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Atherosclerosis newsletter

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The endothelium plays multiple roles in the pathogenesis of atherosclerosis and other vascular diseases. The two December issues of *Atherosclerosis* contain three reviews focusing on its role as a barrier towards the entry of inflammatory cells and lipoproteins from the blood stream into the arterial wall but also the delivery of drugs for therapy as well as tracers for imaging. Another review highlights the importance of the endothelium and endothelial dysfunction in Coronavirus Disease 2019 (COVID-19) and its complications. A fifth review summarizes our current knowledge on the special role of the retinal microvasculature as a reporter of cardiovascular health.

Actin remodelling of the endothelium during transendothelial migration of leukocytes

For leukocytes crossing the vessel wall to solve inflammation, the endothelium acts as customs control. In the past years, some progress has been made to identify the molecular mechanisms used by both the leukocytes and endothelium to allow efficient crossing, although not all the exact rules these vascular customs play by are completely understood. In this review, van Steen et al. focus on the contribution of the endothelium to the process of leukocyte extravasation and summarize the different molecular mechanisms involved in efficient leukocyte passage and prevention of local leakage at the same time. The authors highlight the dynamic regulation of the endothelial actin cytoskeleton, which is a key player in leukocyte transendothelial migration under the influence of different stimuli.

Transendothelial transport of lipoproteins

The accumulation of low-density lipoproteins (LDL) in the arterial wall plays a pivotal role in the initiation and pathogenesis of atherosclerosis. Conversely, the removal of cholesterol from the intima by cholesterol efflux to high density lipoproteins (HDL) and subsequent reverse cholesterol transport shall confer protection against atherosclerosis. To reach the subendothelial space, both LDL and HDL must cross the intact endothelium. Traditionally, this transit is explained by passive filtration. This dogma has been challenged by the identification of several rate-limiting factors namely scavenger receptor SR-BI, activin like kinase 1, and caveolin-1 for LDL as well as SR-BI, ATP binding cassette transporter G1, and endothelial

lipase for HDL. In addition, estradiol, vascular endothelial growth factor, interleukins 6 and 17, purinergic signals, and sphingosine-1-phosphate were found to regulate transendothelial transport of either LDL or HDL. In this review, Jang et al. discuss transendothelial lipoprotein transport; thorough understanding of this mechanism is expected to elucidate new therapeutic targets for the treatment or prevention of atherosclerotic cardiovascular disease and the development of strategies for the local delivery of drugs or diagnostic tracers into diseased tissues including atherosclerotic lesions.

Surmounting the endothelial barrier for delivery of drugs and imaging tracers

The endothelium serves as a refined barrier between blood components and tissue, crucial in guarding vascular homeostasis. In atherosclerosis, this barrier function is impaired, which is characterized by secretion of chemoattractants and cytokines, upregulation of adhesion molecules and increased vascular permeability. This facilitates enhanced leukocyte migration through the vessel wall. These features can be used to deliver drugs and imaging tracers into the interstitial space by means of nanomedicine. This leads to targeted, local delivery of therapeutic agents, which enhances the specificity and efficacy of these agents and thus, could be used to inhibit disease progression. Additionally, delivery of imaging tracers in the interstitial space gives insight into the vulnerability of atherosclerotic plaques by targeting resident macrophages and activated endothelial cells, providing pivotal information that is currently lacking in the clinic. In this review, Schnitzler et al. discuss how the endothelial barrier is affected during atherosclerosis and how to surmount this barrier for successful delivery of nanomedicine carrying drugs and imaging tracers to both the endothelium and macrophages.

Endothelial dysfunction in COVID-19: Current findings and therapeutic implications

Coronavirus disease 2019 (COVID-19) increases the risk of several non-pulmonary complications such as acute myocardial injury, renal failure or thromboembolic events. A possible unifying explanation for these phenomena may be the presence of profound endothelial dysfunction and injury. Nägele et al. provide an overview on the association of endothelial dysfunction with COVID-19 and its therapeutic implications.

Endothelial dysfunction is a common feature of the key comorbidities that increase risk for severe COVID-19 such as hypertension, obesity, diabetes mellitus, coronary artery disease or heart failure. Preliminary studies indicate that vascular endothelial cells can be infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and evidence of widespread endothelial injury and inflammation is found in advanced cases of COVID-19. Prior evidence has established the crucial role of endothelial cells in maintaining and regulating vascular homeostasis and blood coagulation. Aggravation of endothelial dysfunction in COVID-19 may therefore impair organ perfusion and cause a procoagulatory state resulting

in both macro- and microvascular thrombotic events. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and statins are known to improve endothelial dysfunction. Data from smaller observational studies and other viral infections suggests a possible beneficial effect in COVID-19. Other treatments that are currently under investigation for COVID-19 may also act by improving endothelial dysfunction in patients. Focusing therapies on preventing and improving endothelial dysfunction could improve outcomes in COVID-19. Several clinical trials are currently underway to explore this concept.

Physical activity and exercise improve retinal microvascular health as a biomarker of cardiovascular risk: A systematic review

Physical activity (PA) and fitness are important modulators of vascular ageing and may therefore help expand individual health span. Streese et al. aimed to systematically review the association of PA and fitness, as well as the effects of exercise interventions on the new microvascular biomarkers retinal arteriolar (CRAE) and venular (CRVE) diameters and the retinal flicker light-induced dilatation (FID) in children and adults since the microcirculation is a promising vascular bed for cardiovascular (CV) risk stratification and risk prediction.

PubMed, Ovid, The Cochrane, EMBASE and Web of Science were searched. Eight hundred and five studies were found, and 21 articles were included in this systematic review.

Higher PA levels were associated with narrower CRVE in children and adults. Physical inactivity was associated with wider CRVE in both age groups. Combined aerobic and motor skill training in school settings lead to wider CRAE in children. Aerobic exercise interventions in adults with or without CV risk factors induced wider CRAE and narrower CRVE. Studies on the effect of exercise on FID are scarce. In a twelve-week randomized controlled trial, high-intensity interval training significantly improved FID in older patients with CV risk factors.

Higher PA and fitness levels were associated with improved retinal microvascular health in children and adults. Short-term exercise interventions in healthy children and adults, as well as CV risk patients, improved retinal microvascular structure and function. Physical activity behaviour affects retinal microvascular health in all age groups. Exercise has the potential to counteract development of small vessel disease. Retinal vessel analysis can differentiate the beneficial effects of exercise on target microvascular organ damage.