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ELLUCIDATING THE ROLE OF INFLAMMATION IN CARDIOVASCULAR DISORDERS

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ABSTRACT Atherosclerosis is a progressive pathology leading to cardiovascular disorders (CVDs) viz., stroke, coronary artery disease, and peripheral arterial diseases. Current understanding of atherosclerosis has established the role of vascular inflammation along with the lipid accumulation. Molecular mechanism of vascular inflammation elucidates the role of both innate as well as adaptive immunity in the initiation and progression of atherosclerosis. Atherosclerosis is initiated by the endothelial injury or deposition of low-density lipoproteins (LDLs) within the arterial wall. These LDLs are highly prone to oxidation or modification and trigger innate and adaptive immunity. As a result of the activation of the immune response, monocytes/macrophages, neutrophils, T lymphocytes, and B lymphocytes are triggered. Monocytes/macrophages take up oxidized LDLs and initiate the formation of foam cells that eventually results in plaque formation. T-cells along with neutrophils have been reported to further promote the formation of foam cells. These inflammatory responses are triggered due to the release of various cytokines viz., high-sensitivity C-reactive protein and interleukin-6, which now serve as biomarkers and prediction tools for the CVDs. Understanding of the role of inflammation in CVDs has opened up a new therapeutic approach for the prevention and the treatment of CVDs. Current research and trials are now focused on reducing chronic vascular inflammation for the treatment of CVDs. The present review will focus on the molecular mechanism of the inflammation leading to atherosclerosis, cytokines that are being used as a diagnostic tool and the novel treatment approaches for reducing vascular inflammation that are being evaluated in trials for the treatment of CVDs.

KEYWORDS :

Cardiovascular diseases (CVDs) remains one of the leading causes of death worldwide. The majority of patients with CVDs suffer from atherosclerosis. Essentially, atherosclerosis is a progressive pathology leading to CVDs viz., stroke, coronary artery disease, and peripheral arterial diseases. Atherosclerosis is the primary cause of approximately 80% of all sudden cardiac deaths. Atherosclerosis is a complex process that involves the interplay of inflammation and genetic factors at all stages (Moriya, 2019). Rudolf Virchow's observations in the 1850s, lead to the establishment and recognition of chronic inflammation as a leading cause for atherosclerosis along with lipid accumulation in the arterial walls (Tsalamandris et al., 2017). This development has led to the hypothesis that targeting inflammation can reduce cardiovascular risks and events (Moriya, 2019). Researchers have also discovered various inflammatory biomarkers as prediction tools for CVDs. Nevertheless, in-depth search for an ideal reliable biomarker for CVD and approaches of targeting chronic inflammation for reducing CVDs is still underway. The present review focus on the inflammatory mechanism leading to atherosclerosis, cytokines that are being used as a diagnostic tool and the novel therapeutic targets for reducing vascular inflammation that are being evaluated in trials for the treatment of CVDs.

PATHOPHYSIOLOGY OF ATHEROSCLEROSIS

Atherosclerosis occurs in large and medium-sized vascular arteries. Atherosclerosis is characteristically delineated by endothelial dysfunction, vascular inflammation, and eventually the build-up of lipids, cholesterol, calcium, and cellular debris within the intima of the vessel wall. Consequently, this buildup leads to plaque formation, vascular remodeling, acute and chronic luminal obstruction, abnormalities of blood flow, and diminished oxygen supply to the target organs (Tsalamandris et al., 2017).

Endothelial injury or deposition of low-density lipoproteins (LDLs) within the arterial wall initiates atherosclerosis. These LDLs are highly liable for oxidation or modification and trigger innate and adaptive immunity. As a result of the activation of the immune response, monocytes/macrophages, neutrophils, T lymphocytes, and B lymphocytes, production is triggered. Monocytes/macrophages take up or engulf the oxidized LDLs and initiate the formation of foam cells that eventually results in plaque formation (Fig 1).

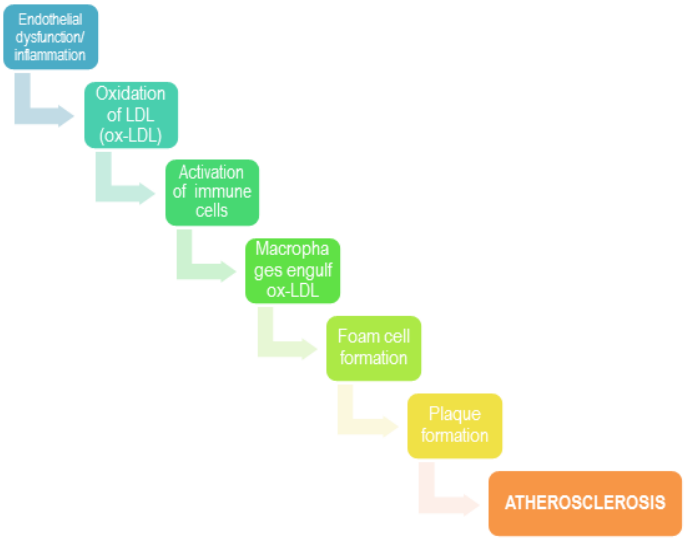

Fig 1. Cascade of events leading to Atherosclerosis

Production of reactive oxygen species (ROS) along with the uncoupling of endothelial nitric oxide synthase (eNOS) leads to the reduced production of nitric oxide (NO) (Tsalamandris et al., 2017). Endothelial NO is a vasoactive peptide that aids in maintaining vascular tone, impedes platelet adherence and aggregation, suppresses vasoconstriction & proliferation of vascular smooth muscle cells and diminishes adherence of leukocytes to the endothelium. Consequently, reduction in NO activity sets up a proinflammatory and prothrombotic environment that eventually activates the innate and adaptive immune response. Thus, diminished NO production is an important clinical biomarker for all the known CVDs. C-reactive protein has also been found to suppress the production and reduce the bioavailability of NO (Willerson, 2004). Several reports suggest that subendothelial retention and modification of atherogenic lipoproteins trigger the primary vascular inflammation in atherosclerosis (Shah, 2019). Low-grade inflammation upregulates various cell adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule- 1 (ICAM-1), and selectin, resulting in adherence and migration of monocytes to endothelial cells. Once migrated to endothelial cells, monocytes differentiate into macrophages via., macrophage colony-stimulating factor (M-CSF). Differentiation of monocytes to macrophages is a critical step in atherosclerosis as this event is followed by expression of various scavenger receptors viz., scavenger receptor class A (SR-A), cluster of differentiation (CD), lectin-like oxidized LDL receptor-1 (LOX-1), scavenger receptor for phosphatidylserine and oxidized lipoprotein (SR-PSOX), on the macrophages. Eventually, these macrophages scavenge oxidized LDL via scavenger receptors, resulting in lipid accumulation and eventually foam cell formation. Oxidized LDL also activates toll-like receptors that further aggravates plaque formation. Neutrophils, first-line defense in acute inflammation, also aid in recruiting monocytes at the site of endothelial lesions via granule proteins such as azurocidin, cathepsin G, and α-defensins, thereby promoting foam cell formation and eventually aggravating atherosclerosis (Moriya, 2019). T-cells also contribute to activate macrophages and produce pro-inflammatory cytokines via Th1 cells viz., interferon-γ and TNF (Hedin & Matic, 2019). Th1 cells are the most abundant T cells found in atherosclerotic lesions. Cytokines such as IL-18 and IL-12, also stimulate Th1 cells, thereby aggravating atherosclerosis. On the other hand, B-lymphocytes especially B1 cells, is reported to diminish atherosclerosis. B1 cells promote the production of antibodies that recognizes oxidized LDL, thereby attenuating atherosclerosis. While B2 cells are reported to further promote atherosclerosis. Thus, enhancing B1 cell production can be used as a therapeutic approach to prevent CVDs (Moriya, 2019).

TRANSLATION OF INFLAMMATION HYPOTHESIS INTO CLINICAL THERAPEUTIC APPROACHES

Establishment of inflammation hypothesis in the progression of atherosclerosis has paved pathway for its two-pronged clinical translational approach in CVDs.

A. Inflammatory biomarker as a diagnostic and predictive tool
B. Reducing vascular inflammation as a therapeutic target

INFLAMMATORY BIOMARKERS AS DIAGNOSTIC AND PREDICTIVE TOOL FOR CVDs

Given the in-depth understanding of the inflammatory pathway in atherosclerosis, various inflammatory biomarkers are now used as a predictive and diagnostic tool for CVDs. The most commonly studied and used inflammatory biomarkers include- High-sensitivity C-reactive protein and IL-6.

HIGH-SENSITIVITY C-REACTIVE PROTEIN (HSCRP):

hsCRP is the leading biomarker for the prediction of cardiovascular risk. C-reactive protein (CRP), a polypeptide of 206 amino acid, is secreted by hepatocytes upon stimulation by inflammatory cytokines. Inflammatory cytokines, IL-6, promotes and regulates the production of CRP during acute inflammation. In endothelial cells, CRP downregulates eNOS, enhance superoxide production, reduced NO production and alters eNOS phosphorylation. CRP stimulates the expression of VCAM-1, ICAM-1, E-selectin, and monocyte chemoattractant protein-1, thereby facilitating leukocyte adhesion and internalization into the arterial wall (Tsalamandris et al., 2017). Essentially, CRP is associated with arterial stiffness and cardiovascular disease and can, therefore, be used as an indicator of low-grade systemic inflammation (Christen et al., 2019). CRP levels are measured using a high-sensitivity assay (hsCRP) and this predictive tool for future cardiovascular events is independent of traditional risk factors (Moriya, 2019). Various studies have used hsCRP as an indicator of CVD risks. One such major study that utilized hsCRP as a predictive tool was Cholesterol and Recurrent Events (CARE) trial. CARE trial established that statins lower hsCRP independent of LDL cholesterol, and also patients with high hsCRP draws the greater clinical benefit of statin therapy (Ridker et al., 1998). Another trial, Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) also concluded that patients with the low level of LDL but higher levels of hsCRP will draw therapeutic benefits from statin therapy (Mora and Ridker 2006). hsCRP is a dependable measure of primary systemic inflammation and a strong predictor of future myocardial infarction and stroke (Willerson, 2004).

INTERLEUKIN-6 (IL-6) AND INTERLEUKIN-1 (IL-1)

IL-6 is well established to induce CRP production in the hepatocytes and is indicative of upstream cytokine production that reflects inflammation (Moriya, 2019). IL-6 is known to correlate with endothelial dysfunction, subclinical atherosclerosis and has been found to be independent of traditional risk factors. Thus, IL-6 is a potential inflammatory biomarker for CVDs (Kaptoge et al., 2004).

While, IL-1 induces the production of IL-6, hence its role is also critical in atherosclerosis and can be potentially used as a biomarker for CVDs. Out of the two circulating forms of IL-1, IL-1β, and IL-1α, IL-1β plays a critical role in the progression of atherosclerosis.

REDUCING VASCULAR INFLAMMATION AS A THERA PEUTIC TARGET FOR REDUCING CVDs

In-depth knowledge about the involvement of the inflammatory pathway in the progression of atherosclerosis has led to an exploration of the possibility of preventing the progression of atherosclerosis by targeting chronic inflammation. CRP is known to play a significant role in atherosclerosis and can be a potential therapeutic target for treating CVDs. The critical role of CRP was also confirmed from the findings of the JUPITER trial. However, statins that were used in JUPITER trials are known to lower lipids as well as act on inflammation. Therefore, it is difficult to pinpoint the mechanism involved in the reduction of cardiovascular risk on the administration of statins (Libby, 2012). Concurrently, the causative action of CRP in atherosclerosis is still to be established. Though, various *in-vitro* and *in-vivo* studies suggest the causative and accelerative role of CRP in atherosclerosis. Still further in-depth research is needed to establish the role of CRP in atherosclerosis and eventually its use as a therapeutic target for reducing the risk of CVDs (Moriya, 2019).

On the other hand, the causative role of IL-6 in atherosclerosis is quite well studied and established. Hence, IL-6 is being studied as a potential therapeutic target for reducing atherosclerosis and thereby CVDs (viz., CIRT trial) (Ridker et al., 2018). Similarly, the link between IL-1β and atherogenesis is well established and inhibition of IL-1β is a potential target for atheroprotection. Based on these findings, the CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) trial was carried out. Canakinumab, a human monoclonal antibody, is a selective IL-1β neutralizer which does not affect IL-1α. Additionally, canakinumab does not affect LDL or HDL. The objective of CANTOS trial was to assess whether canakinumab treatment can prevent recurrent cardiovascular events in patients with previous myocardial infarction and high hsCRP. The CANTOS trial was a randomized, double-blind, placebo-controlled trial carried out in 10,000 patients with a history of myocardial infarction. Canakinumab was evaluated at a dose of 50 mg, 150 mg, and 300 mg. At the end of the study period (3.7 yrs), it was found that canakinumab reduced the hsCRP levels at all doses and there was a significant reduction in hsCRP levels in canakinumab group as against the placebo group. At a median dose, 150 mg canakinumab was found to have a 0.6% reduction in the incidence of MI, which was the primary endpoint. As expected, canakinumab was found to have no effect on LDL or HDL levels. Thus, it was concluded that canakinumab reduced the risks of recurrent cardiovascular events without affecting or altering the lipid profile. The findings of CANTOS trial provided validation of the inflammation pathway hypothesis in atherosclerosis and its therapeutic utility for reducing the risk of CVDs (Ridker et al., 2017). CANTOS trial was the first large scale trial to provide validation to the inflammation hypothesis in atherosclerosis.

Encouraged by the findings of CANTOS, another trial, Cardiovascular Inflammation Reduction Trial (CIRT) was undertaken (Ridker et al., 2018). Canakinumab is a monoclonal antibody and is very expensive thus limiting its widespread usage. Consequently, there is a need for an effective anti-inflammatory molecule that can provide an atherop

rotective effect and reduce CVDs risks. Thus, in CIRT trial, methotrexate was evaluated for its atheroprotective effect. Metho rexate is a commonly used immunosuppressant in patients with rheumatic disease and has a well-established safety profile. Low dose methotrexate is known to reduce various inflammatory biomarkers viz., CRP, IL-6, and TNF-α in patients with rheumatoid arthritis without affecting the lipid profile, hemostasis, or platelet function. Thus, low-dose methotrexate was considered to be a good candidate to further strengthen the inflammation hypothesis of atherosclerosis and establishing the therapeutic rationale for its use as an atheroprotective agent. The CIRT trial was a multicenter, randomized, double-blind, placebo-controlled trial carried out in 4,786 patients with a history of myocardial infarction or type 2 diabetes and/or metabolic syndrome patients. The study was, however, terminated at the end of 2.3 years, as it was found that methotrexate offered no benefit in reducing the cardiovascular events in patients with established cardiovascular disease. There was no significant difference in the primary endpoint of nonfatal MI, nonfatal stroke, hospitalization for unstable angina leading to revascularization, or cardiovascular death in methotrexate and placebo group. There were 4.13 incidences per 100 person-years with methotrexate treatment versus 4.31 incidences per 100 person-years with placebo treatment. Also, there was no alteration in the baseline levels of inflammatory biomarkers viz., CRP, IL-1β, or IL- 6 on the administration of methotrexate. Thus, the search for a suitable, cost-effective anti-inflammatory agent that can be effectively utilized as an atheroprotective agent is still underway.

CONCLUSIONS

Inflammation plays a crucial role in the progression of atherosclerosis that eventually leads to various CVDs. Inflammatory biomarkers viz., hs-CRP, IL-1, and IL-6 have been found to accelerate the process of atherosclerosis. Establishment of the causative or accelerative role of these inflammatory biomarker has opened up two possibilities in the treatment approach for CVDs. One of the approaches involves the usage of these inflammatory biomarkers as a diagnostic tool to predict the risk of CVDs, both in patients with a history of CVDs as well as in normal patients. The other approach is to target these inflammatory markers to deaccelerate the progression of atherosclerosis and thus reducing the risk of CVDs. This approach was strengthened by the findings of CANTOS trial, wherein selective IL-1β neutralizer monoclonal antibody, canakinumab, was found to significantly reduce the inflammatory biomarkers and eventually reducing the cardiovascular events. CANTOS trial was the first trial to establish the inflammation hypothesis in atherosclerosis. However, the high cost of canakinumab limits its wide-spread usage. Hence, there is further need to search for a cost-effective anti-inflammatory agent that can provide an atheroprotective effect. Further in-depth studies and large scale trials with well-defined therapeutic targets and endpoints are required to translate the inflammation hypothesis as a clinical therapeutic approach to predict as well as reduce CVDs. Additionally, new therapeutic targets viz., enhancing B1 cell production, should be further evaluated for their atheroprotective activity.

REFERENCES

1. Christen, T., Trompet, S., Rensen, P. C. N., Willems van Dijk, K., Lamb, H. J., Jukema, J. W., … de Mutsert, R. (2019). The role of inflammation in the association between overall and visceral adiposity and subclinical atherosclerosis. Nutr Metab Cardiovasc Dis, 29(7), 728–735.
2. Hedin, U., & Matic, L. P. (2019). Recent advances in therapeutic targeting of inflammation in atherosclerosis. J Vasc Surg, 69(3), 944–951.
3. Kaptoge, S., Seshasai, S.R., Gao, P., Freitag, D.F., Butterworth, A.S., Borglykke, A., et al. (2014). Inflammatory cytokines and risk of coronary heart disease: new prospective study and updated meta-analysis. Eur Heart J 35:578–89.
4. Mora, S., Ridker, P.M., (2006). Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER)--can C-reactive protein be used to target statin therapy in primary prevention? Am J Cardiol. 97(2A):33A-41A.
5. Moriya, J. (2019). Critical roles of inflammation in atherosclerosis. J Cardiol, 73(1), 22–27.
6. Shah, P. K. (2019). Inflammation, infection and atherosclerosis. Trends Cardiovasc Med. https://doi.org/10.1016/j.tcm.2019.01.004
7. Ridker PM, Rifai N, Pfeffer MA, Sacks FM, Moye LA, Goldman S, et al. (1998). Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events (CARE) Investigators. Circulation 98:839–44.
8. Ridker, P.M., Everett, B.M., Thuren, T., MacFadyen, J.G., Chang, W.H., Ballantyne, C., Fonseca, F., Nicolau, J, et al. (2017) Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. New Engl J Med. 377(12):1119-1131.
9. Ridker, P.M., Everett, B.M., Pradhan, A., MacFadyen, J.G., Solomon, D.H., Zaharris, E., Mam, V., Hasan, A., et al. (2018). Low-dose methotrexate for the prevention of atherosclerotic events. New Engl J Med.. 2018-11-10:1-11.
10. Libby P. (2012). Inflammation in atherosclerosis. Arterioscler Thromb Vasc Biol 32:2045–51.
11. Tsalamandris, S., Oikonomou, E., Papageorgiou, N., & Tousoulis, D. (2017). The Role of Inflammation. Coronary Artery Disease, 67–94.
12. Van Tassell, B.W., Toldo, S., Mezzaroma, E., Abbate, A. (2013). Targeting interleukin-1 in heart disease. Circulation 128:1910–23.
13. Willerson, J. T. (2004). Inflammation as a Cardiovascular Risk Factor. Circulation, 109(21_suppl_1), II-2-II–10.