CARDIOVASCULAR IMMUNITY

Viruses and cardiovascular disease: from bad to worse

Viral infections and cardiovascular disease (CVD) share a two-way connection: viral infection can raise CVD risk, and people with CVD are more prone to severe viral infection. Zhao et al. now detail a molecular mechanism whereby macrophages from patients with CVD inhibit antiviral T cell responses via immune checkpoint activation.

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The COVID-19 pandemic has highlighted the heightened risk of CVD in the months following acute viral infection[1], but this phenomenon was first recognized 90 years ago. In the 1930s, it was observed that influenza resulted in increased non-respiratory mortality, particularly from CVD[2]. The directionality was proven later, when influenza vaccination was shown to reduce CVD events[3]. Analogous findings are reported in patients with chronic viral infections, such as hepatitis C and HIV; patients living with HIV have a higher incidence of CVD than uninfected peers[4].

But all coins have two sides. In a large study in the UK Biobank, patients with cardiometabolic disease showed an increased risk of death from infection[5]. The pandemic revealed a similar pattern: patients with CVD and associated risk factors, such as obesity and diabetes, had worse outcomes from COVID-19[6]. And the same seems to be true for other viruses, such as varicella zoster virus or Epstein–Barr virus[7]. Are patients with CVD more prone to severe viral disease, which in turn increases their risk of later cardiovascular events? While we try to differentiate the chicken from the egg, the COVID-19 pandemic has highlighted the urgency of understanding the underlying mechanisms, both to reduce risks in adults with existing CVD or with acute viral infections, and also to minimize longer-term consequences from infections earlier in life, which are increasingly recognized to contribute to adult CVD risk and events.

In this issue of *Nature Cardiovascular Research*, Zhao et al. aimed to address some of these knowledge gaps[7]. In an elegant co-culture model, they show that monocyte-derived macrophages from patients with coronary artery disease (CAD) — when stimulated with proteins from SARS-CoV-2 or Epstein-Barr virus — are less capable, compared to those from healthy control individuals, of presenting antigens and subsequently activating autologous T cells to help clear the virus. These CAD macrophages overexpress a methyltransferase called METTL3, which promotes the accumulation of N^6-methyladenosine (m6A) on the mRNA for the CD155 receptor. Methyltransferases add methyl groups (creating m6A sites, among others) to mRNA transcripts, resulting in the stabilization of the transcript directing protein translation. This leads to inappropriate overexpression of CD155 on the macrophages of patients with CAD, resulting in increased inhibitory signaling to T cells that express CD96 or TIGIT receptors. Ultimately, individuals with

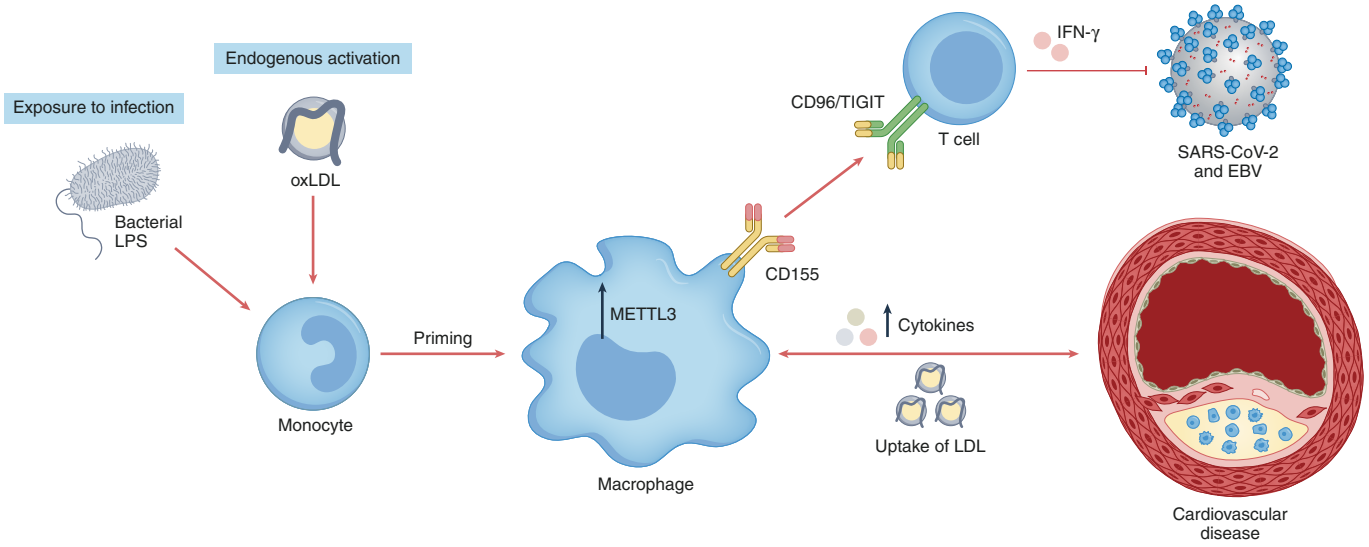

Fig. 1 | Exposure to LPS or high levels of LDL can prime monocytes or their progenitors in the bone marrow. These monocytes will differentiate into macrophages that in turn sends inhibiting signals to T cells to downregulate their response to viruses via the METTL3–CD155 axis as well as increase cardiovascular disease via their proinflammatory phenotype. EBV, Epstein–Barr virus; oxLDL, oxidized LDL.

CAD have a diminished antiviral T cell response both in vitro and, in a murine system, in vivo. The authors then explored the therapeutic potential of their findings: when they knocked down METTL3, nothing changed with the T cell activation of healthy-control-derived macrophages, but the T cell activation by macrophages from patients with CAD was restored. Second, when they only inhibited m6A, they observed the same effect, with healthy control macrophages again unaffected. Suppression of m6A induction in their mouse model also restored the T cell response in vivo. Finally, the authors report that hypermethylated *CD155* mRNA is already present in circulating monocytes, concluding that these post-transcriptional RNA modifications must be originating from the bone marrow microenvironment. They show that in healthy monocytes, the phenotype is inducible by high low-density lipoprotein (LDL), as well as lipopolysaccharide (LPS), but not by triglycerides or by other endogenous or microbial stimuli (Fig. 1).

The findings reported by Zhao et al. have implications not only for patients with CVD but also for those with other comorbidities, such as obesity and diabetes. Patients with underlying cardiometabolic diseases are more prone to severe influenza and have suboptimal vaccine responses[8]. In keeping with this, patients with underlying cardiometabolic comorbidities have an increased proinflammatory phenotype together with a decreased antiviral interferon responses[9]. The broad molecular mechanisms described by Zhou et al. could therefore also be important in those with obesity and/or diabetes.

Previous studies have suggested that aberrant m6A modifications could affect the development of CVD[10]. Patients with CVD have markedly elevated METTL3-induced m6A methylation. It has been proposed that this could serve as a diagnostic biomarker and possibly as a potential therapeutic target[10]. Further work is needed to clarify the effects of METTL3 inhibition; as with any epigenetic inhibitor, what other genes will be affected, and what is the best way to target the critical cells and avoid nonspecific effects?

Another key point — common to any cross-sectional study — is the directionality of the findings. As the authors touch upon, previous exposure to either high levels of LDL or stimulation by LPS could prime circulating monocytes (or their progenitors in the bone marrow) for increased METTL3 activity. Although the authors used a short monocyte priming model, longer-term 'training of innate immune cells' has already been implicated both in animal models of CVD pathogenesis and in numerous cross-sectional and longitudinal human studies of CVD[11]. Interestingly, although many proinflammatory effects of trained macrophages have been studied, antigen presentation has not been investigated. It is therefore reasonable to investigate the consequences of METTL3 activation in trained immunity. In addition, longitudinal studies, in which the training or priming stimulus is removed by treatment, are needed to understand the effects of innate immune training on the immune response against viruses in patients with CVD. Ultimately, as the authors speculate, this mechanism could partly explain the well-documented associations between previous infection and CVD. More broadly, it is plausible that heightened susceptibility to both CVD and viral infections might reflect the legacy of common proximal exposures that result in a trained, proinflammatory phenotype with suboptimal antigen presentation, thereby affecting both CVD and antiviral responses. Understanding these complex, interconnected relationships necessitates longitudinal sampling but will potentially enhance both prevention and treatment strategies. ❐

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Competing interests

The authors declare no competing interests.