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Review

Critical roles of inflammation in atherosclerosis

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ABSTRACT

There is accumulating evidence that vascular inflammation plays critical roles in pathophysiology of atherosclerosis. It is widely accepted that both innate and adaptive immune responses are important for initiation and progression of atherosclerosis, which mainly consist of monocytes, macrophages, neutrophils, T lymphocytes, and B lymphocytes. Moreover, inflammatory biomarkers such as high-sensitivity C-reactive protein and interleukin-6 are known to predict future cardiovascular events, as well as conventional low-density or high-density lipoprotein cholesterol. Thus, current understanding of the inflammatory mechanisms of atherosclerosis have led us to explore novel therapeutic approaches that reducing vascular inflammation itself could lower the rates of critical cardiovascular events. To address the inflammatory hypothesis of atherosclerosis, results of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) trial have been recently reported that anti-inflammatory therapy using canakinumab, a monoclonal antibody targeting interleukin-1β, significantly reduced recurrent cardiovascular events for secondary prevention of myocardial infarction at high inflammatory risk. In this review, we will first outline the mechanisms of atherosclerosis, especially focusing on their inflammatory aspects. Then we will introduce several critical inflammatory biomarkers that contribute to risk stratification of clinical cardiovascular events. Lastly, we will discuss potentiality and future perspectives of reducing inflammation as a novel therapeutic target for atherosclerotic cardiovascular diseases.

Contents

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Introduction

Atherosclerosis is known to be a progressive pathology that causes several clinically important cardiovascular diseases (CVDs) such as coronary artery disease, stroke, and peripheral arterial disease. Since Rudolf Virchow's observations in the 1850s, it is now well recognized that atherosclerosis not only results from accumulating lipid within the arterial wall but also is a chronic inflammatory disease in response to vascular injury. Numerous studies have elucidated molecular mechanisms of inflammation in atherosclerosis, and it is widely accepted that both innate and adaptive immune responses play key roles for initiation and progression of atherosclerosis, leading to clinical manifestations of CVDs.

Current understanding of the inflammatory mechanisms of atherosclerosis has led to exploration of the hypothesis that targeting inflammation itself will reduce cardiovascular events and risks. Recently, the results of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) trial have been reported with a significant reduction in recurrent cardiovascular events in patients with stable coronary artery disease at high inflammatory risk by using canakinumab, a therapeutic monoclonal antibody targeting interleukin (IL)-1β [1]. In this review, we will overview the pathophysiology of atherosclerosis, including an update on the role of inflammation. Then we will focus on several inflammatory biomarkers that contribute to risk prediction for atherosclerotic CVDs. Finally, we will discuss current understanding and future clinical perspectives of anti-inflammatory therapies, including the results of the CANTOS trial.

Pathophysiology of atherosclerosis

A number of studies have shown that atherosclerosis is initiated by endothelial injury or accumulation of low-density lipoproteins (LDLs) within the arterial wall, which are generally prone to oxidization or modification. These modified or oxidized LDLs, along with low-grade inflammation caused by small endothelial injury, trigger both innate and adaptive immune responses. These immune responses are now known to play important roles in the development of atherosclerosis. Monocytes/macrophages, neutrophils, T lymphocytes and B lymphocytes are the chief cell subtypes in the context of atherosclerosis.

Monocytes/macrophages

Endothelial injury characterized by low-grade inflammation triggers upregulation of cell adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and selectin. These molecules enable monocytes to attach endothelial cells. Monocytes migrate under endothelium after they attach to injured endothelial cells, and some chemokines are reported to be related to this process. For example, monocyte chemoattractant protein-1 (MCP-1) promotes migration and infiltration of monocytes through its receptor C-C chemokine receptor 2 (CCR2) [2]. Likewise, IL-8 and fractalkine are known to be associated with cell migration through C-X-C chemokine receptor type 2 (CXCR2) expressed in leukocytes. Monocytes differentiate into macrophages by macrophage colony-stimulating factor (M-CSF) once they migrate into endothelium, which is considered to be a crucial phase for atherosclerosis development.

Macrophages express scavenger receptors to take up oxidized LDLs. Families of scavenger receptors contain scavenger receptor class A (SR-A), cluster of differentiation (CD) 36, lectin-like oxidized LDL receptor-1 (LOX-1), scavenger receptor for phosphatidylserine and oxidized lipoprotein (SR-PSOX), and scavenger receptor class B type 1 (SR-B1). Macrophages take up oxidized LDLs through these receptors, leading to lipid accumulation and formation of foam cells. Moreover, toll-like receptors (TLRs) expressed on macrophages, which are known to play a key role in innate immunity, are also suggested to be associated with atherosclerosis. Oxidized LDLs are considered to activate TLR signaling pathway, resulting in aggravating plaque inflammation.

In addition to modified or oxidized LDLs, several lines of evidence suggest that bacterial products such as lipopolysaccharides and heat shock proteins may also contribute to plaque progression, by acting on vascular cells and eliciting innate immunity. While macrophages account for the vast majority of leukocytes found in atherosclerotic plaques, evidence supports that mast cells also release many vasoactive mediators such as histamine and leukotrienes, which are implicated in atherogenesis [3].

Neutrophils

Neutrophils have been classically recognized as the first line of defense cells under acute inflammatory response and received little attention in the pathophysiology of atherosclerosis. However, recent advances in understanding of the mechanisms of atherosclerosis have placed neutrophils as one of the most important contributors to the development of atherosclerosis. Indeed, like monocytes, neutrophils are recruited to atherosclerotic lesions by certain chemotactic signals, especially chemokines produced by activated platelets. Moreover, neutrophils are also capable of recruiting monocytes into atherosclerotic lesions by releasing granule proteins such as azurocidin, cathepsin G, and α-defensins, thereby aggravating atherosclerosis. In addition, these granule proteins have been reported to activate macrophages and promote foam cell formation [4]. Taken together, involvement of neutrophils in the pathogenesis of atherosclerosis may widen therapeutic anti-inflammatory approaches. However, it should be noted that because neutrophils belong to the first line of defense cells, strategies to inhibit neutrophil function have to be carefully controlled so as not to incur any serious adverse effects.

T lymphocytes

T lymphocytes, as well as monocytes and macrophages, are among the earliest cells to be related to formation of atherosclerotic plaques [5]. Most adhesion molecules and chemokines that promote monocyte migration into intima are also implicated in T cell recruitment. Indeed, it has been reported that there are a large number of T cells in advanced human atherosclerotic plaques. Most T cells express CD3, CD4, and T cell receptor (TCR), and they interact with phagocytes specialized in antigen presentation such as macrophages and dendritic cells (DCs). In response to exposure to the specific antigen, these T cells produce cytokines and trigger inflammation, and some T cells (CD8+ T cells) even have mechanisms for killing cells, thereby contributing to the development of atherosclerosis.

Helper T cells, which are differentiated from CD4+ T cells and have a critical role for antigen recognition, are divided into Th1 and Th2 subtypes. While the ratio of Th1 and Th2 subtype is controlled by local cytokines or antigen presenting cells, most T cells observed in atherosclerotic lesions are Th1 cells. Th1 cells secrete cytokines such as interferon-γ (IFN-γ), IL-2, and tumor necrosis factor (TNF), which are all known to promote inflammation by acting through macrophages or vascular cells. Moreover, cytokines such as IL-18 and IL-12, that stimulate Th1 cells, have also been shown to promote atherosclerosis. Taken together, Th1 responses generally accelerate atherosclerosis by enhancing proinflammatory pathways.

Th2 cells also secrete cytokines that may modulate inflammation such as IL-4, IL-5, and IL-10. However, in contrast to Th1, the role of Th2 responses in atherosclerosis remain controversial. A more recently recognized T cell subtype, Th17, is known to be

associated with a wide range of autoimmune diseases including rheumatoid arthritis. Th17 cells mainly produce IL-17, although their role in CVDs remains to be elucidated. Another T cell subtype, known as regulatory T cells (Tregs) are subdivided into natural Tregs (nTregs) and induced Tregs (iTregs). While nTregs develop in the thymus and have a role for maintaining self-tolerance, iTregs are generated extrathymically at peripheral sites. Several lines of evidence have shown that both nTregs and iTregs are important for atheroprotection by dampening inflammatory responses or through deactivation of DCs [6].

B lymphocytes

B lymphocytes secrete antibodies that play a central role for humoral immunity. Accumulating evidence has suggested that humoral immunity seems to attenuate rather than promote atherosclerosis. However, the effect of B cells on atherosclerosis has also been known to depend on certain cell subtypes, especially known as B1 and B2 cells. B1 cells mainly produce IgM antibodies, and they have been shown to play a protective role against atherosclerosis by generating antibodies that can recognize oxidized LDLs [7]. On the other hand, the majority of studies have shown that B2 cells, which produce IgG and IgE antibodies, promote atherosclerosis. Thus, it can be suggested that an ideal therapeutic strategy to prevent atherosclerosis would be to reduce B2 cells while preserving or increasing B1 cells [5].

Inflammatory biomarkers

Based on the concept that chronic inflammation contributes to the pathogenesis of atherosclerosis, numerous studies have been reported that various biomarkers of inflammation could predict future cardiovascular events in not only patients with CVDs but also in apparently healthy individuals.

High-sensitivity C-reactive protein

Although C-reactive protein (CRP) levels increase after various unspecific inflammatory stimuli, there is accumulating evidence that CRP measured by a high-sensitivity assay (hsCRP) can predict future cardiovascular events independent of traditional risk factors. Moreover, the magnitude of cardiovascular risk for hsCRP was reported to be at least as large as those for traditional risk factors such as hyperlipidemia or hypertension [8]. On the basis of these observations, hsCRP has emerged as a leading biomarker of cardiovascular risk prediction. Indeed, hsCRP serves as a useful tool to heighten cardiovascular risk assessment. For example, in the Reynolds risk score, the addition of hsCRP, along with family history to traditional risk factors is reported to improve overall future risk prediction [9].

Moreover, whether hsCRP could also be used to monitor patients with cardiovascular treatment has been primarily investigated in the context of statin therapy. For instance, the Cholesterol and Recurrent Events (CARE) trial showed that statins lowered hsCRP independent of LDL cholesterol, and clinical benefit of statin therapy tended to be greater among those with hsCRP [10]. These findings are consistent with several subsequent trials such as Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL), Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT), and Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) [11]. Of note, the Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial enrolled over 17,000 individuals and prospectively tested the hypothesis that individuals with low levels of LDL cholesterol but elevated levels of hsCRP would also benefit from statin therapy. The results of this trial clearly showed that statin treatment reduced cardiovascular events among apparently healthy individuals with high levels of hsCRP, suggesting that the clinical benefit of statins stems from both LDL cholesterol lowering and anti-inflammatory effect by reduction in CRP [12].

IL-6

Like hsCRP, IL-6 has been drawn attention to as a candidate biomarker for predicting cardiovascular risk, because it is known to induce CRP production in the liver and is classified as an upstream cytokine to reflect inflammation. More than two dozen prospective cohort studies indicate that as well as hsCRP, IL-6 is associated with cardiovascular risk independent of traditional risk factors [13]. Moreover, IL-6 levels have been shown to correlate with endothelial dysfunction and subclinical atherosclerosis [11].

IL-1

Because IL-1 induces the synthesis and expressions of various secondary inflammatory cytokines including IL-6, one can easily imagine that IL-1 signaling pathways are also critical for progression of atherosclerosis. Two genetically coded proteins, IL-1α and IL-1β, have been shown to bind the same receptor. While IL-1α is generally membrane-bound and mainly exerts its effect locally rather than systemically in response to injury, IL-1β is a primary form of circulating IL-1 and is initially synthesized as a precursor that is activated by caspase-1 cleavage in the setting of the nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3 (NLRP3) inflammasome [14]. Thus, IL-1β is implicated as being more crucial rather than IL-1α for its role in systemic inflammation. Unlike hsCRP and IL-6, there are no epidemiological studies demonstrating IL-1β as a biomarker for cardiovascular risk because direct measurement of plasma IL-1β is difficult and usually unreliable. However, a large number of studies have suggested that IL-1β is critically involved in the pathogenesis of atherosclerosis, making IL-1 signaling pathway an attractive target for atheroprotection.

Reducing inflammation as a therapeutic target

The concept and mechanisms of inflammation contributing to atherosclerosis have led to exploration of possibilities that targeting chronic inflammation itself could prevent progression of atherosclerosis and subsequently reduce cardiovascular events (Fig. 1). However, it should be pointed out that inflammation involves a pathway that will contribute to atherosclerosis and its complications by traditional risk factors. Indeed, the cardioprotective effects of aspirin, the traditional anti-inflammatory drug, are considered to be due to its antiplatelet properties rather than its direct anti-inflammatory effects. Thus, validation of the concept should be cautiously performed and interpreted. Specifically, testing the inflammatory hypothesis of atherosclerosis requires an intervention that inhibits inflammation without having significant impact on other pathways of atherothrombosis, and has a safety profile allowing evaluation in trial settings [15].

CRP

Although the JUPITER trial clearly demonstrated that hsCRP is a clinically important biomarker for future cardiovascular events, the trial could not address whether CRP itself plays any causal role for atherogenesis, nor could it prove that direct anti-inflammatory therapies reduce atherosclerotic cardiovascular events [16]. Indeed, because statins could reduce both LDL cholesterol and inflammation, statin trials cannot be evaluated for whether reducing

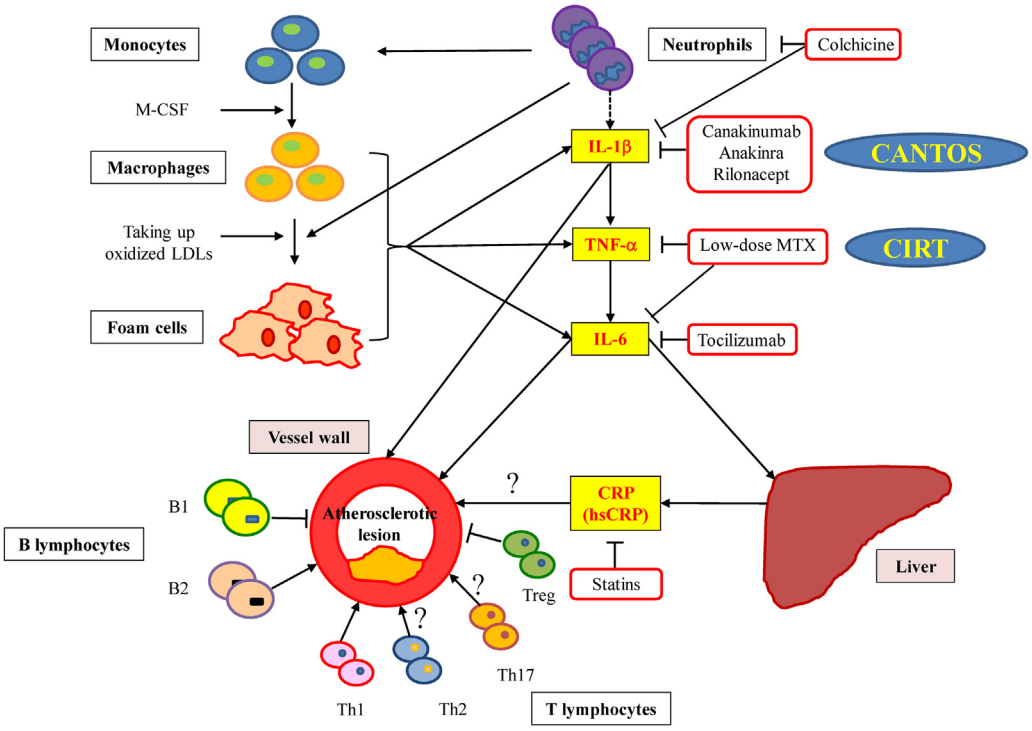

Fig. 1. Schematic representation of mechanisms and potential targets of inflammation in atherosclerosis. Various immune cell subtypes are involved in the pathogenesis of atherosclerosis. Inflammation triggered by these cells is accompanied by releasing inflammatory cytokines. At present, IL-1β, TNF-α, and IL-6 are considered to be potential therapeutic targets for atherosclerosis. CANTOS, Canakinumab Anti-inflammatory Thrombosis Outcomes Study; CIRT, Cardiovascular Inflammation Reduction Trial; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; LDL, low-density lipoprotein; M-CSF, macrophage colony-stimulating factor; MTX, methotrexate; TNF, tumor necrosis factor; Treg, regulatory T cell.

inflammation itself actually decreases cardiovascular risk. Several *in vitro* and *in vivo* studies have implied that CRP has direct proinflammatory effects and accelerate atherosclerosis. However, there are also conflicting results regarding a role for CRP in development of atherosclerosis, and whether CRP plays causal roles remains controversial. Further research would be required to validate the role of CRP in atherosclerosis, yet there is no doubt that hsCRP as a diagnostic test is a clinically useful biomarker for primary and secondary prevention of cardiovascular diseases.

IL-6

In contrast to CRP, there are consistent reports from multiple studies indicating that IL-6 signaling has a causal role in atherothrombosis. Notably, it has been reported that polymorphism in the IL-6 signaling pathway is associated with lower levels of cardiovascular risk, along with lower hsCRP levels [17,18]. These positive results have provided a new strategy that targets IL-6 as a therapy for atherosclerosis. However, interpretation of clinical trials of IL-6 inhibition by certain drugs such as tocilizumab, a humanized anti-IL-6 receptor antibody, need to be carefully evaluated. Firstly, it should be kept in mind that randomized trials to test the effect of tocilizumab on cardiovascular risk, such as the MEASURE trial or the ongoing ENTRACTE trial, all participants have symptomatic rheumatoid arthritis and therefore need active anti-inflammatory therapy [19]. Second, several studies have implied that direct IL-6 inhibition leads to an increase in LDL cholesterol, which might counteract assumed atheroprotective effects. In addition, undesirable side effects of known drug toxicity such as infection and potential reactivation of tuberculosis should be closely monitored.

Low-dose methotrexate (MTX) is routinely and safely used among patients with rheumatoid arthritis and psoriasis. Moreover, low-dose MTX decreases several inflammatory biomarkers including CRP, IL-6, and TNF-α in patients with rheumatoid arthritis without affecting lipid levels, hemostasis, or platelet function [20]. Thus, low-dose MTX is suggested to be a proper anti-inflammatory regimen to test the hypothesis that inflammation contributes to atherosclerosis without affecting other important risk factors. For these reasons, the Cardiovascular Inflammation Reduction Trial (CIRT) was designed to test the inflammatory hypothesis of atherosclerosis. The CIRT trial is a randomized, double-blind, and placebo-controlled trial that will enroll 7000 patients with stable post-myocardial infarction and either type 2 diabetes or metabolic syndrome. The primary objective of the CIRT trial is to determine whether low-dose MTX as compared with placebo will reduce the rate of recurrent cardiovascular events among patients [21]. Results of the trial are expected in 2018.

IL-1

IL-1 is an apical proinflammatory mediator in inflammation, and it plays a substantive role in progression of atherosclerosis among other inflammatory cytokines [22]. Convincing links between IL-1β and atherogenesis as mentioned above have made this cytokine a promising therapeutic target. Several agents that can inhibit IL-1 activity, such as anakinra (an IL-1 receptor antagonist), rilonacept (an IL-1 trap), and canakinumab (an anti-IL-1β antibody), are currently available. Among them, canakinumab is known to be effective for some inflammatory diseases such as Muckle-Wells syndrome, rarer forms of juvenile inflammatory arthritis, and acute gouty arthritis [23]. Canakinumab has attracted special attention as a proper candidate to test the inflammatory hypothesis because it is a human monoclonal antibody that selectively neutralizes IL-1β but not IL-1α, whereas anakinra and

rilonacept block both. Moreover, it had no effect on LDL or high-density lipoprotein (HDL) cholesterol in patients with well-controlled type 2 diabetic patients [24]. Taken together, canakinumab was thought to provide a specific method to verify that reducing inflammation itself would improve cardiovascular outcomes, as well as low-dose MTX.

Therefore, the CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) trial was designed as a large-scale trial to test the hypothesis that administration of canakinumab to inhibit IL-1β activity could prevent recurrent cardiovascular events. The CANTOS trial is a randomized, double-blind, placebo-controlled trial, and the primary aim is to evaluate whether canakinumab treatment will prevent recurrent cardiovascular events. The study enrolled over 10,000 patients with previous myocardial infarction who were at increased cardiovascular risk due to persistently elevated levels of hsCRP, defined as 2 mg or more per liter [25]. The patients were randomly assigned placebo or canakinumab at a dose of 50 mg, 150 mg, and 300 mg, respectively. These doses were subcutaneously administered every three months, and the primary endpoint was the occurrence of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death [1].

The results showed that canakinumab lowered levels of hsCRP in all three doses, and that the median reduction from baseline hsCRP was significantly greater in all of the canakinumab groups than in the placebo group. However, consistent with the previous results [24], canakinumab did not have a significant influence on lipid levels including LDL and HDL cholesterol. At a median follow-up of 3.7 years, the 150 mg and 300 mg doses of canakinumab significantly reduced incidence of the primary endpoint by 15%, although no significant effect in the primary endpoint was observed in the 50-mg group compared to the placebo group, demonstrating that anti-inflammatory therapy with canakinumab significantly lowered recurrent cardiovascular events without change in lipid levels. Furthermore, additional analysis of the CANTOS trial revealed that canakinumab significantly reduced incident lung cancer and lung cancer mortality, although lung cancer was not a predefined study endpoint [26].

As a first large-scale, randomized, double-blind, and placebo-controlled trial, the CANTOS trial affirmed the inflammatory hypothesis of atherosclerosis and opened up a new avenue of direct targeting of inflammation as a strategy for secondary prevention of CVDs.

Other immunomodulatory therapies

The promising results of the CANTOS trial have rendered immunomodulation a new role for therapeutic approaches toward atherosclerosis. Immunomodulation in atherosclerosis can basically have three targets: anti-inflammation, cholesterol synthesis, and immunization against neoantigens [27]. Because multiple and various mediators have been involved in inflammation, one can assume that targeting only one specific mediator such as IL-1β might not inhibit all inflammatory pathways implicated in atherosclerotic development. Although an unblinded and relatively small trial, use of colchicine, a traditional anti-inflammatory drug, has been shown to reduce cardiovascular events [28]. With regard to targeting T cells, a preliminary study indicated that administration of anti-CD3 antibody exerted atheroprotective effects by reducing CD4+ T cells and instead increasing Tregs [29]. Moreover, several targets have been explored as a novel anti-atherosclerosis vaccine therapy. For example, apolipoprotein B100 derived peptides or using modified LDL as antigen, have been shown to reduce atherosclerotic lesions in experimental models [30]. All of these potential immunomodulatory therapies need elaborate clinical evaluation and should be directly tested by randomized trials.

Conclusions

Following a large body of evidence implicating that lowering inflammation may be a promising novel strategy for reducing atherosclerosis, the CANTOS trial clearly validated the concept that inflammation is directly involved in the pathogenesis of atherosclerosis. Targeting inflammation as a trigger of atherosclerosis is now becoming a new therapeutic option for reducing CVDs in clinical practice. However, caution is needed that anti-inflammatory strategies may aggravate or elicit unfavorable effects such as infection. Actually, higher incidence of fatal infection and sepsis with canakinumab than with placebo was observed in the CANTOS trial [1]. Moreover, considering that IL-1β is merely one of many potential therapeutic targets for inflammation, further investigation is definitely required to which anti-inflammatory strategies could be most feasible or applicable for prevention of atherosclerosis.

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Conflicts of interest

None.

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