

Linking the sympathetic nervous system to the inflammasome: towards new therapeutics for atherosclerotic cardiovascular disease

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This editorial refers to 'IL-18 cleavage triggers cardiac inflammation and fibrosis upon β -adrenergic insult'[†], by H. Xiao *et al.*, on page 60.

Inflammation in atherosclerotic cardiovascular disease

There is solid evidence that atherosclerosis is an inflammatory disease, and that inflammation represents an important component of atherosclerotic cardiovascular disease (CVD).¹ Subclinical inflammation is considered to be involved in all stages of the atherosclerotic process, from the initiation of fatty streaks to the development of plaque instability and rupture, causing myocardial ischaemia and infarction.²

Unravelling the function of cytokines as inflammatory messengers provided a mechanism by which risk factors for atherosclerosis can alter arterial biology, and produce a milieu that favours atherothrombotic events.² Translation of these findings has enabled both novel mechanistic insights and practical clinical advances in the form of biomarkers and potential therapeutic instruments to lower inflammation and thereby CVD. For example, multiple studies showed a significant contribution of inflammatory biomarkers, such as C-reactive protein (CRP), secretory phospholipase A2 (sPLA2), and lipoprotein-associated phospholipase A2 (Lp-PLA2), to coronary risk prediction. To this effect, JUPITER (Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin) was the first large-scale inflammatory biomarker-guided clinical trial. JUPITER evaluated whether subjects with increased subclinical inflammation might benefit from the anti-inflammatory effects of statins. Within the trial 17 802 subjects with elevated CRP levels >2 mg/L (median, 4.2 mg/L) and normal LDL cholesterol levels <130 mg/dL were

randomly allocated either to rosuvastatin or to placebo.³ Besides the decrease in LDL cholesterol, rosuvastatin caused a steep decline in CRP levels and a 44% reduction in cardiovascular event rate. Yet, JUPITER could not discriminate the lipid-lowering effect from the anti-inflammatory effect of the statin,⁴ and thereby was never translated into clinical routine.

Linking inflammation to sympathetic nervous system activation

Increased subclinical inflammation occurs not only as a stand-alone condition but also as a consequence of activation of the sympathetic nervous system, which has a crucial role in cardiovascular homeostasis. During the acute stress response, the sympathetic nervous system acts on cardiac myocytes mainly via the β -adrenergic signalling system,⁵ resulting in the induction of proinflammatory cytokines. Consequently, an overactivation of the β -adrenergic system results in detrimental cardiotoxic effects, triggered by the inflammatory response. The inflammatory response is mediated by inflammasome multiprotein complexes that promote the conversion of procaspase-1 into caspase-1, which in turn is able to activate interleukin-18 (IL-18) and IL-1 β .⁶

Although molecular alterations in components of the β -adrenergic signalling pathway are known, the precise mechanism by which β -adrenergic signalling leads to an inflammatory response in the heart is poorly understood. In order to bridge this gap, Xiao and colleagues present experimental results⁷ characterizing the spatial and temporal changes of inflammasome activation, and add clinical relevance by investigating the therapeutic potential of cytokine-neutralizing antibodies.

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In mice, infiltrating proinflammatory M1 macrophages were identified as primary cells in the heart at various time points upon stimulation with the β -adrenergic agonist isoproterenol (ISO), and a dynamic pattern of various chemokines and cytokines could be observed. To identify the crucial upstream regulator that might trigger this induced inflammatory response, the authors assessed the components of the NLRP3 inflammasomes in a series of well-conducted experiments. Caspase-1 activation and activation of IL-18 by the NLRP3 inflammasome were detected only in the heart and as early as 1 h after β -adrenergic stimulation. In contrast, cleavage of pro-IL-1 β was not detected, indicating that the inflammatory cascade in the heart is triggered by IL-18. Evidence was provided that the β 1-adrenergic receptor and reactive oxygen species pathway is the first line that mediates the ISO-induced inflammasome stimulation in the heart. Finally, loss of IL-18 and NLRP3, by means of knock out mice, showed an impaired production of chemokines and proinflammatory cytokines, and significantly reduced macrophage infiltration, directly indicating the functional requirement for IL-18 and the NLRP3 inflammasome in triggering cardiac inflammation upon β -adrenergic overactivation.

Measurement of plasma levels of the catecholamine norepinephrine and IL-18 in patients with acute coronary syndrome (ACS) showed a correlation between both levels. In addition, heart function was reduced in patients with higher IL-18 levels, and cardiac fibrosis as well as ventricular stiffness were increased after ISO administration in mice. In order to prove the clinical relevance of their findings, the authors utilized an IL-18-neutralizing antibody and tested its potential to block the IL-18-mediated inflammatory response in mice. The antibody was able to block several inflammatory cytokines upon

β -adrenergic stimulation, and an early administration of the antibody significantly reduced macrophage infiltration in the heart, cardiac fibrosis, as well as diastolic dysfunction. By this work, Xiao *et al.*⁷ provide novel insights into the molecular mechanism of β -adrenergic insult and identified IL-18 as a novel and selective therapeutic alternative for stress-induced inflammatory diseases. These findings provide reassurance that therapeutic approaches can be used to lower inflammation in order to promote cardiovascular health.

Inflammation as a therapeutic target?

There are already several clinical trials addressing the hypothesis that lowering inflammation might lower vascular event rates, which, however, fell short. Specific targets in these trials were Lp-PLA2⁸ and sPLA2,⁹ as well as the p38 mitogen-activated protein kinase (MAPK);¹⁰ all crucial in inflammatory processes. In SOLID-TIMI 52, direct inhibition of Lp-PLA2 with darapladib did not reduce the risk of major coronary events in patients with ACS.⁸ Similarly in the VISTA-16 trial, varespladib, a specific inhibitor of sPLA2, did not reduce the risk of recurrent cardiovascular events in 5145 ACS patients, and even significantly increased the risk of subsequent acute myocardial infarction (AMI) by 66%.⁹ Most recently, losmapimod, as a specific MAPK-p38 inhibitor, failed to reduce the risk of major ischaemic cardiovascular events among 3503 patients with AMI.¹⁰

Despite these drawbacks, the cytokines linking the inflammasome and the sympathetic nervous system investigated by Xiao *et al.*,⁷ namely IL-18 and IL-1 β , are still subject to current research. The

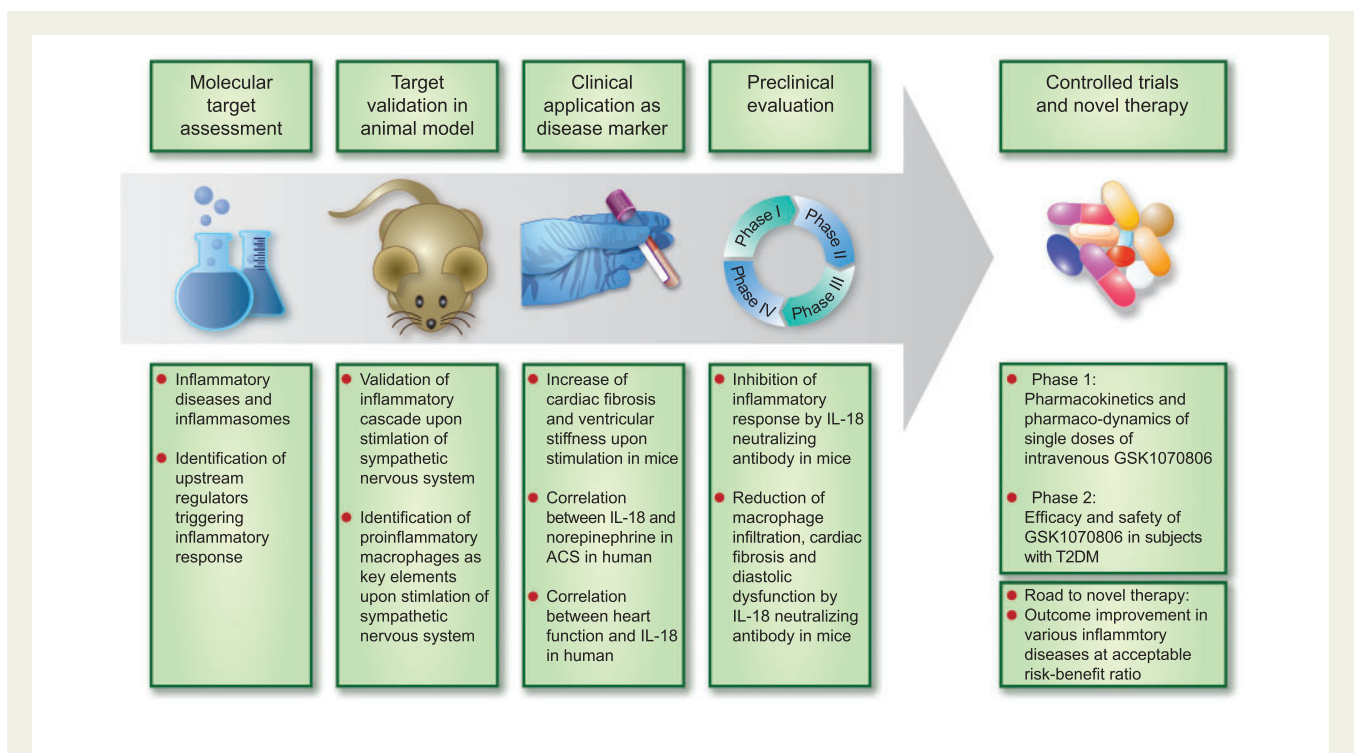


Figure 1 The translational chain: from molecular evidence to therapy. IL-18, interleukin-18; ACS, acute coronary syndrome; GSK1070806, humanised monoclonal IL-18 antibody; T2DM, type 2 diabetes mellitus.

phase III Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) is evaluating whether IL-1 β inhibition with canakinumab reduces event rates among stable coronary artery disease patients who remain at high vascular risk due to elevated CRP levels (≥ 2 mg/L).⁴ Results from this trial will be reported in 2017. Regarding specific inhibition of IL-18, after proof of concept was reported in pre-clinical animal models,¹¹ its safety was recently confirmed in 25 patients with diabetes.¹²

Still the question remains of whether inflammation is a target for therapeutic intervention. Studies such as that presented by Xiao *et al.* perfectly demonstrate the translational chain from molecular–experimental approaches to the evaluation for novel immunomodulating therapeutic targets, but, ultimately, only well-powered, controlled clinical trials can provide the adequate answer (Figure 1).

Conflict of interest: none declared.

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