

EDITORIAL

The role of PCSK9 in atherogenesis and other inflammatory diseases

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Inflammation is a key factor playing fundamental roles in the development of disorders accounting for the large part of morbidity and mortality in developed countries including infections and autoimmunity, but also cardiovascular or malignant afflictions [1-2]. Accordingly, very recent trials expanded the potential therapeutic applications of anti-inflammatory molecules to secondary cardiovascular prevention showing also strong positive signals towards prevention of cancer progression [3-4]. Firstly described in 2003 as a protein with function in hepatocyte regeneration and neuronal differentiation [5], Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) fastly gained attention as a master regulator of cholesterol homeostasis and PCSK9 inhibitors are now included in most recent dyslipidemia guidelines [6]. As previously happened with statins, also the inhibition/neutralization of PCSK9 showed pleiotropic effects independently of cholesterol regulation that fostered the investigation of other PCSK9 “pleiotropic” functions. Being principally secreted by hepatocytes, PCSK9 is also expressed to a lesser extend also by other cells including those of the immunity system and to date this molecule is listed among the regulators of inflammation [7]. Given this scenario, approaches that interfere with PCSK9 may have major therapeutic impact in modulating inflammation not only in atherogenesis.

The current Hot Topic Issue for *Current Medicinal Chemistry*, invited authors discussed the mechanisms regulating PCSK9 levels and functions, as well as its potential as a diagnostic/prognostic biomarker or a therapeutic target in different diseases.

Bonaventura and colleagues explored PCSK9 function in cancer biology, suggesting a role for anti-PCSK9 therapies to reduce tumor growth and invasivity by increased intratumoral infiltration of cytotoxic T cells [8].

Then, *Ministrini* reports on the potential of PCSK9 as a common inflammation and lipid mediator in autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus with particular focus on the fact that some findings remain controversial likely reflecting the still suboptimal knowledge on this molecule [9].

From Iran, *Montazi-Borojeni* and co-workers reports on the different approaches explored to date in order to inhibit PCSK9 function from small molecules inhibitor to futuristic vaccines through the approved monoclonal antibodies [10]. Discussing both experimental and clinical evidence, this piece provides a comprehensive view on the role of PCSK9 inhibitors in cholesterol lowering and cardioprotection.

In a further contribution, *Magnasco* and colleagues expands on the role of PCSK9 in infectious diseases highlighting ongoing investigations in the field of HIV and HCV, but also Dengue fever, bacterial sepsis and the most recent SARS-CoV-2 [11].

In a last piece, *Gencer* and *Mach* explore the role of PCSK9 and its inhibition in patients after acute myocardial infarction [12]. Indeed, with mechanistic and epidemiologic studies suggesting PCSK9 to increase coronary plaque vulnerability through different pathway, the use of PCSK9 inhibition might prove beneficial in this setting leading to reduced cardiovascular mortality. Also, the authors warn on the absence of appropriately powered trials to test such hypothesis [12].

Editors and authors hope that the present issue provides an updated overview on the intriguing and always evolving field of PCSK9 “pleiotropic” functions. In consideration of ongoing studies, we envisage for PCSK9 a future of clinical-therapeutic applications that was not initially foreseeable. PCSK9 might become an important biomarker for stratification or to predict the development of different afflictions. Similarly, applications of PCSK9 inhibition/silencing might be broader in a near future expanding from current cardiology indications to oncology, infectious disease, neurology and immunology.

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