin network through agrin, nidogen, and the heparan sulfate chains of perlecan. Laminins are essential for BM assembly and play a role in lymphangiogenesis (Durbeej, 2010).

Anchoring filaments (AnchFs)

In areas devoid of BM, LECs of initial lymphatics are connected to the ECM via specific AnchFs. These filaments running parallel to each other appear in organized tufts and link focal adhesions of the LEC cytoplasmic membrane with ECM components, especially collagen and elastin. The focal adhesion complex contains the focal adhesion kinase and $\alpha3\beta1$ integrin (Gerli et al., 2000), and other molecules.

AnchFs are formed at certain stages of LyV embryonic development that involve a transition from originally formed novel vessels with "zipper" junctions to mature vessels with "button" junctions (Yao et al., 2012). AnchFs are also constituents of postnatal initial vessels, after maturation of newly formed vessels, which is followed by a transition from "zipper" to "button"-like junctions (Yao et al., 2012). Therefore, AnchFs are a peculiar morphological feature of mature lymphatic capillaries but presumably not young lymphatic capillaries, precollector, or collector vessels; and, of note, they are not found in the blood microvascular tree.

The first description defining AnchFs was presented in a detailed ultrastructural study of various organ lymphatics by Leak at al. (Leak and Burke, 1968; Leak et al., 1978). Subsequent TEM studies demonstrated a fibrillar apparatus with fibers 10-12 nm in thickness present around LyVs (Gerli et al., 1991) which was confirmed by automated electron tomography imaging after rotatory shadowing (Sakai et al., 1986; Baldock et al., 2001).

The chemical nature and composition of AnchFs have not been definitively defined but are suggested to predominantly consist of large glycoproteins rich in cysteine, FBNs-1 and -2, (Gerli et al., 1991, 2000; Sawada, 2010; Hann and Fautsch, 2011; Yamanouchi et al., 2012), and emilin1 (Danussi et al., 2008; Pivetta et al., 2014, 2016).

Fibrillin (FBN) is a predominant component of AnchFs linking lymphatic endothelium with the elastin via RGD-sensing $\alpha v\beta3$ and $\alpha5\beta1$ integrins (Weber et al., 2002; Rossi et al., 2007; Sawada, 2010) as discussed previously by Isokawa et al. (2004). FBNs in fibril complexes, such as non-elastin associated fibrils, interact with growth factors forming a niche for TGF-β, BMP, and ECM molecules, such as LTBP, and microfibril-associated proteins (Jensen et al., 2012; Sengle and Sakai, 2015). Mutation in FBN-1 leads to increased TGF-β activity (Loeys et al., 2010b) and causes a systemic disorder in Marfan syndrome (Loeys et al., 2010a), displaying severe periodontal disease, cardiovascular and skeletal complications, emphysema, and ocular lens dislocation.

Of interest, both LEC and BEC *in vitro* are sources of FBNs (Rossi et al., 2010).

Asprosin is a derivative of FBN fibers. This peptide, which consists of the 140 C-terminal amino acids of FBN-1, has glucogenic function and is secreted from adipose tissue during fasting; it acts on the hypothalamus and stimulates the appetite (Romere et al., 2016). Asprosin serum levels are positively correlated with MetS. It has been discussed whether asprosin can be produced independently from FBN or is only derived from fibrillin degradation (Summers et al., 2023), and how it affects LyV properties in obesity.

Observations on other tissues, such as developing periodontal ligament expressing emilin-1 and FBN1 (Nakatomi et al., 2011) or areas adjacent to Schlemm's canal endothelium, expressing FBN1 (Hann and Fautsch, 2011), would suggest that FBN and emilin-1 are linked together and constitute oxytalan fibers of the ECM associated with periodontal ligament and with LyV-like structures. The Schlemm canal is considered as a hybrid vessel, i.e., one sharing BEC and LEC antigens/markers (Kizhatil et al., 2014; Wu et al., 2020).

Emilin fibrills (composed of Emilin1, Elastin Microfibrillar Interface-Located proteIN-1) as components of AnchF are involved in interaction of LEC with elastin and collagen and other ECM proteins

(Danussi et al., 2008), linking a cell to elastic fibers/lamellae via α4β1- and/or α9β1-integrins (Danussi et al., 2011).

Emilin-1 can form multimers of million Dalton MW via S-S bonding. Emilin-1, emilin-2 and the multimerins (multimerin-1, multimerin-2) family comprise proteoglycans containing the gC1q domain. This domain is an active part of these molecules; however, the effect of the gC1q domain can also be exerted via the interaction of soluble proteins with cellular receptors or with other domains of emilin molecules.

Emilin-1 is a component of elastic laminas and microfibrills in blood vessel walls and is important for maintenance of blood vessel wall structure and its compactness as well as TGF-β bioavailability regulating blood hypertension, SMC hypertrophy and proliferation (Sakai et al., 1986; Bressan et al., 1993; Zacchigna et al., 2006; Colombatti et al., 2011).

Emilin-1 function in LyV biology involves stabilization of LyV walls and their integrity, promotion of lymphatic capillary formation (Capuano et al., 2019a) and presumed maintenance of their absorbing capacity (Pivetta et al., 2016). Moreover, emilin-1 is important for valve formation and proper valve function in precollectors/collectors (Danussi et al., 2013). Emilin-1 deficiency or mutation in its gC1q domain, known to interact with α4β1- and/or α9β1-integrins, leads to abnormal LyV formation and persistence of inflammatory cell infiltration in an inflammation-induced colon cancer tumorigenesis environment (Capuano et al., 2019b). Lack of emilin-1 results in abnormal LyVs with large lumina and a diminished amount of anchoring filaments, which shows that emilin-1 is a component of AnchFs and is crucial for LyV integrity (Danussi et al., 2008).

The role of AnchFs in active opening of primary lymphatic valves, as has been suggested previously by several authors (Tammela and Alitalo, 2010) is still not entirely clear. Only hypotheses exist regarding the nature of the mechanisms behind the opening of initial flaps that facilitate fluid and solute absorption and immune cell transmigration into LyV lumina. Some authors consider AnchFs as interstitial tissue pressure sensing structures that transform extracellular signals via integrins through cell membranes to cytoskeleton and, subsequently, to cytosol (Tammela and Alitalo, 2010; Burridge, 2017). In this way AnchFs would be active players in primary valve opening, which favors drainage of interstitial fluid, molecules, and inflammatory cells into LyV lumina, as previously suggested (Rossi et al., 2007) but this has not been confirmed experimentally. According to Lynch et al., only molecules ranging from 0.5 to 0.8 μm in size can enter this flap valve system. Inflammatory conditions compromise this flap system as well as junctional connections, which impairs the vessel wall barrier (Lynch et al., 2007). Emilin-1 degradation by neutrophil elastase was observed in early pathogenesis of inflammation-associated lymphedema; this would confirm AnchF-dependent impairing of LyV

absorbing activity. Moreover, indirect confirmation of emilin-1-dependent functional role in flap opening comes from the observation that emilin-1-deficiency compromises inflammatory cell transmigration to LyV lumina (Pivetta et al., 2016, 2022).

Another theory of valve opening is based on mathematical models of bioengineered lymphatics and dermal lymphatic mechanomotion, and the appropriate proportion of the length-to-diameter ratio of an initial capillary to its first branching point (Reddy and Patel, 1995). Another theory is based on a higher suction pressure of precollectors and collectors, which drives fluid flow and primary valve opening in initials (Sloas et al., 2016). Mendoza et al. suggested that primary valve opening and unidirectional fluid flow is caused by increased interstitial tissue pressure (Mendoza and Schmid-Schönbein, 2003).

There was also a suggestion that AnchFs maintain LyV shape and patency during changes in interstitial pressure and transmit signals between the ECM and LECs.

Thus, there is a need to further explore the functional significance of these filaments. (Fig. 5).

Other ECM molecules closely associated with LyVs

Reelin has been described to be expressed in developing and adult LyVs of various organs and in lymphangiomas by immunohistochemistry (Samama and Boehm, 2005; Norgall et al., 2007). Further studies by Lutter et al. (Lutter et al., 2012) revealed that reelin is synthetized by the LECs of initial and collecting vessels, but only the latter have shown efficient reelin secretion following contact with adjacent SMCs. LECs, in turn, respond to reelin by up-regulating the expression of monocyte chemotactic protein 1 (MCP1), a factor which promotes recruitment of SMCs to collector vessels. Reelin-deficient mice have disabled collectors that do not propel lymph efficiently and are leaky with a reduced SMC cover (Lutter et al., 2012). These changes in collector vessels and SMC cover differ depending on tissue location. Mesenteric collectors which are covered with a thick SMC layer look normal in reelin-deficient mice, whereas dermal collectors look disabled (Lutter et al., 2012). Of interest are unusual roles of the reelin released from LECs in various tissues: reelin stimulates cardiac cell proliferation (in early postnatal mice) and supports cardiomyocyte survival. Mouse embryos that lack LECs develop smaller hearts, as a consequence of reduced cardiomyocyte proliferation and increased apoptosis. The major player in this process is reelin, known to be released by LECs during development. Apart from stimulating cardiomyocyte proliferation, reelin exerts a cardioprotective role (Liu et al., 2020).

Lymphatics have been recently recognized as major intestinal crypt niche residents serving as a critical signaling hub in regulating stem cell differentiation. Reelin and other LyV-derived factors (WNT2, R-SPONDIN-3) maintain intestinal crypt stem cells

preventing them from their precocious differentiation, i.e., maintaining their "stemness" (Niec et al., 2022). In summary, reelin plays a role both in LyV collector biology and in other non-classical lymphatic-associated LyV functions.

Polydom (multidomain: Sushi repeats, vWF domains, EGF domain, and Pentraxin domain-containing protein 1, SVEP1) is a mesenchymal factor deposited in a fibrillar pattern around LyVs and in luminal valves, and is crucially involved in LyV development, remodeling, and patterning in various organs (Karpanen et al., 2017). Polydom is a high-affinity ligand for integrin α9β1 - the putative polydom receptor responsible for the sprouting of new capillaries and the formation of collecting LyVs (Sato-Nishiuchi et al., 2012). However, polydom action on LyV patterning and upregulation of Foxc2 (a transcription factor involved in LyV collector remodeling), seems to be mediated in an Ang2/Tie1-

dependent fashion rather than via the α9β1 integrin (Morooka et al., 2017). Probably, polydom exerts its effect on Foxc2 expression in LECs by potentiating Ang-2. Polydom mutant mice develop severe intrauteral edema, defective lympho-venous connections, missing valves, and remodeling defects, such as blunted lymphatic sprouts with a lack of interstitial fluid absorption (Karpanen et al., 2017). Polydom promotes Tie-1 and Tie-2 expression, which indicates its role in lymphangiogenesis regulation, as well as Foxc2 transcription factor expression in LECs, thus influencing valve formation (Karpanen et al., 2017; Morooka et al., 2017). Thomson et al. reported that Svep1 in association with Angiopoietin1 and TEK (tunica interna endothelial cell tyrosine kinase, also known as Tie2) are risk alleles in developing of primary glaucoma, a disease with defects in eye trabelule and Schlemm's canal (Thomson et al., 2021). Of note, Schlemm's canal has been considered as a hybrid vessel (having an intermediate
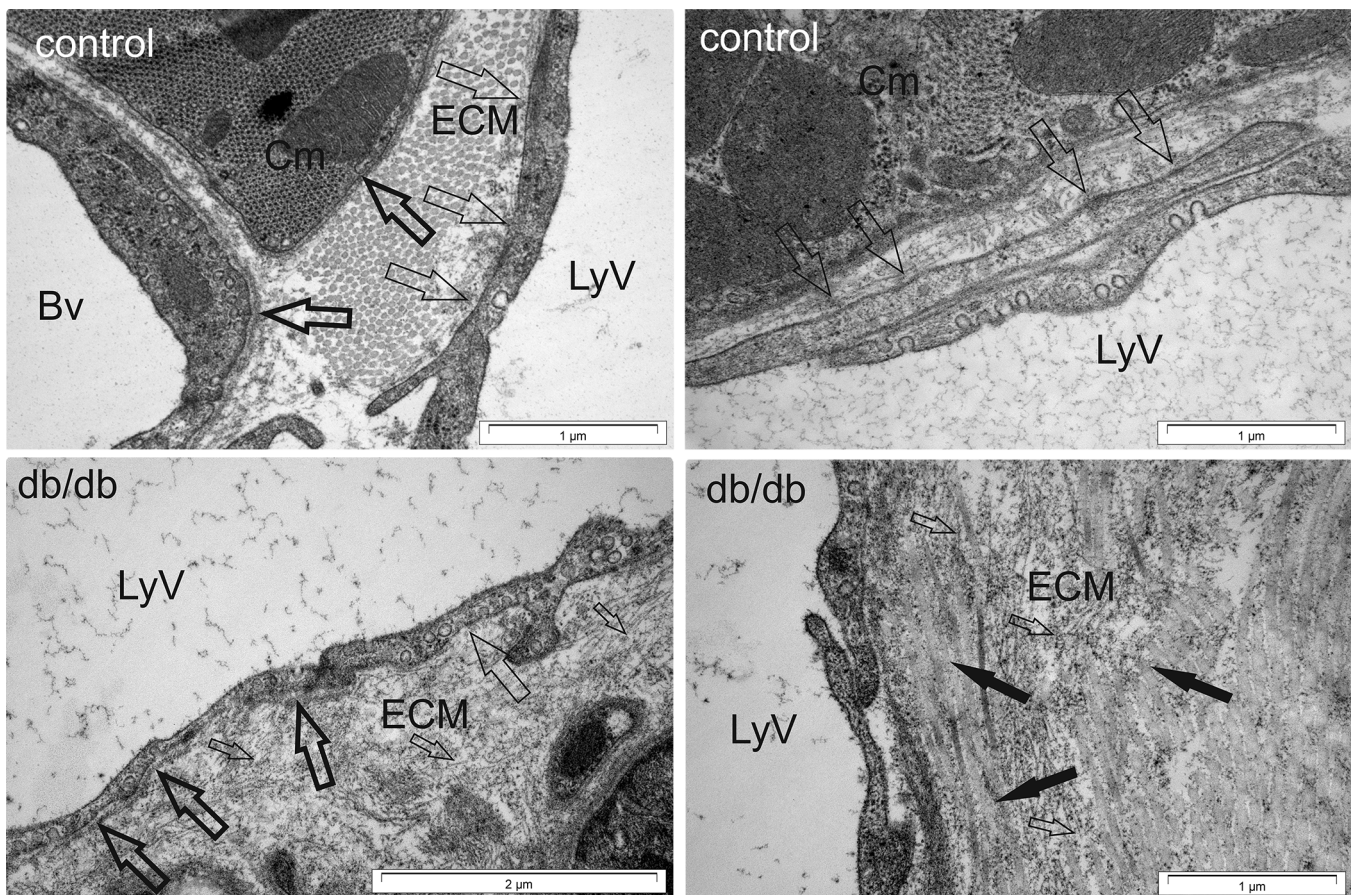

Fig. 5. Transmission electron microscopic (TEM) upper panels presenting cross sections of myocardial tissue with an initial LyV and a blood capillary (Bv) of a healthy adult mouse; note the anchoring filaments (fine open arrows) at abluminal surface of LyV, and BM (thick open arrows) at abluminal surface of blood capillary and around cardiomyocyte (Cm); bundles of collagen fibers in extracelluar matrix (ECM). TEM lower panels presenting cross sections through the wall of a myocardial LyV of a db/db mouse; note short flaps (F) in the wall of LyV, abnormal AnchFs (fine open arrows) and discontinous BM (thick open arrows) at the abluminal surface of a LyV. ECM contains haphazardly oriented individual collagen fibers embedded among numerous thin fibers (small open arrows) and elastin fibers of opaque transparency (black arrows). LyV - lymphatic vessel lumen; Bv - blood microcapillary lumen.

characteristics between blood and lyV phenotype) (Kizhatil et al., 2014; Wu et al., 2020) therefore, Svep1 genetic mutations described in this paper might be involved in the malfunction of lymphatic-like vessels. Moreover, Michelini et al. described recently a novel human disease with clinical symptoms of lymphedema associated with Svep1 mutation (OMIM #611691) (Michelini et al., 2021).

Tenascin C is deposited around lymphatic precollectors/collectors at the level of valves and is essential for proper valve formation (Bazigou et al., 2009; Paupert et al., 2011).

Concluding remarks

ECM molecules are important components of LyV walls, act as a supporting medium maintaining the stability, integrity and elastic properties of LyV cellular elements, and are crucial for proper functioning of LyVs under normal conditions. In diseases, ECM components undergo remodeling, which affects LyV function and properties impairing tissue homeostasis, fluid and solute retention, immune cell trafficking, vessel wall stability and permeability. In spite of a broad knowledge on molecules positioned adjacent to LyVs, the exact chemical composition and functional implications of some of these structural elements on LyV biology need to be further explored.

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