Atherosclerosis development

Atherosclerosis development: lipoproteins and beyond

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Even the most sceptical cardiovascular scientists can now rest assured: LDL demonstrates a causal relationship to atherosclerotic cardiovascular disease (CVD) [1▪▪]. A combined dataset of meta-analyses of over 200 cohort-based, mendelian randomization, and randomized trials covering 2 million subjects, followed for more than 20 million person years with more than 150 000 major adverse cardiovascular events (MACEs) showed 1) a dose-dependent linear relationship between LDL-c levels and MACE, and 2) if LDL plasma particles are reduced without off-target effects, the risk of MACE is reduced. This is timely news in light of recent clinical outcomes concerning a new type of LDL-lowering compound, proprotein convertase subtilisin/kexin type 9 (PCKS9) antibody inhibitors, such as evolocumab, bococizumab, and alirocumab [2–4]. These antibodies prevent degradation of the LDL receptor, lower plasma LDL by ~60% on top of statin treatment, and associated MACE by 15% (reviewed in [5]). Although this represents one of the most effective and fastest developments in recent years, it remains that 74 patients need to be treated with evolocumab to prevent one major event. This leaves considerable room for new therapeutic approaches. This could possibly be provided by anti-inflammatory treatment, such as IL1-β inhibitor canakinumab, clinical results of which are eagerly awaited at ESC 2017 [6,7]. Nevertheless, more insight in the pathogenesis of atherosclerosis is still warranted and a welcome recommendation on the design, execution, and reporting of murine atherosclerosis studies will ensure reproducibility of animal pathogenesis studies and, hopefully, improve translation of mechanisms to human disease [8,9▪▪].

Growing evidence points toward the highly plastic nature of vascular smooth muscle cells (SMCs) [10–12], endothelial cells [13], and macrophages [14] in the development of experimental atherosclerosis. Adding to recent insights on plaque macrophages originating, at least partly, from cholesterol-loaded SMC [10–12], recent papers now report on a reciprocal transition between adventitial progenitors and plaque-residing SMCs [15▪,16▪▪]. Majesky *et al.* show evidence to support SMCs as the source of a subpopulation of adventitial progenitors [16▪▪], while previous reports support the reverse transition [15▪].

In addition, the contribution of proliferation and clonal expansion of resident vessel wall cells receives increasing attention. Chappell *et al.* show conclusively that Acta2+ and MAC3+ SMC populations in lesions can arise from a subset of Myh11+ SMCs visualized by multicolor lineage labelling in mice [17▪▪]. However, Gomez and Owens addressed some further clarifications that are needed in their accompanying editorial, concerning clonal expansion versus clonal selection and the mechanistic contribution of such defined populations to SMC function and lesion development, necessitating further research [18▪].

Related to clonal expansion, two studies now show compelling evidence that an ageing-associated mutation of TET2 in bone marrow can cause clonal hematopoiesis and accelerate murine atherosclerosis [19▪,20▪▪]. Moreover, patients with otherwise unexplained clonal hematopoiesis have a two-fold higher risk of coronary heart disease [20▪▪]. As this mutation is associated with early-onset myocardial infarction, monitoring of clonal expansion and mutation analysis might improve current risk prediction.

The amount of factors influencing plaque progression is still greatly underestimated and further research into key mechanisms including cell plasticity and clonal expansion is still needed. New therapy strategies to combine with existing therapies could greatly improve patient treatment.

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Conflicts of interest

None.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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16. Majesky MW, Horita H, Ostriker A, *et al.* Differentiated smooth muscle cells ■■ generate a subpopulation of resident vascular progenitor cells in the adventitia regulated by Klf4. Circ Res 2017; 120:296–311.

Although SMCs as cell of origin for other vascular cells in atherosclerosis has been described; this article shows the other side of the coin: SMCs can migrate to an adventitial niche and as a consequence loose their SMC markers and gain progenitor markers by upregulation of KLF4.

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This review addresses whether creation of SMC subpopulations in the plaque as described by Chappell *et al.* is a consequence of clonal expansion or if this is a consequence of obtained epigenetic advantages.

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This study reports the causal role for ageing-associated mutations in clonal hematopoiesis and murine atherogenesis.

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FURTHER RECOMMENDED READING

Rahman K, Vengrenyuk Y, Ramsey SA, *et al.* Inflammatory fLy6Chi monocytes and ■ their conversion to M2 macrophages drive atherosclerosis regression. J Clin Invest 2017; 127:2904–2915.

This article clarifies the source of, and molecular triggers in macrophages driving inflammation resolution in regression of murine atherosclerosis, knowledge that may be used to drive plaques into regression

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This article shows miRNA function in atherosclerosis extends beyond lipoprotein biology.

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