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Report from the 2023 workshop on endothelial permeability, edema and inflammation

A key consequence of increased and sustained vascular permeability in several inflammatory and cardiovascular disorders is the development of interstitial protein-rich proinflammatory edema. This response remains poorly understood mechanistically and its potential adverse effect on local and systemic diseases is often underestimated. To discuss current findings and identify crucial unresolved questions, a workshop was held in Berlin from 12–15 April 2023. Key topics that were discussed included regulation of endothelial cell junctions, neutrophil-dependent vascular leakage, resolution of edema, exemplar diseases, and anti-edema therapies. This report is a summary of the meeting.

Edema, originally designated by the Latin term tumor, is one of the classical signs of inflammation, together with rubor (redness), calor (heat) and dolor (pain). Under normal conditions, the hydrostatic pressure within blood vessels is balanced by an opposing colloid oncotic pressure gradient generated by the higher protein concentration in plasma than in interstitial fluid. The net outward movement of plasma filtrate bathes tissues and is then cleared by the lymphatic system and returned to the venous bloodstream. Maintaining this equilibrium relies on balancing endothelial permeability to macromolecules, which is typically low but varies among organs, and lymphatic clearance. Endothelial permeability is governed by intercellular tight and adherens junctions formed by transmembrane proteins, and influenced by the endothelial glycocalyx and other vessel wall components[1]. Tissue fluid clearance depends on lymphatic abundance, efficient interstitial fluid entry into initial lymphatic capillaries, and the transport of lymph fluid through nodes and efferent lymphatic vessels to the venous circulation. The properties of blood vessels as well as lymphatic vessels differ among organs and adapt rapidly in pathological conditions.

Endothelial permeability can increase in response to trauma, infection and other inflammatory stimuli, leading to plasma extravasation. This is driven by the formation of focal gaps between endothelial cells, predominantly in venous capillaries and postcapillary venules, in response to activation of endothelial cell receptors that trigger changes in intercellular junctions[1]. Edema occurs when the clearance capacity of extravasated fluid by lymphatic capillaries is exceeded. This is an essential feature of the inflammatory response that delivers important plasma components to tissues for host defense, tissue repair and resolution. However, when sustained, plasma leakage can lead to detrimental consequences such as persistent swelling, tissue damage and fibrosis.

Histamine, the inflammatory mediator discovered in 1910, rapidly induces reversible leakage from venous capillaries and postcapillary venules[1]. Many permeability-increasing molecules have since been identified, including bradykinin, substance P, platelet activating factor (PAF) and vascular endothelial growth factor (VEGF). These mediators bind directly to cell surface receptors on endothelial cells. A second class of molecules that are also potent permeability-increasing mediators are neutrophil chemoattractants, typified by complement-derived peptide C5a, that induce rapid-onset, neutrophil-dependent plasma leakage. Neutrophils recruited by these molecules are stimulated to release secondary mediators that act on endothelial cells, particularly when the leukocytes have attached to the luminal cell surface, are emigrating through junctions, or are crawling beneath the endothelium. Among other important molecules generated in inflammatory reactions are prostaglandins E_2 and I_2 that weakly induce leakage but strongly potentiate the effects of direct-acting and neutrophil-dependent permeability factors. This synergistic action on edema (tumor) is dependent on the vasodilator effect of the prostaglandins on arterioles (responsible for calor and rubor), which increases transmural, hydrostatic pressure downstream within venules.

In acute inflammation, plasma leakage is transient and reverses spontaneously. In chronic conditions, in which inflammatory stimuli persist, plasma extravasation and tissue swelling continue and contribute to organ dysfunction. Sustained edema is found in numerous cardiovascular conditions (such as myocardial infarction and stroke), cancers, retinopathies such as wet, age-dependent macular degeneration (AMD), and arthritis, among others. The frequency and seriousness of these disorders provide a strong incentive to identify agents that can effectively prevent, reduce or reverse plasma leakage. Angiopoietin1 (ANGPT1), sphingosine-1-phosphate (S1P) and VEGF inhibitors have potent anti-leakage effects through their direct actions on endothelial cells[1–3]. VEGF inhibitors are now widely used in the treatment of macular

degeneration and other retinal conditions, as well as in certain cancers[3].

The following sections review topics discussed at the workshop (see Figures for participants), with the goal of identifying promising research directions that can lead to improvements in the treatment of conditions in which reduction in plasma leakage is clinically beneficial.

Junctional regulation of endothelial cells

Endothelial cells are tethered by adherens and tight junctions, which contribute to the vascular barrier and restrict vascular permeability in an organotypic manner. The molecular composition of endothelial junctions is well studied in vitro, whereas less is known about these structures in different vascular beds and organs in vivo. VE-cadherin is a major player in the regulation of vascular leakage in pathological settings. Although blocking its function or expression disrupts junctions in cultured endothelial cells, the lack of VE-cadherin in vivo causes vascular leakage in some organs (lung or heart) but not in others, highlighting the importance of additional regulatory mechanisms. This illustrates fundamental differences between the structural basis of mature endothelial junctions in vivo and in vitro that are not yet well understood. Numerous leakage-inducing agonists, such as VEGF, histamine and bradykinin, affect junctions by targeting VE-cadherin. This is partly based on stimulating tyrosine phosphorylation of VE-cadherin that triggers its endocytosis. Interestingly, phosphorylation of distinct VE-cadherin tyrosine residues affects leukocyte diapedesis and cellular responses to shear forces.

Several members of the SRC family kinases phosphorylate VE-cadherin. Endothelial excision of the SRC kinase YES1 results in exaggerated blood vascular leakage, whereas deletion of SRC suppresses vascular leakage, which indicates that SRC kinases have distinct roles in opening and closing gaps at endothelial adherens junctions[4]. Of the many phosphotyrosine phosphatases (PTPs) expressed in endothelial cells, vascular endothelial protein tyrosine phosphatase (VE-PTP) and density enhanced phosphatase-1 (DEP1, also known as PTPRJ or CD148) are of particular interest. They act on various targets and kinases implicated in junction regulation. VE-PTP dephosphorylates TIE2, a tyrosine kinase receptor known to promote junction stability by regulating the tension of the actin cytoskeleton through RHO GTPases. VE-PTP also controls the phosphorylation of VE-cadherin and VEGF receptor-2 (VEGFR2), pathways that can destabilize junctions[5]. Therefore, depending on their substrates, kinases and PTPs can either strengthen or weaken endothelial junctions.

In vitro studies show that the organization of F-actin is another crucial determinant of junctional permeability. Evidence suggests that actin stress fibers perpendicular to the cell edge exert contractile forces that open cell–cell junctions and increase permeability, whereas actin bundles parallel to the edge reduce leakage. Cortical actin, the thin mesh of actin fibers tethered to the plasma membrane, likely also contributes to permeability control. Cross-talk between basal, integrin-mediated focal adhesions that anchor stress fibers and VE-cadherin-mediated junctions also affect permeability. How these results apply to endothelial cell types (such as post-capillary venules) in which large F-actin bundles are absent remain unknown.

In summary, vascular permeability is regulated by the actions of SRC family kinases and endothelial phosphatases, which balance the stability of endothelial adherens junctions. Leakage agonists act on VE-cadherin to destabilize adherens junctions while leakage suppressors enforce the actin cytoskeleton. The regulation of endothelial tight junctions is less well understood.

Neutrophil-dependent edema

The vascular barrier regulates the extravasation of plasma proteins and controls the entry of leukocytes into inflamed tissues, which, in acute inflammation, predominantly involves rapid infiltration of neutrophils. Although increased vascular permeability and neutrophil migration into inflamed tissues occur together, these events have definitively been uncoupled mechanistically and anatomically. Direct permeability-inducing factors (such as VEGF) are unable to elicit neutrophil diapedesis owing to their inability to provide directional cues for migrating immune cells. Moreover, neutrophil diapedesis does not inherently cause an increase in vascular leakage, possibly linked to the tight contact between neutrophils and endothelial cell junctions during diapedesis. With respect to the latter, there is evidence for actomyosin filaments within endothelial cells that surround the diapedesis site and are stimulated by local RhoA, to function as elastic straps and help maintain the membrane integrity near the transmigrating leukocyte.

Neutrophil accumulation at inflammatory sites initiated by local pathogens and/or sterile injury, such as an ischemic insult, is mediated by the local generation of soluble chemoattractant molecules. Examples are C5a, a product of local extravascular complement activation, and molecules secreted locally by tissue and inflammatory cells, such as LTB_4 and the chemokine CXCL8 (also known as IL-8). These molecules potently increase permeability via neutrophil-dependent mechanisms. Neutrophils respond by secreting direct-acting permeability mediators when in close apposition to venular endothelial cell junctions.

Recent studies have shed light on the complex interplay between vascular leakage and neutrophil extravasation. Specifically, leaky microvessels support the reverse migration of neutrophils via endothelial cell junctions and their re-entry into the systemic circulation[6]. This aberrant behavior, termed neutrophil reverse migration, is promoted by permeability-increasing stimuli through disrupted localization of chemotactic cues

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across the venular wall. Importantly, neutrophils that exhibit reverse migration form an activated sub-population that, once back in the circulation, disseminate to other organs, most notably lungs, where they cause vascular leakage. This cascade of events offers a mechanism to explain how local tissue inflammation and vascular leakage can induce downstream pathological effects in remote organs, which suggests that targeting vascular leakage can have beneficial therapeutic effects both locally and in distal organs. Of note, because increased vascular leakage is a characteristic feature of inflamed aged tissues, anti-edema therapeutics could be beneficial in protecting from tissue damage in age-linked disorders.

In summary, neutrophil diapedesis and vascular leakage are regulated by different molecular pathways and occur at distinct anatomical sites. Nonetheless, these processes are temporally closely aligned, with one capable of augmenting the other to promote inflammation.

Edema resolution

Inflammatory edema affects the tissue architecture by increasing the interstitial pressure in the acute phase, compressing the microcirculation, and when sustained, increasing tissue hypoxia that causes cell damage. This cascade of events can potentially drive an acute inflammatory response towards a prolonged, non-resolving chronic state. In later phases, edema causes tissue remodeling, typically resulting in increased stiffness. Edema resolution in the acute phase occurs by the clearance of fluid promoted by the high interstitial pressure and by the colloidal pressure of the blood. A major route for the clearance of fluid, macromolecules and cells is the lymphatic vasculature. Here, interstitial fluid is drained by lymphatic capillaries made of endothelial cells with discontinuous button-like junctions to enable the entry of fluid into the vessels. Lymphatic capillaries drain into collecting vessels that have continuous 'zipper' junctions, valves and a smooth muscle coat to propel the lymph fluid forward. Recent work has shown that button junctions will tighten, or zipper, after bacterial or viral infection, and studies have shown that VEGFR2 signaling may lead to zippering of button junctions, leading to impaired absorption[7]. By contrast, VEGFR3 signaling opposes button formation in lymphatic capillaries during postnatal development[8].

Efficient fluid drainage requires the formation and maintenance of lymphatic valves in collecting lymphatic capillaries. Several studies have shown that valves form in response to oscillatory shear stress. Lymphatic mechanotransduction induces AKT and β-catenin signaling pathways that are dependent on VE-cadherin. These pathways then activate transcription factors (PROX1, FOXC2 and GATA2) to initiate valve growth. FOXO1 is another transcription factor that is inactivated by AKT phosphorylation and is a negative regulator of valve formation; thus, inhibition of FOXO1 holds potential clinical value to induce valve growth in patients with disease. Although evidence supports a mechanosensory complex containing PECAM-1 and VE-cadherin in lymphatic endothelium, direct experiments are needed to show whether this complex is identical to blood endothelium and probe for VE-cadherin-binding partners.

Another potential physiological mode of resolving inflammatory edema is the generation of specialized pro-resolving mediators such as lipoxins, E-series, D-series and T-series resolvins, protectins and maresins that are enzymatically derived from essential fatty acids. These molecules act as mediators that limit acute inflammatory responses and orchestrate wound healing. Moreover, anti-inflammatory and tissue-protective proteins (such as alpha-1 antitrypsin or gelsolin) are abundant in resolving exudates. The mechanism and extent to which these mediators regulate inflammation-induced edema are unknown.

In summary, resolution of edema depends on the capacity of the lymphatic vasculature to clear interstitial fluid. The architecture of lymphatic junctions involving VE-cadherin and tight junction proteins, organized in buttons and zippers, and formation of functional valves, are key aspects of fluid uptake and propagation. Pro-resolving mediators, SMPs, may also be implicated in edema resolution.

Disease examples

Almost all cardiovascular and inflammatory diseases are accompanied by interstitial edema that frequently has an important pathogenic role, most notably in aged individuals. Sustained edema likely has pro-inflammatory effects and prolongs adverse effects of the initial injury and of conditions that subsequently develop.

Cardiovascular diseases. Tissue damage by infarction and ischemia–reperfusion injury strongly increase vascular leakage and the accumulation of interstitial fluid. Consequently, edema is a key feature of cardiovascular disorders such as myocardial infarction or stroke. Extensive edema of the myocardium, persisting for up to 30 days in patients after large infarcts, has been documented by magnetic resonance imaging (MRI). However, the contribution of edema to outcome remains unresolved. Mouse studies suggest that the edema is driven by VEGF and adversely affects ventricular function.

The endothelium overlying atherosclerotic plaques is known to be abnormally permeable. However, whether restoration of endothelial integrity in plaques can reduce or delay atherosclerosis development and progression of local inflammation in patients is unknown. In mice, the VE-PTP inhibitor AKB9778 can reduce plasma leakage in atheroprone regions of the aorta and suppress atheroma formation in a high-fat-diet model of atherosclerosis[9].

In stroke, acute ischemia leads to breakdown of the blood–brain barrier with peri-infarct inflammation and vasogenic edema. In vivo studies indicate that brain edema emerges 12–24 h after the onset of cerebral ischemia. The ensuing mass effects lead to compression of adjacent brain tissue and the vasculature, contributing to poor outcomes and potentially to fatal brain herniation syndromes. Animal models suggest that VEGF is a principal driver of vascular permeability and that inhibition of VEGF-induced edema results in a roughly 50% reduction in infarct size in pre-clinical models[10]. Claudin-5 is an important molecular component of blood–brain barrier tight junctions and its dysfunction has been aligned with multiple sclerosis, Alzheimer's disease, depression and stroke. VE-cadherin is also central to the maintenance of brain vascular integrity, although under neuroinflammatory conditions this process is complex, with several signaling pathways affecting VE-cadherin stability.

Intracerebral hemorrhage generates a massive inflammatory response where the extent of edema robustly predicts outcome, even after adjusting for the size of the hemorrhage. Subarachnoid hemorrhage can also result in widespread edema in the CNS. This phenomenon is related to diffuse ischemic injury and the inflammatory effects of blood and its breakdown products, and is considered an independent risk factor for mortality and poor outcome. Traumatic brain injury is also complicated by edema, although the consequences remain to be established.

Neurodegenerative diseases. Many neurodegenerative diseases are exacerbated by increased vascular permeability, inflammation and edema. Thus, cerebral amyloid angiopathy results in immune activation and

inflammation with vasogenic edema leading to a precipitous cognitive decline in some patients. New immune-mediated treatments for Alzheimer's disease can be accompanied by inflammation and edema, most likely related to concurrent amyloid angiopathy that requires cessation of treatment. There is also an emerging concept that brain edema precedes the development of Alzheimer's neurodegeneration, exerting overt symptoms in mouse models and in patients.

Wet AMD and related diseases. Macular edema is the leading cause of vision loss and blindness worldwide. In wet AMD, structurally abnormal, leaky and fragile vessels are formed, leading to vision deterioration[3]. The mechanisms of VEGF-dependent leakage in eye diseases are complex. Anti-VEGF agents, including neutralizing anti-VEGF antibodies and recombinant receptor fragments, administered through intravitreal injection are used in the clinic to effectively suppress edema, leading to vision improvement[3].

Pulmonary diseases. Pulmonary hypertension is associated with interstitial edema. The driver for edema formation and its pathogenic importance have not been established. It is not clear whether edema contributes to chronic inflammation seen in patients with pulmonary hypertension, and to the associated endothelial-to-mesenchymal transition that is often observed. Acute inflammation of the lung (for example in acute respiratory distress syndrome, sepsis or COVID-19) is accompanied by extensive interstitial edema. Circulating BMP9, a member of the TGFβ family that signals selectively in endothelial cells, has been identified as an endogenous negative regulator of endothelial hyperpermeability. Emerging data suggests that BMP9 can maintain endothelial cell barrier properties and reduce plasma leakage and lung injury associated with sepsis and ARDS[11].

Cancer. Many solid tumors are accompanied by hypoxia, VEGF production, and edema that promote metastatic spread, and hinder treatment. The tumor vasculature is structurally abnormal and has impaired perfusion, which limits the delivery of neutralizing VEGF antibodies and other drugs. Although anti-VEGF antibodies are used in the treatment of metastatic colorectal cancer, renal cancer, gastric cancer, and some other tumor types, they are usually used in combination with chemotherapy or other agents, including immunotherapy that boosts immune cell infiltration and anti-tumor immunity. Agents that target VEGF signaling reduce edema, lower interstitial pressure, and facilitate delivery of other therapeutics.

In summary, a broad range of diseases, ranging from cardiovascular, cancer, retinopathy and pulmonary hypertension to neurodegenerative diseases, are accompanied by reduced integrity of endothelial junctions, tissue edema and inflammation. Whether therapeutic stabilization of the vascular barrier and resolution of edema can halt/suppress inflammation and disease progression requires further exploration.

Pharmacological therapies

Surprisingly, there are no therapies that can selectively reduce inflammation-associated interstitial edema. Anti-inflammatory drugs such as corticosteroids can reduce edema by reducing inflammation, but they affect several biological pathways and carry considerable risks. Anti-VEGF agents, approved for the treatment of cancer and retinopathies including wet AMD, restore vascular integrity in inflammatory settings, but potentially cause vessel rarefaction that can lead to fibrosis and augment tissue ischemia. Because reducing vascular permeability and edema is an attractive strategy, therapeutic approaches that do not impair endothelial survival are being developed.

The restoration (or preservation) of vascular integrity can be achieved by maintaining the plasma membrane localization of VE-cadherin, or by tightening the cytoskeletal machinery associated with adherens and tight junctions. Specifically, stabilization of VE-cadherin expression at the plasma membrane can be achieved by RNA interference-mediated prevention of its degradation. One such agent, CD5-2, has been reported to restore vascular integrity in chronic inflammatory settings[12]. Another approach has focused on selective regulation of VEGF-induced permeability while leaving other VEGF signaling pathways intact. This has been achieved by using an antibody that blocks endocytosis of the tyrosine phosphatase DEP1 and induces DEP1-dependent dephosphorylation of the VEGFR2 site involved in activation of the permeability cascade[10]. Studies using this antibody reported extensive suppression of edema after acute stroke or laser retinal injury with significant beneficial functional effects.

Other key strategies involve tightening of adherens and tight junctions by activation of cytoskeletal machinery. One approach uses a S1P pathway to achieve junction stabilization and pericyte coverage[13]. A further approach is based on stimulating TIE2. This receptor is known to stabilize junctions, but its natural agonist ANGPT1 forms complex multimeric structures that are difficult to handle. An alternative mode of TIE2 stimulation is provided by VE-PTP, which counteracts its activity. A highly selective VE-PTP inhibitor (AKB-9778) was found to stabilize the ocular vasculature in a phase 2a trial[14]. Finally, CU06-1004, a pseudo-sugar derivative of cholesterol that increases cAMP and activates RAC, has shown anti-edema efficacy in several experimental disease models, including models of myocardial infarction, and is currently undergoing clinical trials[15].

Overall, although there is ample evidence for the beneficial effects of anti-leakage therapies in experimental disease models, controlling pathological responses while maintaining the physiological role of vascular leakage is important for successful therapeutic intervention. Moreover, as with all anti-inflammatory therapies, particularly when targeting neutrophil-dependent edema, the benefits of anti-edema strategies must be balanced against the potential deleterious effects of interfering with host defense and tissue repair mechanisms.

In summary, new therapeutics that stabilize endothelial junctions by blocking inflammatory mediator-induced effects, or by enforcing the junction-proximal cortical actin cytoskeleton, are being developed, with a focus on ocular disease, such as age-related macular degeneration, and stroke. Such therapies include VE-cadherin-targeted RNA interference, reagents that regulate phosphatase activities, S1P agonists, TIE2 agonists, and other drug candidates with as-yet uncertain mechanisms.

Key unresolved issues

Despite substantial progress in recent decades, more work is needed to understand fundamental issues related to regulation of endothelial junctions. The dynamics of actin formation and tension across actomyosin filaments is key to the regulation of endothelial junctions. It will be important to determine how the regulation of junction-destabilizing and junction-supporting components of the actin filament network by Rho GTPases and actin nucleation factors is coordinated. This is also central to understanding the regulation of adhesion molecules, with previous studies mainly focusing only on mechanisms that regulate their biosynthesis or endocytosis. Other important questions are how the barrier properties of adherens and tight junctions

are coordinated in response to inflammatory mediators and how the regulation of junctions in cultured endothelial cells compares with the process in intact blood vessels.

In addition to determining vascular permeability, cell–cell junctional complexes are signaling centers that have a major role in decoding and integrating extracellular stimuli. Shear stress is one example, but cell cycle and growth factor or cytokine signaling are also highly dependent on cell–cell junctions. So far, a fraction of the components of cell–cell junctions have been identified, a smaller proportion of the physical interactions between these components have been decoded, and very few regulatory interactions have been determined. Future works is needed to decipher the full network of physical and regulatory interactions, how they are controlled by external stimuli and mediate downstream regulation of endothelial phenotypes.

Furthermore, how organs differently regulate plasma flux in different conditions is not known. Some organs (such as lung, liver and kidney) can handle high flux of plasma without causing collateral damage to the tissue parenchyma, whereas others (such as brain, retina, testes) cannot. Differential processing of plasma constituents, such as proteins, lipids and nucleic acids by tissue parenchyma of various tissues often determine the outcome of such perturbations. This needs to be understood at systems level as well as defined signaling hubs. Key questions include how plasma-derived bioactive factors (such as products of fibrin degradation or bioactive lipids) affect tissue reactions, and whether increased hydrostatic pressure in relation to matrix composition in organs signal to vascular and lymphatic endothelial cells in a biophysical way in addition to chemical signaling processes.

The molecular basis of localized neutrophil attachment and activation in different vascular beds, in different physiological or pathological setting and in different contexts, such as ageing, deserves better understanding. Furthermore, at present it is not clear whether neutrophil-mediated vascular leakage involves a distinct subset of neutrophils and at which stage of the diapedesis process neutrophil-derived permeability enhancing factors are released and are most efficacious. Finally, the role of other leukocytes (such as monocytes) in vascular leakage, most notably in chronic inflammatory conditions, requires further exploration. Of note, aged tissues are known to express greater number of mast cells, a phenomenon that supports aberrant neutrophil trafficking or activation and could contribute to enhanced edema in aging-associated pathologies.

With respect to lymphatic vessels, how button junctions form is not well understood, and little is known about the tight junction proteins that regulate lymphatic junctions. In addition, we do not understand which inflammatory mediators, if any, can affect lymphatic junctions in a similar manner to that in blood vessels (such as VEGF, bradykinin and histamine). As VEGFR2 signaling seems to convert discontinuous button junctions into zipper junctions in lymphatic capillaries, inflammatory signaling mediators could stabilize lymphatic junctions rather than disrupt them. Whether lymphatic permeability can be increased (or decreased) in both initial lymphatic capillaries and collecting vessels is unknown. Collectively, more research is needed to delineate the signaling regulators of button and zipper junction formation as well as their composition, and identify which signaling pathways could represent therapeutic targets to alleviate the effects of congenital gene mutations or treat infection.

Finally, considering the growing body of evidence indicating the pathogenic role of interstitial edema in numerous disease states, there is now much focus on whether preventing, reversing or controlling vascular leakage would be clinically beneficial. Data emerging from experimental disease models support the notion that selective anti-leak therapies will be protective in multiple disease conditions. Crucially, however, effective use of such therapeutics requires comprehensive understanding of their mode of action at the molecular, cellular and tissue level.

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Competing interests

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