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Interplay between hypercholesterolaemia and inflammation in atherosclerosis: Translating experimental targets into clinical practice

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Abstract

Dyslipidaemia and inflammation are closely interconnected in their contribution to atherosclerosis. In fact, low-density lipoprotein (LDL)-lowering drugs have anti-inflammatory effects. The Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS) has shown that interleukin (IL)-1β blockade reduces the incidence of cardiovascular events in patients with previous myocardial infarction and C-reactive protein levels >2 mg/L. These data confirm the connection between lipids and inflammation, as lipids activate the Nod-like receptor protein 3 inflammasome that leads to IL-1β activation. LDL-lowering drugs are the foundation of cardiovascular prevention. Now, the CANTOS trial demonstrates that combining them with IL-1β blockade further decreases the incidence of cardiovascular events. However, both therapies are not at the same level, given the large evidence showing that LDL-lowering drugs reduce cardiovascular risk as opposed to only one randomized trial of IL-1β blockade. In addition, IL-1β blockade has only been studied in patients with C-reactive protein >2 mg/L, while the benefit of LDL-lowering is not restricted to these patients. Also, lipid-lowering drugs are not harmful even at very low ranges of LDL, while anti-inflammatory therapies may confer a higher risk of developing fatal infections and sepsis. In the future, more clinical trials are needed to explore whether targeting other inflammatory molecules, both related and unrelated to the IL-1β pathway, reduces the cardiovascular risk. In this regard, the ongoing trials with methotrexate and colchicine may clarify whether the cardiovascular benefit of IL-1β blockade extends to other anti-inflammatory mechanisms. A positive result would represent a major change in the future treatment of atherosclerosis.

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Introduction

Lipids play a pivotal role in atherosclerosis. Inflammation has also been acknowledged as a key biological process in this disorder.[1] Importantly, dyslipidaemia and inflammation are closely intertwined in their contribution to atherosclerosis and cardiovascular risk.[2] Hence, low-density lipoprotein (LDL)-lowering drugs that effectively decrease cardiovascular events have also anti-inflammatory effects.[3] However, some of the anti-inflammatory effects reported for statins, and also for aspirin and renin–angiotensin modulators,[3–5] may result from LDL-lowering, antithrombotic or anti-proliferative effects, and from an improved endothelial function.

Observational studies have suggested beneficial effects of anti-inflammatory drugs in terms of cardiovascular risk reduction.[6] However, until recently, evidence on the efficacy of anti-inflammatory strategies to reduce cardiovascular events in humans was lacking. Thus, there was a need for a definitive study to specifically address the potential influence of inflammatory suppression on the incidence of cardiovascular events.

The recent Canakinumab Antiinflammatory Thrombosis Outcomes Study (CANTOS) has shown, in patients on statin therapy but with elevated C-reactive protein (CRP) levels, a significant reduction of cardiovascular events by the inhibition of interleukin-1β (IL-1β) without further influencing lipid levels.[7] These results introduce a new paradigm for the treatment of human atherosclerosis and cardiovascular disease. In this Consensus Paper, we highlight the role of inflammation and dyslipidaemia in atherosclerosis and aim to outline the new issues and challenges that are brought up by the interplay between these two risk factors in cardiovascular prevention.

Lipid-induced inflammatory responses (Figure 1)

A key trigger of atherosclerosis is subintimal retention of LDL at regions of complex flow or low shear stress.[8]

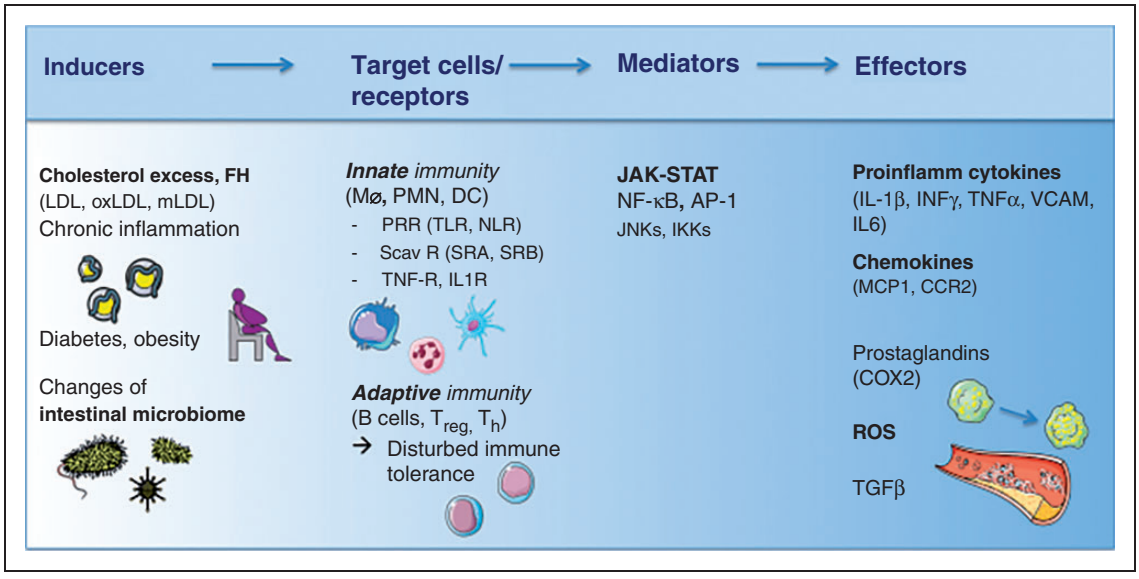

Figure 1. Lipid dysregulation triggers inflammatory and immune responses.
AP-1: activator protein-1; CCR2: chemokine receptor type-2; COX2: cyclooxygenase-2; DC: dendritic cells; FH: familial hypercholesterolaemia; IKK: IκB kinase; IL-1β: interleukin-1β; IL-6: interleukin 6; IL1R: interleukin-1 receptor; INFγ: interferon-γ; JAK-STAT: Janus kinase and signal transducer activator of transcription proteins; JNK: Jun kinase; LDL: low-density lipoprotein; mLDL: modified LDL; Mø: macrophages; MCP-1: monocyte chemoattractant protein-1; NF-κB: nuclear factor-κB; NLR: Nod-like receptors; oxLDL: oxidized LDL; PMN: polymorphonuclear; PRR: pattern recognition receptors; ROS: reactive oxygen species; Scav-R: scavenger receptors; SRA and SRB: scavenger receptor class A and B; TGFβ: transforming growth factor-β; T_h: T helper cell; TLR: toll-like receptor; TNFα: tumour necrosis factor-α; TNF-R: tumour necrosis factor-receptor; T_{reg}: T regulatory cell; VCAM: vascular cell adhesion molecule.

Modified LDLs are strong inducers of inflammation and have a marked impact on atherosclerosis. They alter vascular physiology by activating pattern recognition receptors, such as toll-like receptors (TLRs), which trigger proinflammatory signals and reactive oxygen species and promote matrix degradation.[9–12] These TLRs will prime the Nod-like receptor protein 3 (NLRP3) inflammasome for activation by cholesterol crystals leading to IL-1β activation[13] (Figure 2). This leads to the increased release of cytokines and activates the endothelium by enhancing the expression of adhesion molecules and chemokines, costimulatory molecules, such as CD40, and pro-inflammatory transcription factors such as nuclear factor-κB (NF-κB),[14–16] promoting the recruitment of inflammatory cells into the vascular wall. Among them, macrophages are of key relevance since they can scavenge oxidized LDL[17] evolving into pro-atherogenic foam cells.[1,6,18] Also, in atherosclerosis there is an enhanced haematopoietic activity in the bone marrow and LDL stimulates the capacity of haematopoietic stem and progenitor cells to differentiate into inflammatory cells.[19]

Adaptive immune responses play a key role in atherogenesis. Activated T lymphocytes are present in both peripheral blood and coronary atherosclerotic plaques in patients with acute coronary syndromes,[1,20] and especially T helper h1-derived cytokines such as tumour necrosis factor α (TNFα), and interferon-gamma are associated with atherosclerosis. The notion of immunomodulatory effects of LDL-lowering agents emerged from both experimental and clinical studies,[21,22] thus, the causal relation between lipids and immunity with regard to atherogenesis has been heavily investigated in the recent two decades.

Anti-inflammatory effects of LDL-lowering therapies

There is overwhelming evidence indicating that statins have anti-inflammatory and immunomodulatory effects. They decrease the activity of the transcription factor NF-κB,[3] with subsequent diminution in the expression of adhesion molecules, cytokines[23] and metalloproteinases (MMPs), interfering also with the arachidonic/cyclooxygenase pathway.[24] Also, they reduce plasma levels of inflammatory markers such as CRP.[25] Although most evidence has been obtained with statins, other LDL-lowering approaches have shown some anti-inflammatory effects. For instance, ezetimibe and fibrates also inhibit the NF-κB pathway and decrease CRP levels.[26–29] Similarly, low fat diet reduces CRP levels[30] and Mediterranean diet, which decreases the LDL/high-density lipoprotein cholesterol ratio,[31] reduces CD40 expression on monocytes and plasma levels of cell adhesion molecules and cytokines.[32]

Recently, another class of LDL-lowering drugs, proprotein convertase subtilisin/kexin type 9 (PCSK9) human monoclonal antibodies (mab), has been demonstrated to reduce the incidence of cardiovascular events.[33,34] PCSK9 mab do not decrease plasma levels of CRP and other inflammatory markers.[35–37] However, they reduce levels of lipoprotein(a)[38] – a molecule that promotes inflammation, oxidative stress and coagulation – and decrease monocyte activation and

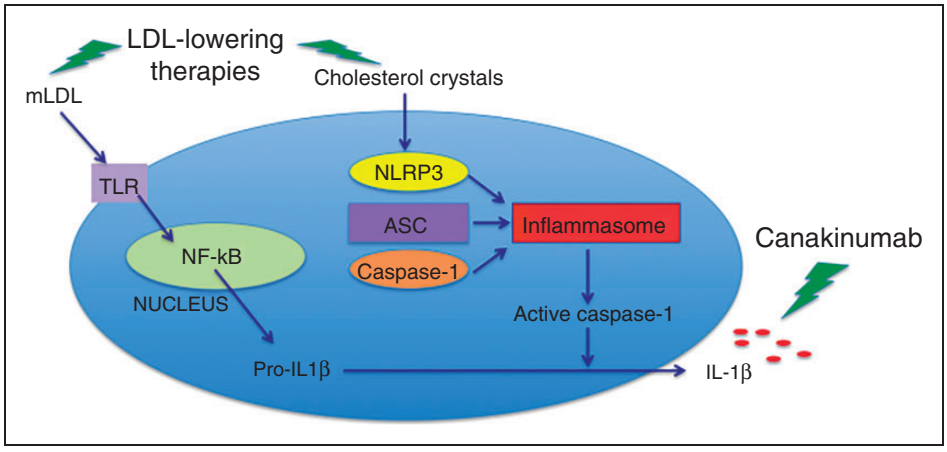

Figure 2. Interleukin-1β as a connection in the mechanism of action of LDL-lowering therapy and canakinumab. Modified LDL promotes the synthesis of pro-IL-1β, while cholesterol crystals, among other stimuli, assemble the components of the inflammasome activating caspase-1, leading to IL-1β synthesis. Then, IL-1β synthesis may be inhibited by LDL-lowering therapies, while canakinumab binds to IL-1β, inhibiting its effects.
ASC: adaptor protein; IL-1β: interleukin-1β; LDL: low-density lipoprotein; mLDL: modified LDL; NF-κB: nuclear factor-κB; NLRP3: Nod-like receptor protein 3; TLR: toll-like receptor.

transmigration in patients with familial hypercholesterolaemia.[35] Moreover, PCSK9 inhibition in atherosclerotic mice diminished macrophage and necrotic core content.[39] These findings suggest that plasma biomarkers may not always represent an exact indicator of the degree of inflammation at the arterial wall. In addition, up-regulation of hepatic LDL receptors (LDLRs) by PCSK9 inhibition results in increased lipopolysaccharide clearance, and decreased inflammatory response during sepsis in mice.[40,41] In this regard, patients with PCSK9 loss-of-function variants exhibit improved clinical outcomes during septic shock.[42]

Likewise, PCSK9 expression can be experimentally induced by pro-inflammatory molecules, such as lipopolysaccharide and TNFα among others.[43,44] Also, PCSK9 modulates LDLR expression in macrophages,[45] promoting the expression of pro-inflammatory markers and inhibiting anti-inflammatory molecules.[45] In humans, plasma PCSK9 concentrations are positively associated with white blood cell count and fibrinogen in patients with coronary artery disease.[46] Then, these evidences show that LDL-lowering therapies other than statins can decrease inflammation.

Anti-inflammatory therapy and cardiovascular risk

Inflammatory cytokines such as IL-1β[47] and TNF-α[48] have been detected in human coronary atherosclerosis. Observational studies have revealed an association of different anti-inflammatory treatments, when used for their indications, with reduced cardiovascular risk, providing support for the concept of inflammation reduction in cardiovascular prevention.[6] This is the case for anti-TNF therapy in rheumatoid arthritis[49,50] and anti-leukotrienes in asthmatics[51] that apparently decreased the incidence of cardiovascular events but were never tested in randomized clinical trials. On the other hand, other anti-inflammatory drugs failed to decrease the cardiovascular risk, as was observed for steroids in patients with unstable angina.[52] However, large studies and clinical trials until now have shown that, with the exception of aspirin, non-steroidal anti-inflammatory drugs in general are associated with an increased cardiovascular risk,[53–56] indicating that their use should be limited to patients without other alternatives.[54]

The recent CANTOS trial sheds new light on the relationship of inflammation with atherosclerosis.[7] In this randomized, double-blind trial, 10,061 patients with a previous myocardial infarction, the majority using moderate to high intensity statin therapy, and CRP > 2 mg/L received canakinumab, a monoclonal antibody that blocks IL-1β, or placebo. After a median follow-up of 3.7 years there was a ~15% decrease in the incidence of the primary end point composed of non-fatal myocardial infarction and non-fatal stroke. While there was an increase in the incidence of fatal infections, neutropenia or thrombocytopenia in patients on canakinumab, there were also non-cardiovascular benefits, comprising a reduction in the incidence of lung cancer, cancer mortality, arthritis and gout, although no difference in total mortality was observed between groups.[7,57]

Impact of the CANTOS trial on our understanding of interplay between lipids and inflammation

In addition to demonstrating that targeting inflammation can be effective in the treatment of atherosclerosis, the results from the CANTOS trial provide a first proof of principle about the link between lipids and inflammation. As mentioned above, cholesterol crystals activate the NLRP3 inflammasome, leading to IL-1β activation[13] (Figure 2) and non-canonical pathways of activation also exist.[58] Since IL-1 can activate itself,[59] blocking this pathway with canakinumab could attenuate this effect of lipids.

Interestingly, it has been shown that inflammation can induce dyslipidaemia through different mechanisms.[60,61] However, the effects of anti-inflammatory and immunosuppressive therapies on lipids are variable, with both favourable and adverse lipid profiles having been reported,[62–64] probably depending of the population studied and the drug used.[63] In this trial, canakinumab did not decrease lipid levels, while it slightly increased triglyceride levels.[57] Thus, the CANTOS data exclude the possibility that canakinumab reduces cardiovascular risk through lipid-dependent mechanisms linked to IL-1β.

Patients in the CANTOS trial had mean LDL levels of approximately 80 mg/dL and CRP > 2 mg/L. Efforts to further reduce residual cardiovascular risk now have multiple options. The prespecified analysis of the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk study showed that the cardiovascular-benefit of LDL lowering with PCSK9 mab is extended to very low LDL values, finding a 31% reduction in the incidence of the primary end point in patients achieving levels of 10 mg/dL as compared with those with 100 mg/dL or higher.[65] Similarly, CANTOS demonstrates that in patients showing a reduction of CRP levels below 2 mg/L following canakinumab administration, a 31% risk reduction in both total and cardiovascular mortality is observed as compared with no benefit in those with CRP levels of 2 mg/L or above.[66] However, the large body of evidence linking LDL lowering to a reduction in cardiovascular risk clearly favours the use of PCSK9 mab.[33,67] In the future, it would be interesting to

explore the cardiovascular effect of other anti-inflammatory therapies, including those directed at regulating IL-1, for example, anakinra[68] or other upstream IL-1 related molecules.[69] In this regard, the Colchicine Cardiovascular Outcomes Trial (COLCOT) (https://clinicaltrials.gov/ct2/show/NCT02551094) and the Cardiovascular Inflammation Reduction Trial (CIRT)[70] are investigating whether colchicine and methotrexate, respectively, reduce the incidence of cardiovascular events in patients with coronary artery disease. Finally, the benefit of canakinumab was demonstrated in patients with high CRP levels but its effects in patients with low CRP remain to be established, while that of LDL-lowering drugs does not seem to be restricted to this subgroup. Although lipid-lowering therapy is not free of adverse effects,[71] it has been consistently demonstrated to be a safe therapy, and even achieving very low LDL levels shows an acceptable risk/benefit balance.[65] On the other hand IL-1β blockade may confer a higher risk of developing fatal infections and sepsis[7] and requires further study due to the scarce amount of information available regarding this point.

Finally, the inclusion criteria of CRP > 2 mg/L in CANTOS and the subgroup analysis performed according to CRP in this trial underline the need to improve risk stratification in patients with atherosclerosis. In addition to assessing LDL levels, it is true that CRP levels and even IL-1β genotype[72] have been suggested to guide personalized medicine in an effort to further reduce the residual burden in high cardiovascular-risk patients. However, the role of these and other inflammatory biomarkers or even imaging strategies to better select high-responders to therapeutic moieties targeting either residual lipid or inflammatory pathways remains to be established[73] and their use is not recommended at present.[74,75]

Concluding remarks and open questions

1. *Interplay between lipids and inflammation*. The reduction in cardiovascular events observed with IL-1β blockade confirms the link between lipids and inflammation. The mechanism involves cholesterol crystals (and possibly other lipid species) that activate major inflammatory pathways (TLRs or the NLRP3) inducing maturation and release of IL-1β, which is blocked by canakinumab.
2. *Other pro-inflammatory targets appear worth testing*. Although IL-1β blockade is today the only anti-inflammatory approach shown to significantly reduce cardiovascular risk in a randomized clinical trial for patients with cardiovascular disease, the wealth of evidence linking inflammation with atherosclerosis indicates that other potential targets exist to be evaluated in future trials. In addition, tools other than antibodies, such as interference RNAs, may be tested to inhibit IL-1β.
3. *Anti-inflammatory vs. LDL-lowering therapy in cardiovascular prevention*. Canakinumab is not a competitor of LDL-lowering therapies given, among other reasons, that the large evidence supporting these therapies cannot be compared with the results of only one clinical trial.
4. *Potential role of anti-inflammatory therapy in cardiovascular prevention*. Although the results of the CANTOS trial can be considered a milestone in cardiovascular medicine, canakinumab prescription for patients with cardiovascular risk to improve their prognosis needs to overcome certain hurdles. In this regard, the results of the ongoing CIRT and COLCOT trials will clarify whether the cardiovascular benefit of IL-1β blockade extends to other anti-inflammatory drugs that work through different mechanisms, as this could represent a change on the horizon of the treatment of atherosclerosis.

Author contribution

The first and second authors contributed equally. JT: contributed to conception and design, drafted the manuscript, critically revised the manuscript, gave final approval and agrees to be accountable for all aspects of work ensuring integrity and accuracy. MB, BC, DK and CM: contributed to conception and design, drafted the manuscript, critically revised the manuscript, and gave final approval. LB, MB-P, MD, JE, PE, SF, EL, CM, SS, ES, CV, CW and IH: contributed to conception and design, drafted the manuscript, critically revised the manuscript and gave final approval.

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