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Editorial

Editorial: **Lipids: fueling the fire in tuberculosis?**

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Reciprocal interactions between the metabolic and immune systems are required for successful execution of energy-intensive events, such as adaptive immune responses to pathogenic insult. It is established that undernutrition or malnutrition predisposes individuals to mortality and morbidity from bacterial infections as a result of defects in innate as well as adaptive immunity [1]. Chronic overnutrition, manifested as a metabolic syndrome with elevated triglycerides, low HDL, and insulin resistance, also impairs leukocyte function and increases the risk and severity of infections [2–4]. Given a dramatic, world-wide increase in the incidence of obesity, Type-2 diabetes, and metabolic syndrome, the re-emergence of latent infections and increased severity of infections in a metabolically and potentially immunologically compromised host are of high public health concern [4]. Despite these alarming data, the mechanisms of how the chronic dyslipidemia and hypercholesterolemia affect immune cell function in response to chronic infections are largely unknown.

The cholesterol in blood is complexed with lipoproteins, and increased LDL and low HDL seen in metabolic syndrome are associated with inflammation and are risk factors for several chronic diseases. Importantly, the FC levels within a cell are tightly regulated through several mechanisms, including cholesterol efflux and esterification of FC into relatively inert cholesterol esters [4]. The ApoE is a glycoprotein with a molecular mass of 34 kDa, which can be synthesized by macrophages and secreted from liver and other tissues. The ApoE regulates lipid transport by binding to the LDLR, and ApoE also controls cellular FC through regulating the cholesterol efflux pathway. In addition, the LDLR mobilizes cholesterol-rich intermediate density lipoproteins and LDLs from plasma and regulates circulating cholesterol levels. Similar to ApoE, the genetic deficiency of the LDLR in mice and humans causes hypercholesterolemia [5]. Prior studies indicate that deficiency of ApoE and LDLR, and the associated hypercholesterolemia causes impaired immune responses to several bacterial infections, suggesting the potential role of dyslipidemia in compromising host defense [6].

The recent studies by Martens et al. [7] in the current issue of *JLB* show that despite similar degrees of hypercholesterolemia in high fat-fed ApoE$^{-/-}$ and LDLR$^{-/-}$ mice, these genetic mouse models exhibited divergent, protective adaptive immune responses to *Mycobacterium tuberculosis* infection (**Fig. 1**). Consistent with prior findings, the ApoE$^{-/-}$ animals infected with *M. tuberculosis* succumbed to infection [6]. However, the LDLR$^{-/-}$ mice fed a high-fat diet mounted an unexpectedly successful, protective immune response and survived the TB infection, despite greater lung inflammation, necrosis, and presence of lipid-containing foamy macrophages [7]. The LDLR null mice infected with TB and fed a low-fat diet do not develop severe lung inflammation, suggesting that the degree of hypercholesterolemia is linked to activation of innate immune cells but does not impair Th-1-driven adaptive immunity against TB.

The development of active TB in humans is associated with up-regulation of genes involved in lipid metabolism and accumulation of lipid droplets in infected macrophages [8]. During the chronic phase of *M. tuberculosis* infection, the bacterium co-opts the host metabolism by importing and degrading the host cholesterol for bacterial growth and virulence [8]. Martens et al. [7] found that despite similar levels of circulating cholesterol in high-fat-fed LDLR and ApoE null mice, the bacterial burden in LDLR$^{-/-}$ mice was similar to WT controls and significantly lower than the ApoE$^{-/-}$ animals. The similar bacterial burden in WT and LDLR$^{-/-}$ mice was associated with comparable frequency of TB antigen-specific CD4^{+} and IFN-γ^{+} T cells but dramatic increases in lung inflammation and pathology in the hypercholesterolemic LDLR$^{-/-}$ mice [7]. These data implicate high levels of LDL cholesterol and byproducts of fatty acid metabolism in activating innate immune cells, such as macrophages and neutrophils, which lead to excessive inflammation and local tissue damage in TB-infected lungs. Several recent studies suggest that metabolic "danger signals", such as choles-

Abbreviations: $^{-/-}$=deficient, ApoE=apolipoprotein E, FC=free cholesterol, TB=tuberculosis

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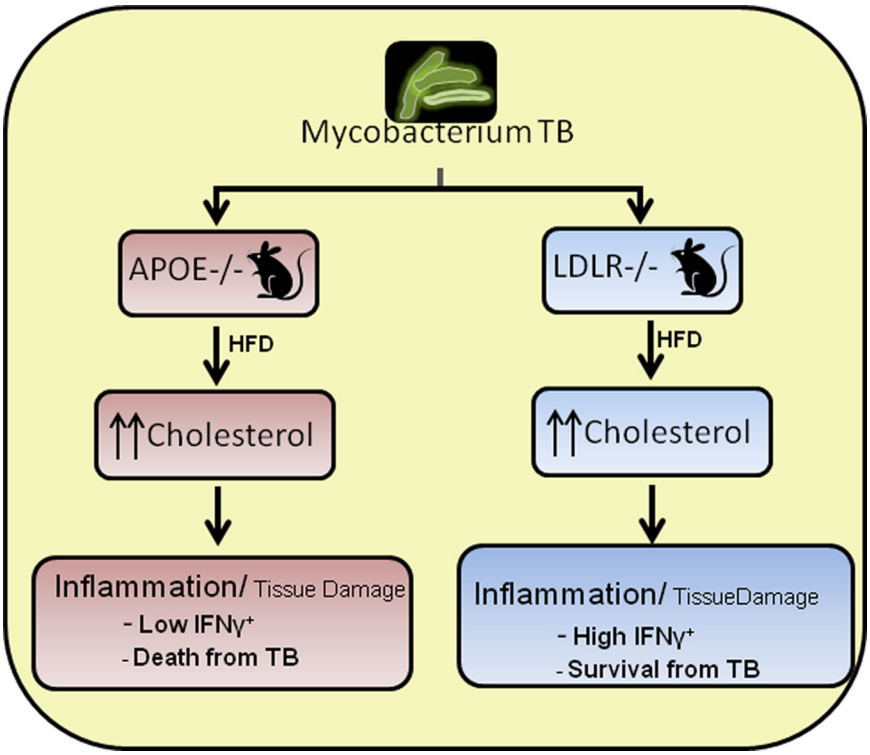

Figure 1. Dysregulated cholesterol metabolism alters protective immune responses against TB. HFD, High-fat diet.

terol crystals, and sphingosine-linked lipids, such as ceramides, which are elevated in response to a high-fat diet, cause activation of the nucleotide-binding oligomerization-like receptor family, pryin domain containing 3 inflammasome and induce organ dysfunction and cell death [9, 10] . Although, Martens et al. [7] did not measure the levels of FC in lung and inflammasome activation in LDLR$^{-/-}$ mice, their study raises the possibility that exaggerated IL-1β- and IL-18-driven responses, downstream of inflammasome activation, may provide a strong adjuvant effect for a robust, Th1-mediated adaptive immune response but may also cause inflammation-induced lung damage. In the absence of any experimental data, however, this mechanism remains speculative. In addition, an important, unanswered question relates to how the effects of hypercholesterolemia in TB models are manifested distinctly between ApoE and LDLR null mice.

It is well known that during inflammation, the cholesterol acceptor activity of HDL, required for the cholesterol efflux pathway, is reduced significantly [11, 12]. Martens et al. [7] provide initial evidence that a neutrophilic response in hypercholesterolemic LDLR knockout mice is involved in host defense. The neutrophil-derived MPO can make the HDL dysfunctional and via the modifications of ApoA1, impart pro-inflammatory properties to HDL [12]. Whether the ApoE and LDLR null mice challenged with TB differentially induce MPO and therefore, produce exaggerated inflammation by affecting HDL or by oxidizing LDL remains unknown. Nonetheless, the study by Martens et al. [7] provides intriguing, initial insights into a potential role of cholesterol metabolism in modifying the immune responses to TB infection. As the "epidemi" of obesity-associated dyslipidemia spreads to tropical countries with high TB incidence, how the metabolic dysregulation may impact the immune response to chronic infectious diseases remains to be ascertained.

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