***Atherosclerosis* newsletter**

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The two April issues of *Atherosclerosis* contain several articles with data from population studies, intervention studies, and animal experiments that investigated the role of inflammation in cardiovascular disease

Systemic immune-inflammation index and incident cardiovascular diseases among middle-aged and elderly Chinese adults: The Dongfeng-Tongji cohort study

Emerging data have shown that some inflammation and immune indices based on the complete blood count, such as platelet-lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR), can serve as predictors of cardiovascular events in patients at risk of primary cardiovascular disease (CVD). However, a novel inflammation and immune marker, defined as systemic immune-inflammation index (SII), which is calculated using platelet, neutrophil and lymphocyte counts, has not yet been examined for its link with CVD. In this study, Xu et al. aim to prospectively assess the association of SII with incident CVD and its main subtypes in Chinese adults.

Using data from the Dongfeng-Tongji cohort study, 13,929 middle-aged and older adults with a mean age of 62.56 years, who were free of CVD and cancer, were included in the analysis. The SII was calculated as platelet count (/L) × neutrophil count (/L)/lymphocyte count (/L). Cox regression models were used to examine the associations of SII with incident CVD, including stroke and coronary heart disease (CHD).

Over a median 8.28 years of follow-up, 3386 total CVD cases, including 801 stroke cases and 2585 total CHD cases, were identified. In multivariable Cox regression analyses, higher levels of log-transformed SII were significantly associated with total and ischemic stroke.

These results suggest that SII may serve as a useful marker to elucidate the role of the interaction of thrombocytosis, inflammation, and immunity in the development of cerebrovascular diseases in the middle-aged and elderly population.

Cardiovascular effects of omega-3 fatty acids: Hope or hype?

Omega-3 fatty acids have emerged as a new option for controlling the residual risk for cardiovascular disease (CVD) in the statin era, after a clinical trial (REDUCE-IT) reported positive results with icosapent ethyl (IPE) in patients receiving maximally tolerated statin therapy. However, another

trial, which used high dose eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) combination (STRENGTH), has failed. Together, these results raise clinically important questions. Are effects of omega-3 fatty acids neutral or beneficial in patients on statin therapy, or perhaps even harmful? The current contradictory results could be attributed to different types of omega-3 fatty acids (only EPA or combination of EPA + DHA), doses (higher *vs.* lower dose) of omega-3 fatty acids or different comparators (corn oil or mineral oil), as well as the underlying severity of the CVD risk or use of statins. Together with these issues, Jo et al. discuss different biological and clinical effects of various types of omega-3 fatty acids and then interpret different results of past and current clinical studies and propose practical suggestions, which could be applied to patient management.

Impact of myeloid *RIPK1* gene deletion on atherogenesis in ApoE-deficient mice

Atherosclerosis is a chronic inflammatory disease characterized by the accumulation of atherosclerotic plaques in medium- and large-sized arteries. During plaque development, macrophages and vascular smooth muscle cells undergo necrosis and release their cytoplasmic content in the plaque, which initiates the formation of a central necrotic core. Targeting macrophage death is a promising strategy for stabilizing the atherosclerotic plaques. Recently, necroptosis was identified as a form of regulated necrosis in atherosclerosis. Receptor-interacting serine/threonine-protein kinase (RIPK)1 is an upstream regulator of RIPK3, which is a crucial kinase for necroptosis induction. Coornaert et al. aimed to investigate the impact of myeloid-specific *RIPK1* gene deletion on atherogenesis.

RIPK1$^{F/F}$*LysM-Cre*$^{+}$*ApoE*$^{-/-}$ and *RIPK1*$^{+/+}$*LysM-Cre*$^{+}$*ApoE*$^{-/-}$ mice were fed a western-type diet (WD) for 16 or 24 weeks to induce plaque formation.

After 16 weeks of western diet (WD), plaque area and percentage necrosis in *RIPK1*$^{F/F}$*LysM-Cre*$^{+}$*ApoE*$^{-/-}$ mice were significantly decreased as compared to plaques of *RIPK1*$^{+/+}$*LysM-Cre*$^{+}$*ApoE*$^{-/-}$ mice. Moreover, plaques of *RIPK1*$^{F/F}$*LysM-Cre*$^{+}$*ApoE*$^{-/-}$ mice showed more apoptosis and a decreased macrophage content. After 24 weeks of WD, plaque size and percentage necrosis were no longer different between the two groups. Free apoptotic cells strongly accumulated in plaques of *RIPK1*$^{F/F}$*LysM-Cre*$^{+}$*ApoE*$^{-/-}$ mice. In addition to apoptosis, necroptosis was upregulated in plaques of *RIPK1*$^{F/F}$*LysM-Cre*$^{+}$*ApoE*$^{-/-}$ mice. *In vitro*, TNF-α triggered apoptosis in *RIPK1*$^{F/F}$*LysM-Cre*$^{+}$*ApoE*$^{-/-}$, but not in *RIPK1*$^{+/+}$*LysM-Cre*$^{+}$*ApoE*$^{-/-}$ macrophages. Moreover, *RIPK1*$^{F/F}$*LysM-Cre*$^{+}$*ApoE*$^{-/-}$ macrophages were not protected against RIPK3-dependent necroptosis.

The impact of myeloid *RIPK1* gene deletion depends on the stage of atherogenesis. At 16 weeks of WD, myeloid *RIPK1* gene deletion resulted in increased apoptosis, thereby slowing down plaque progression. However, despite decreased macrophage content, plaque and necrotic core size were no

longer reduced after 24 weeks of WD, most likely due to the accumulation of free apoptotic and necroptotic cells.

HDAC3 protects against atherosclerosis through inhibition of inflammation *via* the microRNA-19b/PPARγ/NF-κB axis

Atherosclerosis is recognized as the leading cause of morbidity and mortality associated with cardiovascular diseases and studies have revealed critical roles of microRNAs (miRNAs) in its progression, due to their regulation of cellular and molecular processes associated with atherosclerosis development, ranging from risk factors, to plaque initiation and progression, to atherosclerotic plaque rupture. A previous study suggested that one of these miRNAs (miR-19b) contributes to the occurrence of atherosclerosis by activating perivascular adipose tissue inflammation in ApoE deficient ($ApoE^{-/-}$) mice. Wang et al. aimed to further elucidate the role and mechanism by which miR-19b influences atherosclerosis.

Human umbilical vein endothelial cells (HUVECs) were treated with oxidized-low-density lipoprotein (ox-LDL), and an atherosclerosis mouse model was generated with the help of $ApoE^{-/-}$ mice using a high-fat diet regimen. The expression patterns of peroxisome proliferator-activated receptor γ (PPARγ), nuclear factor κB (NF-κB)/p65, miR-19b and histone deacetylase 3 (HDAC3) were then characterized by reverse transcription quantitative polymerase chain reaction and Western blot analysis. In addition, the relationship among PPARγ, NF-κB/p65, miR-19b and HDAC3 was evaluated by co-immunoprecipitation, chromatin immunoprecipitation and dual-luciferase reporter gene assays. Gain- and loss-of-function experiments were also performed to examine their functional significance on ox-LDL-induced inflammation in HUVECs. Enzyme-linked immunosorbent assay was applied to determine the expression patterns of inflammatory factors in the mice.

PPARγ and HDAC3 were poorly expressed, while miR-19b and NF-κB/p65 were highly expressed in ox-LDL-induced HUVECs and arterial tissues of mice. PPARγ inhibited ox-LDL-induced inflammation in HUVECs by ubiquitination and degradation of NF-κB/p65. miR-19b, downregulated by HDAC3, targeted PPARγ and negatively-regulated its expression. Upregulated PPARγ or HDAC3 or downregulated miR-19b or NF-κB/p65 reduced TNF-α and IL-1β expression levels in ox-LDL-induced HUVECs and mice.

The results show that HDAC3 upregulation prevents inflammation to inhibit atherosclerosis by inactivating NF-κB/p65 via upregulation of miR-19b-mediated PPARγ.

Coronavirus disease-19: The multi-level, multi-faceted vasculopathy

The new coronavirus disease (COVID-19) is a systemic disease. Mounting evidence depict signs and symptoms involving multiple organs, most of which supported by pathological data. A plausible link to these manifestations is vascular and endothelial dysfunction/damage. However, much of the current knowledge relies on opinion and incipient evidence. Quinaglia et al. aimed to objectively appraise current evidence on the association between COVID-19 and vascular disease, specifically endotheliitis and vasculitis.

Two researchers independently entered the search terms COVID-19 OR SARS-CoV-2 AND vasculitis, endotheliitis OR endothelium in MedRxiv and LitCovid (PubMed). The search period was set from November 1, 2019 to August 28, 2020. Manuscripts with unavailable full texts, not in English, mainly on pre-clinical data, presenting only study designs or not directly related to the topics of this review were excluded. Retrospective and prospective studies, especially longitudinal ones, were given priority. Since there was paucity of prospective controlled evidence, case reports/series were also considered.

A total of 318 manuscripts were initially found. Sixty-seven (21%) were excluded: 59 (18.5%) met exclusion criteria and 8 (2.5%) were duplicates. One hundred and forty-two manuscripts (44,6%) did not provide original data and were also excluded: 35 (11%) were comments, 108 (33.9%) reviews; 1 (0.3%) position paper. One hundred and seven (33.6%) studies were considered for the present review: 81 (25,5%) case reports/series; 18 (5.7%) prospective; and 8 (2.5%) retrospective. Viral inclusions in endothelial cells, mononuclear cell infiltrates in the intima of small vessels and markers of endothelial cell apoptosis were demonstrated. Specificities of COVID-19 may lead to diverse vascular manifestations at different levels of the vascular bed.

Evidence indicates that COVID-19 targets the vasculature and endothelium. However, high quality data is still lacking and studies with prospective designs and appropriately matched controls are needed.