SEPSIS

PCSK9 blockade helps clear pathogenic lipids

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Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibits the clearance of cholesterol from the blood by decreasing the density of low-density lipoprotein receptors (LDLRs) on hepatic cells. During infection, these receptors are also involved in the removal of bacterial lipids, such as lipopolysaccharide (LPS), from the circulation. Such lipids are thought to have a key role in initiating the uncontrolled systemic inflammatory response in sepsis. Now, Walley *et al.* show that promoting clearance of such lipids by inhibiting PCSK9 could be a novel therapeutic approach for sepsis.

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The authors first demonstrated that systemic levels of cytokines and chemokines after intraperitoneal injection of LPS were lower in *Pcsk9*$^{-/-}$ mice than in wild-type mice (WTs). Hypothermia and cardiac effects induced by LPS were also attenuated in *Pcsk9* knockouts. Notably, 6 hours after the LPS injection, *Pcsk9*$^{-/-}$ mice had much lower levels of systemic LPS, indicating more-rapid removal of the toxin from the circulation.

Next, the authors tested the effects of a PCSK9-specific antibody in a mouse model of sepsis called caecal ligation and puncture (CLP). Administration of the antibody after CLP attenuated cytokine and chemokine production, reduced bacterial growth in the lungs and, importantly, increased survival.

The authors studied human genetic data from two cohorts who had been treated for sepsis and found that individuals with at least one loss-of-function (LOF) or gain-of-function (GOF) allele of *PCSK9* were more likely or less likely to have survived, respectively. Moreover, healthy individuals carrying a LOF *PCSK9* mutation produced less interleukin-6 in response to an injection of LPS than did individuals without a LOF mutation. These results imply that, during sepsis, LOF mutations of *PCSK9* may be beneficial, whereas GOF mutations may be detrimental.

To investigate the importance of the effects of PCSK9 on LDLRs during sepsis, *Ldlr*$^{-/-}$ mice were pretreated with berberine (which prevents the expression of *PCSK9* mRNA) before injection of LPS. Berberine-treated WTs showed an attenuation of sepsis symptoms, but this effect of berberine was abrogated in *Ldlr*$^{-/-}$ mice. This suggests that, during sepsis, PCSK9 inhibits the clearance of pathogenic lipids by decreasing LDLR activity.

Together, these results provide evidence that, by negatively regulating LDLR function, PCSK9 inhibits the clearance of pathogenic lipids from the circulation and thereby worsens the outcome of sepsis. Antibodies against PCSK9, several of which are nearing approval for cardiovascular disease based on their ability to lower LDL cholesterol levels, might therefore also prove useful in this indication.

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ORIGINAL RESEARCH PAPER Walley, K. R. *et al.* PCSK9 is a critical regulator of the innate immune response and septic shock outcome. *Sci. Transl. Med.* **6**, 258ra143 (2014)
FURTHER READING Fink, M. P. & Warren, H. S. Strategies to improve drug development for sepsis. *Nature Rev. Drug Discov.* **13**, 741–758 (2014)