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INVITED EDITORIAL

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The rationale of PCSK9 inhibitors in sepsis: a viewpoint

Proprotein convertase subtilisin/kexin type 9 (PCSK9) increases LDL cholesterol concentration by accelerating the hepatic degradation of the LDL receptor, thus promoting atherogenesis [1]. The enzyme, however, also exerts proinflammatory effects independent of circulating LDL-C by enhancing local cytokine production and activation of NFkB, a process that might involve Toll-like receptor 4 (TLR4), a crucial component of the innate immunity system. Tissue factor (TF), a glycoprotein which plays an essential role in coagulation and inflammation, is rapidly induced by circulating monocytes stimulated by proinflammatory agents through NFkB-dependent mechanisms.

Recently, the administration of PCSK9 inhibitors compared to placebo has been shown to reduce death or the need for intubation in severe Coronavirus disease 2019 COVID-19, as well as concentrations of IL-6, a prognostically relevant inflammatory marker in this setting [2]. Within this framework, it remains unclear whether the efficacy of PCSK9 inhibitors might be observed also in sepsis, which is characterized by heightened inflammation and increased mortality [3]. It is estimated that patients who are critically ill with severe COVID-19 and other infectious diseases are at higher risk of developing and dying from sepsis. Antimicrobial resistance is a major challenge in sepsis treatment as it complicates the ability to treat infections, especially healthcare-associated infections. Most recently, World Health Organization (WHO) has called for global action on sepsis since it can cause 1 in 5 deaths worldwide [4].

Putative mechanisms of PCSK9-induced inflammation in sepsis

The NF-KB pathway has been widely associated with the pathogenesis of lung injury in diseases burdened by a significant inflammatory component, such as sepsis [5]. In addition, experimental studies have reported that inflammation mediated by IL-6 in viral coinfection may elevate PCSK9 levels [6]. Induction of IL-6 by PCSK9 is supported by data from patients with PCSK9 loss-of-function mutations, displaying lower IL-6 values in response to lipopolysaccharides-induced inflammation [7].

Another potential mechanism might BE related to the effect of PCSK9 on angiotensin-converting enzyme 2 (ACE2) entry receptors in COVID-19 [8]. Likewise, it has been reported that ACE2 suppresses abdominal sepsis and severe acute lung injury [9]. It is known that PCSK9 enhances the degradation of ACE2 which is anti-inflammatory by requiring different domains that those critical for the LDL receptor degradation by PCSK9.

Animal models

PCSK9 inhibition reduced mortality in septic mice, presumably through increased hepatic clearance of pathogen lipids due to increased lipoprotein receptor concentrations.

A study in a cohort of 10,922 patients with infectious diseases showed that the risk of sepsis was not associ-

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Table 1. Human studies on PCSK9 and sepsis

Infection	Study type	Main findings
Patients with sepsis	Single-centre observational cohort study [12]	Plasma PCSK9 levels are greatly increased in sepsis. During sepsis, PCSK9 levels are highly correlated with the development of subsequent multiple organ failure.
Patients with septic shock (VASST derivation cohort/SPH validation cohort) Healthy, nonobese subjects GENE population	Multicentre observational cohort study [7]	Reduced PCSK9 function is associated with increased pathogen lipid clearance via the LDL-R, a decreased inflammatory response, and improved septic shock outcome
Patients with sepsis or sepsis shock	Retrospective observational study [13]	Patients with multiple PCSK9 LOF alleles had a lower risk of 1-year death or infection-related readmission compared with WT/single LOF groups
Patients with Gram-positive septic shock	Multicentre observational cohort study [14]	Patients with PCSK9 LOF allele had significantly higher 28-day survival than those with no LOF alleles
Patients with bacterial infections admitted to intensive care units	Cross-sectional study [15]	There was no significant association between PCSK9 levels and either the severity of the disease (APACHE II, SOFA, and GCS) indices or resistance to antibiotics
Patients with septic shock	Sub-analysis of the Albumin Italian Outcome Sepsis (ALBIOS) study [16]	PCSK9 correlated with a biomarker of disease severity. Patients with septic shock presenting with lower plasma PCSK9 levels experienced a higher mortality rate

LOF — loss of function; PCSK9 — Proprotein convertase subtilisin/kexin type 9

ated with PCSK9 genetic variations [10], however, this report was **[??].**

A study aimed to evaluate the effects of differential PCSK9 expression on systemic infection, inflammation, and coagulation in sepsis [11]. In the study, overexpression of PCSK9 in mice increased liver and kidney pathology, plasma IL-6, ALT, and TAT concentrations during sepsis, whereas PCSK9 knockout mice exhibited reduced bacterial loads, lung and liver pathology, myeloperoxidase activity, plasma IL-10, and cfDNA during CLP-induced sepsis. All septic mice had reduced plasma levels of protein C, but the protein C ratio relative to normal was significantly decreased in PCSK9 transgenic mice. Dyspnoea, cyanosis, and overall grimace scores were greatest in septic mice overexpressing PCSK9, whereas PCSK9 KOmice retained core body temperature during sepsis.

Results were comparable in sepsis models induced by both the Gram-negative and positive bacteria, in which the 28-day survival in the septic patients with PCSK9 LOF gene mutation was significantly higher than those without.

Human studies

Several studies explored the effect of PCSK9 in patients with sepsis (Tab. 1). Most of them showed a worsening of septic status in parallel with increased concentrations of PCSK9, although some heterogeneity in the effect could be noted, depending at least in part on the type and severity of disease (bacterial infection/sepsis) and presumably of related inflammatory burden (Tab. 1).

Conclusive comments

Altogether, these findings suggest that PCSK9 deficiency may confer protection against systemic bacterial dissemination, organ pathology, and tissue inflammation, particularly in the lungs and liver, while PCSK9 overexpression may exacerbate multi-organ pathology as well as the hypercoagulable and pro-inflammatory states in early sepsis. A randomized study to explore the potential impact of PCSK9 inhibition on hard and laboratory endpoints in septic patients is warranted and, if positive, could exert significant implications on public health.

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