In this Issue

**PCSK9 Association with Lipoprotein(a) (p 29)**

*Tavori et al* discover that the atherogenic factor lipoprotein(a) associates with PCSK9.

Lipoprotein(a) (Lpa), a low-density lipoprotein (LDL)-like particle, is considered highly atherogenic, and high levels of Lpa in the blood are associated with an increased risk of myocardial infarction and stroke. Interestingly, a new class of LDL-lowering drugs—monoclonal antibodies that block the activity of Proprotein convertase subtilisin/kexin type 9 (PCSK9)—have been shown to also lower Lpa, although the relationship between PCSK9 and Lpa is currently unclear. PCSK9 binds and degrades the LDL receptor (LDLR), and anti-PCSK9 antibodies prevent this degradation to promote LDL clearance. Recently however, PCSK9 has been found to bind LDL itself. Tavori and colleagues wondered whether PCSK9 might also associate with Lpa. They examined serum from 39 patients with high Lpa levels and from transgenic mice expressing human Lpa and found that PCSK9 did indeed associate with Lpa—indeed, it did so in preference to LDL. Although the functional implication of this association remains unclear, the authors suggest that high plasma levels of PCSK9-bound Lpa might be a potential biomarker for cardiovascular disease.

**The Malaria-High Blood Pressure Hypothesis (p 36)**

*Etyang et al* suggest malaria might lead to hypertension in developing countries.

Hypertension and cardiovascular diseases are widespread in many low and middle-income countries (LMIC) in Asia and Africa, where the burden of infectious diseases such as malaria is also high. Although, some studies have linked inflammation and infections with cardiovascular disease, it has not been considered whether malaria itself might contribute to hypertension. Based on their review of the literature, Etyang and colleagues now propose a hypothesis: that malaria contributes to hypertension in several ways. For example, in pregnant women malaria can lead to underweight babies, and low birth weight has been linked to hypertension later in life. Moreover, malaria can cause chronic inflammation, which can predispose a person to cardiovascular disease. The team suggests that traditional case-controlled studies comparing the prevalence of hypertension between people who have had and not had malaria would be one approach to formally examine this link, but they also point out that a reliable immunological marker of malaria exposure does not exist. They also suggest animal experiments, but note that the mouse models of malaria and hypertension are imperfect approximations of their human counterparts. Should direct testing confirm Etyang and colleagues’ hypothesis, however, it could have far reaching public health implications.

**Fibro-Adipocyte Progenitors in AC (p 41)**

*Lombardi et al* investigate the source of excess adipocytes in arrhythmogenic cardiomyopathy.

Arrhythmogenic cardiomyopathy (AC), which is characterized by excess fibro-adipocytes in the heart, is a primary cause of sudden cardiac death in young individuals. Mutations in genes that encode desmosome proteins, such as desmoplakin (DSP), are considered the main cause of AC, but how desmosome proteins, which are expressed in cardiomyocytes are not the only heart cells to express desmosomes. They found that both human and mouse hearts contain fibro-adipocyte progenitor cells (FAPs), a subset of which express desmosomes as well as an adipogenic marker. In the hearts of mice whose FAPs were genetically engineered to lack DSP, a large excess of adipocytes was observed. These animals also exhibited modest ventricular dilation and dysfunction. While, it is not yet clear how desmosome deficiency leads to excess adipogensis, the team showed that it involved suppression of canonical Wnt signaling. The team found that almost half of the excess adipocytes originated from FAPs in the mutant animals, suggesting that FAPs are likely to be a major contributor to AC pathology, but that other cell types must be involved as well.