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REVIEW

New insights into the emerging effects of inflammatory response on HDL particles structure and function

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Abstract

According to the increasing results, it has been well-demonstrated that the chronic inflammatory response, including systemic lupus erythematosus, rheumatoid arthritis, and inflammatory bowel disease are associated with an increased risk of atherosclerotic cardiovascular disease. The mechanism whereby inflammatory response up-regulates the risk of cardio-metabolic disorder disease is multifactorial; furthermore, the alterations in high density lipoprotein (HDL) structure and function which occur under the inflammatory response could play an important modulatory function. On the other hand, the serum concentrations of HDL cholesterol (HDL-C) have been shown to be reduced significantly under inflammatory status with remarked alterations in HDL particles. Nevertheless, the potential mechanism whereby the inflammatory response reduces serum HDL-C levels is not simply defined but reduces apolipoprotein A1 production. The alterations in HDL structure mediated by the inflammatory response has been also confirmed to decrease the ability of HDL particle to play an important role in reverse cholesterol transport and protect the LDL particles from oxidation. Recently, it has been shown that under the inflammatory condition, diverse alterations in HDL structure could be observed which lead to changes in HDL function. In the current review, the emerging effects of inflammatory response on HDL particles structure and function are well-summarized to elucidate the potential mechanism whereby different inflammatory status modulates the pathogenic development of dyslipidemia.

Keywords Inflammatory response · Endotoxin · HDL · Structure · Function · Reverse cholesterol transport

Introduction

According to the results of previous studies, it has been shown that the chronic inflammatory disorders disease, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and inflammatory bowel disease (IBD) are associated with an increased risk of atherosclerotic cardiovascular disease [1]. For instance, in a meta-analysis which enrolled 24 clinical trial, the authors demonstrated that the patients with RA presented an approximately 48 % increase of the pathogenic development of cardio-metabolic disorder disease mortality [2]. However, within the patients under the SLE status, the authors demonstrated an approximately 2.7 increase of the risk of cardio-metabolic disorder disease mortality via a meta-analysis which enrolled 12 clinical trials [3]. Consistent with these findings, another meta-analysis which contained 14 clinical trials revealed that in patients with severe psoriasis, as another important chronic inflammatory diseases, the risk of cardio-metabolic disorder diseases mortality was approximately 1.40 and the risk of acute myocardial infarction (AMI) was approximately 3.10 higher than those within the general population [4]. Furthermore, under the condition of chronic inflammatory status, the patients have been confirmed to have an up-regulated risk of thickening carotid intima media calculated by ultrasound and the coronary artery calcium measured by tomography (CT) [5–7]. Moreover, several other chronic infections diseases such as human immune-deficiency virus (HIV), periodontal disease, and chronic bronchitis have also been strongly correlated with an increased risk of cardio-metabolic disorder diseases, presumably owing to the chronic inflammatory condition which accompanies these inflammatory diseases

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[8, 9]. On the other hand, the potential mechanisms whereby inflammatory condition modulates the risk of cardio-metabolic disorder diseases is likely to be multifactorial factor. In the current review, the emerging effects of inflammatory response on HDL particles structure and function are well-summarized to elucidate the potential mechanism whereby different inflammatory status modulates the pathogenic development of dyslipidemia.

Modulatory functions of inflammatory response on serum HDL-C concentrations

While inflammatory response induces a variety of alterations in serum concentrations of lipid profiles and lipoproteins, including increased serum concentrations of triglycerides (TG), one of the most consistent alterations is a reduced plasma concentrations of HDL-C [10]. In patients with severe RA, there is a similar reduced serum concentrations of HDL-C and apolipoprotein A1 (ApoA1) [11]. Meanwhile, small HDL are preferentially reduced significantly [12]. The degree of decreased in HDL particles is shown to be greatest within the patients under the condition of severe RA. Furthermore, there is a negative association of the serum levels of C-reactive protein (CRP) with the serum concentrations of HDL-C, including higher plasma CRP concentrations are associated with lower serum concentrations of HDL-C. Consistent alterations in HDL have also been found in patients with SLE, RA, and IBD [13]. Under the status of infection with HIV, the authors observed an early metabolic response was down-regulated in HDL particles, which occurs prior to an elevated in serum concentration of TG [14, 15].

In addition, a recent clinical trial demonstrated that the serum HDL-C concentrations were less than 10 mg/dl within the patient who suffered from severe sepsis, indicating that the status of chronic inflammatory condition could significantly modulate the serum HDL-C concentrations [16]. Moreover, the decreased plasma concentrations of HDL-C which occurs during the infection condition could be reproduced via using the animal models which was administrated by endotoxin to make an experimental animal model of gram (–) infection [13]. Additionally, several investigations have put forward that the extent of decrease in serum concentrations of HDL-C and ApoA1 could be used for the prediction of mortality within the patients who suffer from severe sepsis [17–19]. Notably, both animals and humans studies revealed that the lower serum concentrations of HDL-C were closely correlated with a melodramatic response to the administration of endotoxin [20–22].

Modulatory effects of inflammatory response on HDL particles function

As one of most vital proteins within circulation, HDL embrace several important effect which has been shown to inhibit the development of cardio-metabolic disorder diseases and to be adversely influenced by the progression of inflammatory response. In the present article, the impact of inflammatory response on modulating the functions of HDL particles, especially affecting the process of RCT and protecting LDL particles from oxidation, is well-summarized.

Modulatory effect of inflammatory response on RCT process

The step of excess cholesterol moving from the macrophage in reverse to the hepatocyte for subsequent excretion in the bile, not matter as the form of cholesterol or the form of bile acids, is a comprehensive progression that contains several steps. On the other hand, the vivo studies have revealed that the process of RCT could be measured by loading the macrophage with injecting the labelled cholesterol and next assessing the labelled cholesterol within the circulation, hepatocyte, and egesta [23]. Additionally, via this technical measurement, multiple research has demonstrated that intervention of the mice with endotoxin which lead to severe inflammatory response could further induce an inhibition of RCT [24–26]. Importantly, treatment with the relatively lower dose of endotoxin has been shown to induce a similar reduction of RCT process, revealing that this alteration in the progression of RCT is a sensitive response to the inflammatory status [25].

Recently, using the *SAA* gene-deficient mice with the administration of endotoxin, the authors showed that these mice had a relatively reduced extent of RCT, suggesting that the elevated serum levels of *SAA* is not vital for the reduction in RCT process [27]. Nevertheless, the mice with over-expressed *SAA* gene presented the similar extent of RCT compared to those in the mice which occurred under the inflammatory response, shedding light on that SAA is not vital in modulating RCT [20]. Furthermore, consistently elevating myeloperoxidase to the extents which is similar to that occurs under the inflammatory condition could also inhibit the process of RCT [20]. Similar with these findings, the circulating myeloperoxidase concentrations were shown to be increased significantly under the status of inflammation; meanwhile, the myeloperoxidase-induced oxidation of HDL particles were also reduced which lead to impaired RCT and the inhibition of LCAT [21, 22, 28]. On the contrary, elevated circulating levels

of solute PLA presented no significant function on RCT [20]. Interestingly, the functions of elevated serum levels of SAA or myeloperoxidase on modulating the process of RCT were relatively moderate compared with the regulatory function of severe inflammatory response, showing that several changes might facilitate the impaired extent of RCT [20].

Modulatory effect of inflammatory response on extracellular HDL metabolism

According to the reported article, the inflammatory condition could impair the activity of LCAT which plays an important role in inhibiting the exchange of cholesterol to EC within HDL particles [29]. Importantly, the above step has been considered as the most vital step of the HDL particles maturation which promote HDL to accept excessive cholesterol from macrophages. Reducing the LCAT activity in matured HDL particle has been shown to reduce the effect of HDL to mediate RCT [30]. Similarly, the impaired extent of RCT via inhibiting LCAT activity is almost the same as the impaired extent under the inflammatory status.

On the other hand, the inflammatory response is confirmed to inhibit the activity of CETP and as a consequence, inhibit the transportation of excessive cholesterol from HDL particles to Apo-B containing lipoproteins, including VLDL, LDL, and CM [31]. Notably, this process has been considered as an essential pathway of transferring the cholesterol to the hepatocytes in human beings [32]. Moreover, the inflammatory response could also reduce the expression levels of hepatic lipase (HL), as an essential rate-limiting enzyme within the hepatocyte which plays an important role in removing TG from HDL, and lead to an inhibition in serum HL activity which resultantly influenced the biological function of hepatocytes [33].

Modulatory effect of inflammatory response on anti-oxidant function of HDL

According to the published results, one of the essential properties of HDL particles is to prevent the LDL from oxidation and to inhibit the formation of ox-LDL. Via this function, HDL could improve the process of atherosclerosis [34]. Up to date, there is emerging evidence which showed that several HDL-related proteins, such as ApoA1, paraoxonase 1 (PON1), and transferrin protein, could affect the anti-oxidant functions of HDL proteins [35, 36]. Via the injection of croton oil into rabbits to lead to severe inflammatory response, the authors demonstrated that the HDL particle within the circulation of these rabbits presented loss-of-function alterations in protecting the LDL particles from oxidation [37, 38].

Aside from the croton oil, several other administration of medicine could also modulate the function of HDL. For instance, the mice with acute influenza infection presented a significantly impaired anti-oxidant function of HDL which were inclined to suffer from atherosclerosis [39]. In addition, the serum HDL particles isolated from the patients with chronic inflammatory diseases, such as SLE, RA, and IBD, has been shown to have a reduced function to inhibit LDL from formatting the ox-LDL. Indeed, the loss-of-function of HDL may reversely promote the LDL oxidation and facilitate the development of atherosclerosis [40, 41]. The anti-oxidative function of HDL has been also shown to be strongly associated with the severity of the disease. On the contrary, using the treatment which inhibit the pro-inflammatory response and improve the disease activity could significantly restore the anti-oxidant functions of HDL particles towards normal [42, 43]. With in-depth investigation, under the condition of inflammatory response, the pro-inflammatory cytokines could significantly reduce the expression levels of *PON1* gene and down-regulate the activity of PON1 protein, which could subsequently contribute to reduce the function of HDL particle in inhibiting LDL from oxidation [44]. By contrast, using the cultured cell lines, the authors found that the serum ceruloplasmin concentrations increased under the inflammatory status. As a pro-inflammatory proteins, ceruloplasmin could facilitate the oxidation of LDL particles, so we could infer form these findings that ceruloplasmin modulate the risk of dyslipidemia might via oxidation of LDL [43, 45].

On the other hand, the serum concentrations of transferrin proteins has been confirmed to reduce significantly under the progression of inflammatory response. Besides, multiple research have suggested that the transferrin protein could also protect LDL from oxidation [46, 47]. However, using the intervention of endotoxin to mice could induce the up-regulated concentrations of multiple bio-markers of per-oxidation in serum LDL particles, indicating that the inflammatory response could facilitate the risk of dyslipidemia [48, 49]. Additionally, LDL particles isolated from endotoxin-intervened mice is more inclined to oxidation and to foam cells [49]. In addition, other bio-markers of lipid peroxidation, such as conjugated dienes and lipid hydroperoxides, has been shown to up-regulated within circulation in patients with inflammatory diseases [50–52].

During the process of cardio-metabolic disorder diseases, the oxidant LDL particles within circulation could be taken up via endocytosis induced by macrophages. By this methods, the macrophage has been considered as the most important cell which plays an essential role within the formation of the foam cell. Furthermore, using the anti-bodies to the oxidant LDL particles isolated from the patients with IBD, SLE, and psoriasis, the authors found that these LDL particles presented the increased uptake of

the anti-body via the Fc-receptor on the surface of macrophages, indicating that the under the condition of inflammatory status, the abnormal macrophages could affect the function of LDL metabolism [53, 54]. Consistently, several other research has demonstrated that the LDL particles isolated from individuals with periodontal disease presented the increased endocytosis of CE by macrophages [55]. However, due to the lack of literatures, the potential underlying mechanisms accounting for the enhanced oxidation of LDL particles under the inflammatory conditions is still needed to be further elucidated.

Modulatory effect of inflammatory response on exchange of cholesterol from macrophages to HDL

As is known to us, the first step in the reverse cholesterol transport (RCT) pathway is the movement of cholesterol from macrophages to HDL. Studies have demonstrated that inflammatory stimuli decrease macrophage expression of ABCA1, ABCG1, and SR-B1, transporters that mediate the efflux of cholesterol to HDL [56–58]. Additionally, Apo E expression in macrophages is also decreased by inflammatory stimuli, which could also impede cholesterol efflux [59, 60]. As noted earlier the levels of HDL and Apo A-I are decreased during inflammation, which could limit the acceptors available to promote efflux of cholesterol. Moreover, the structurally altered HDL formed during inflammation is a poor acceptor of cholesterol [61]. As described earlier, HDL enriched in SAA has a decreased ability to mediate cholesterol efflux [62]. In fact some studies have shown that inflammatory HDL instead of removing cholesterol from cells actually delivers cholesterol to cells [61]. HDL isolated from patients with RA, SLE, psoriasis, periodontal disease, HIV infection, and acute sepsis has been shown to be poor mediators of the efflux of cholesterol from macrophages [11, 19, 32, 63].

Furthermore, the administration of LPS to humans also results in the formation of HDL that is a poor facilitator of the efflux of cholesterol from macrophages [8]. Importantly, treatment that reduces inflammation has been shown to improve the ability of HDL from patients with RA, psoriasis, HIV infection, and periodontitis to mediate the efflux of cholesterol from macrophages [64].

Notably, under the condition of HIV infection, the circulating macrophage might also impair the process of excessive cholesterol efflux via down-modulating the ABCA1 concentrations through the NEF protein. It is worth noting that NEF protein could disrupt the exchange of ABCA1 from the endoplasmic reticulum (ER) to the plasma membrane and consequently activating the degradation of ABCA1 [65].

Modulatory effect of inflammatory response on cholesterol uptake by hepatocytes

As is shown in previous research, the cholesterol which is carried by HDL particles has been shown to be delivered into the hepatocyte by two methods. As reported, one of the methods is that the HDL particle could interact with scavenger receptor B1 (SR-B1), which could exchange the excessive cholesterol from the circulating HDL particles into the hepatocyte for the subsequently regenerating smaller HDL particles. It is worth noting that under the inflammatory conditions, several pro-inflammatory cytokines could down-regulate the SR-B1 expression within hepatocyte which resultantly induced an impaired endocytosis of HDL, indicating that the inflammatory process may promote the development of cardio-metabolic disorder disease via affecting the SR-B1 expression [66].

On the other hand, as reported in previous literatures, the cholesterol within HDL particle could be transferred into the ApoB containing lipoproteins, including LDL and VLDL, which subsequently delivered the excessive cholesterol into the hepatocyte by the LDL receptor (LDLR) induced by the endocytosis of ApoB. Concerning on this notion, several in vivo research has put forward that the inflammatory response could reduce the expression of LDLR on the surface of hepatocyte. However, this modulatory function which could not be accounted for by altering in *LDLR* gene concentrations [67]. Nevertheless, the expression levels of *PCSK9* gene in the hepatocyte has been activated by the inflammatory response. Since the PCSK9 within circulation could significantly inhibit the expression of LDLR and resultantly modulate the serum concentrations of LDL-C; as a consequence, this might explain the reduction in LDLR and the increase of serum LDL-C [68]. In addition, the circulating PCSK9 concentrations has been confirmed to be increased in individuals with periodontal inflammation [69]. A reduction in LDLR which is hand in hand with the reduction in serum contents of CETP could synergistically inhibit the HDL-C to be delivered into the hepatocyte by exchange with LDL and VLDL.

Modulatory effects of inflammatory response on HDL particles composition

Aside from the modulatory role in reducing the serum levels of HDL-C, emerging evidence has shown that the inflammatory response could also induce in significant changes in the intra-molecular composition of HDL particles [1]. To be more specific, in terms of the intra-molecular lipid components, several studies has indicated that the concentrations of cholesterol ester are reduced whereas the concentrations of free cholesterol, TG, and free fatty acids (FFA) are increased

remarkably. Additionally, there are remarked alterations in HDL-related proteins with some up-regulating and the others down-regulating. Among these altered components, the most profound alteration is an up-regulated concentrations of serum amyloid A (SAA) and a down-regulated concentrations of ApoA1. Importantly, according to the results, diverse modulatory functions on multiple enzymes and transfer proteins which are strongly correlated with HDL particle. In the following paragraph, the important alterations which occur in the essential proteins that are involved in HDL structure and catabolism has been well-documented.

Alterations in the concentrations of lecithin:cholesterol acyltransferase (LCAT)

Due to the technological advances, major breakthroughs have been made to elucidate the alterations in the concentrations of LCAT. As is known to us, the LCAT is one of the important proteins which has been confirmed to convert the free cholesterol within the HDL particles into cholesterol esters (CE). Importantly, this step has firmly been shown to be essential for the process of RCT and as a consequence, modulates the serum levels of lipid profiles. Multiple studies has used different animal models to further explore the modulatory functions of diverse interventions on the LCAT activity. For instance, administration of endotoxin or pro-inflammatory cytokines, such as tumor necrosis factor α (TNF-α), to hamsters, monkeys, and humans could lead to a significantly reduced LCAT activity within circulation [70]. In addition, in hamsters, the significantly reduction in LCAT activity has also been shown to be accompanied by an importantly reduction in the expression levels of *LCAT* gene within hepatocytes [71]. Furthermore, in patients with RA or severe sepsis, the circulating LCAT activity has been verified to be decreased importantly, suggesting that the inflammatory conditions could modulate the serum LCAT activity [72]. Nevertheless, an independent research demonstrated that under the condition of HIV infection, the circulating LCAT concentrations could be up-regulated importantly [73].

Alterations in the concentrations of cholesterol ester transfer protein (CETP)

CETP is an important protein within circulation which plays a vital role in mediating the exchange of intra-molecular cholesterol esters from the HDL particles for TG that was carried on apolipoprotein B (ApoB) lipoproteins. As a consequence, CETP could promote the process of RCT and resultantly modulate the serum levels of lipid profiles. Due to the potential role in modulating the risk and the development of dyslipidemia, the altered activity of CETP under the inflammatory condition has been given substantial attention in recent year. Notably, an independent research using hamsters and found that via the administration of endotoxin, several pro-inflammatory cytokines, including TNF-α, lnterleukin-1β (IL-1β), and IL-12, could significantly reduce the activity of CETP within circulation; meanwhile, the expression levels of *CETP* gene and CETP protein within different cells, such as adipocytes, myocardial cells, and skeletal muscle cells, were increased significantly, indicating that the pro-inflammatory cytokines could regulate the expression levels of CETP and subsequently influence the serum levels of lipids profiles [74].

Consistently, another important research demonstrated that via using endotoxin on the mice with over-expressing *CETP* gene, the mice presented a rapid remarkably decreased *CETP* gene within hepatocyte; simultaneously, the serum concentrations of CETP were also down-regulated significantly [75]. With in-depth investigations, the authors also revealed that in these mice, the reduced expression levels of *CETP* gene could be significantly regulated by the up-regulated glucocorticoid concentrations. However, the reduced CETP expression was confirmed to be independent of the alterations of glucocorticoids in hamsters [75]. Two independent research showed that in patients with sepsis, administration of endotoxin was found to reduce the serum CETP concentrations significantly, revealing that the pro-inflammatory status could also modulate the expression levels of CETP [70].

On the other hand, the cardiac surgery which also has the potentiality to facilitate the pro-inflammatory condition has been confirmed to down-regulate the serum CETP concentrations and its activity [76]. In addition, the patients under the status of RA presented the reduced plasma CETP activity. Nevertheless, the alterations of CETP activity could be only observed in the individuals who were under-taking the glucocorticoids [77]. Recently, another important research found that under the condition of HIV infection, the serum CETP concentrations has been shown to be up-regulated which was consistent with the paradoxical increase in the LCAT activity [73]. Taken together, we also needed further large-scale clinical trials and in-depth research which could elucidate the accurate relationship between the inflammatory condition with the altered activity of several proteins that play essential role in modulating the risk and the development of dyslipidemia.

Alterations in the concentrations of PON1

As reported in previous studies, the PON1 protein is one of the most important HDL-associated proteins which could protect LDL particles from oxidation and resultantly inhibit the development of atherosclerosis and its related cardio-metabolic disorder diseases [78]. The important function of PON1 in regulating lipid metabolism under the

inflammatory status has begun to gain appreciation since the PON1 could modulate the risk of dyslipidemia in mammals. To be more specific, one research used the mice with *PON1* gene deficiency and found that these mice presented reduction in anti-oxidant function of HDL particles; on the contrary, while used the mice with over-expression of *PON1* gene, the authors found that these mice presented increased anti-oxidant function of HDL particles and the increased protective function to atherosclerosis [78]. In addition, the mice with *PON1* gene deficiency were also shown to be more inclined to cardio-metabolic disorder disease and the lipoproteins within circulation isolated from these mice are more susceptible to be oxidized easily [78]. Another important research has also confirmed that under the inflammatory status in both humans and rabbits, the process of inflammation could significantly lead to a reduction of PON1 activity which inhibited the ability of PON1 to protect the LDL against oxidation and the risk of dyslipidemia [79]. Consistent with this notion, it has been verified that administration of endotoxin could lead to a significantly reduced expression of *PON1* gene in hepatocyte hand in hand with a decreased activity of PON1 within circulation in hamsters [80]. Similarly, several other pro-inflammatory cytokines, such as TNF-α and IL-1β, has also confirmed to have the function to modulate the function in influencing serum lipid profiles [80]. It is also worth noting that the decreased expression levels of *PON1* gene in the hepatocyte and the activity precedes the appearance of LDL-oxidation which follows the administration of lipopolysaccharide (LPS), indicating that the down-regulated expression of *PON1* gene might contribute to the increased extent of LDL oxidation [49]. Likewise, the serum concentrations of PON1 has been found to be reduced in patients with several other infective diseases, such as SLE, IBD, and psoriasis [81]. Besides, after the treatment in patients with psoriasis for a period, the serum concentrations of PON1 increased significantly, putting forward the evidence that anti-inflammatory treatment could improve the functions of PON1 [82].

Alterations in the concentrations of apolipoprotein M (ApoM)

As shown in previous studies, apolipoprotein M (ApoM) is a novel apolipoprotein discovered in recent years which has been shown to combine to the HDL particles. Furthermore, ApoM is also confirmed to be predominantly expressed by the hepatocytes and renal cells [83]. In addition, using the LDL receptor (LDLR)-deficient mice with over-expression of ApoM, the authors found that the risk of cardio-metabolic disorder diseases decreased obviously [83]. On the other hand, the sphingosine-1-phosphate (S1P), which is a biologically active lipid that could combine with ApoM and has the functions on modulating the functions of endothelial cells, has been shown to account for the protective functions of ApoM and have the anti-atherogenic functions [83]. Another important research which used the stimuli administration to induce pro-inflammatory progression in mice demonstrated that under the status of inflammatory, the mice presented reduced expression of *APOM* gene in the hepatocytes and renal cells, leading to a significantly reduced plasma ApoM concentrations [84]. Consistent with this notion, the participants who suffered from the bacterial infections or HIV displayed significantly reduced circulating concentrations of ApoM [84]. Besides, it is also found that the participants with sepsis, psoriasis, and SLE had a reduction in serum concentrations of ApoM. Furthermore, this alteration is confirmed to be strongly associated with the development of pro-inflammatory diseases. The serum ApoM concentrations are reduced in patients with [85].

Alterations in the concentrations of endothelial cell lipase (ECL)

ECL is one of the most vital members of the TG-catabolic lipase family which preferentially hydrolyzes phospholipids. In mammals, ECL is not only synthesized and secreted by the endothelial cells but also by the livers, smooth muscle cells, and macrophages [86]. It is firmly shown that over-expression of ECL significantly decreases serum HDL-C concentrations; however, in contrast, via inhibiting the activity of ECL could significantly elevate the serum concentrations HDL-C, suggesting that alterations of ECL might also influence the development of dyslipidemia and its related cardio-metabolic disorder diseases [86].

Multiple pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, have been confirmed to enhance the gene expression of ECL within endothelial cells. Using endotoxin intervention, it has been shown that the expression of ECL increased significantly within macrophages [87]. Other two independent research has also revealed that the ECL concentrations are strongly positively correlated with the serum concentrations of the bio-markers of inflammatory response, including CRP and IL-6 [88]. Furthermore, injection of endotoxin to the human volunteers could enhance the serum ECL concentrations which were hand in hand with the decreased concentrations HDL-C temporally [88].

Alterations in the concentrations of serum amyloid A (SAA)

SAA is an important protein within circulation which could be synthesized and secreted by several diverse tissues, such as the macrophages. However, the SAA is predominantly synthesized and secreted by the hepatocytes that could account for the majority of SAA within circulation [89]. The functions of SAA on modulating serum lipid

profiles have been given substantial attention in recent years. Under the status of inflammatory status, the serum concentrations of SAA has been shown to increase approximately 1,000 folds compared to those within healthy participants [89]. In addition, the increased serum concentrations of SAA could be found under the status of multiple inflammatory relate diseases including RA, IBD, and SLE.

In details, according to the previous studies, SAA could combine with HDL particles and could subsequently displace the ApoA1 protein within HDL particle, becoming the major intra-molecular protein which is closely correlated within HDL and influencing the biological functions of HDL [89]. Notably, SAA has been shown to displace several other intra-molecular proteins within HDL particles, such as PON1. Nevertheless, the biological effect of SAA in modulating the risk and the development of cardio-metabolic disorder diseases still remains uncertain and controversial [89].

The abnormal HDL which contains SAA presents a significantly reduced ability to facilitate the cholesterol efflux from macrophages [90]. Since the cholesterol efflux process mediated by macrophages is of great significance in the progression of atherosclerosis, it could be reasonably speculated that SAA could modulate the risk of coronary heart diseases via, at least partly, modulating the functions of macrophages. Currently, the functions of SAA on influencing the pathogenesis of coronary heart diseases has been reported by several research. In the mice with *APOE* gene-deficient mice, knockout of *SAA* gene presented no significant functions on the progression of atherosclerotic lesions and the severity of disease [91]. Consistently, in the mice with *LDLR*-deficiency, knockout of *SAA* gene lead to an elevation in atherosclerotic lesions but only seen in the ascending aorta. Due to the modulatory role of SAA on macrophage, we could infer from the research that alteration of *SAA* expression might lead to the development of atherosclerosis via influence the function of macrophages [92].

On the other hand, over-expression of *SAA* gene in *APOE* gene deficient mice has been demonstrated to induce an elevation in the atherosclerotic lesions [93]. Likewise, injecting adenovirus vector to overexpress *SAA* gene enhanced the development of atherosclerosis in *APOE* gene-deficient mice [94]. Intriguingly, it has been reported that a moderate increase of SAA could be sufficient to promote the development of atherosclerosis. By contrast, a prolonged increase of SAA were not required to facilitate the atherosclerotic progression, indicating that the acute episodes of inflammatory response which raise SAA concentrations might be pro-atherogenic functions [78]. Given the discordance of published results, the clearly additional research on the function of SAA on modulating atherosclerotic related cardiovascular diseases are still required to elucidate the important role of SAA in regulating the development of atherosclerosis.

Potential mechanism of the inflammatory response induced alterations of functions in HDL particles

Currently, increasing evidence has been put forward to elucidate the potential mechanism whereby the inflammatory response reduces the circulating HDL-C concentrations and the ApoA1 concentrations has not yet been well-established. However, it is possible that several potential pathways has been shown to be involved. For instance, it has been demonstrated that the expression levels of ApoA1 within the hepatocyte is reduced significantly by pro-inflammatory activation, including injection of endotoxin or the pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-12 [95]. Notably, the reduced circulating ApoA1 contents within circulation could contribute to the reduced in circulating contents of HDL-C which has been featured by inflammatory process. As mentioned above, excessive SAA within circulation significantly up-regulated under the inflammatory condition and displace ApoA1 within the HDL particles [89]. Via this method, the SAA-contained HDL particle has been confirmed to be eliminated from the circulation which might further reduce the serum levels of HDL-C, indicating that SAA modulated the risk of dyslipidemia and the related cardio-metabolic disorder diseases [89].

On the other hand, an independent research showed that ECL could induce a reduction of serum levels of HDL-C. Since the inflammatory response could up-regulate the expression levels of ECL, we could make a reasonable speculation that the inflammatory condition might facilitate the cardio-metabolic disorder disease via, at least partly, modulating the expression of ECL [86]. Consistently, the researcher also found that co-overexpressed SAA and ECL induced a relatively larger reduction in serum concentrations of HDL-C [96]. As a consequence, up-regulated ECL activity might further promote the reduction of circulating levels of HDL-C which occurs under the inflammatory response.

On the other hand, under the inflammatory, mice with over-expressed the PLA2 presented the ability of eliminating serum HDL particles more rapidly compared with that in healthy control mice, which resultantly induced a reduction of serum HDL-C concentrations [97]. Similarly, several research has demonstrated that PLA2 could cleave ApoA1 into multiple diverse protein fragment, which could be considered as an potential mechanism whereby PLA2 influenced the serum quantity and function of HDL [98].

More recently, as mentioned above, the serum concentrations and the activity of LCAT is shown to reduce under the inflammatory response. Finally, HDL particles which

contain abundant TG have been confirmed to be easily hydrolyzed by HL which could further promote the formation of smaller HDL particles and induce the clearance of ApoA1 [99]. However, in mouse models, the serum levels of HDL-C have been shown to reduce prior to the alterations of HDL particles, implying that there are still some other potential mechanisms which played an important role in reducing HDL-C under the inflammatory response [71]. Taken together, it is still necessary to conduct several large-scale clinical trials and animal experiment which could further elucidate the potential mechanism of the inflammatory response induced alterations of functions in HDL particles.

Conclusions and perspectives

By analyzing the results from previous studies, the serum HDL concentrations reduced significantly under the inflammatory response. Within the circulation, there are obvious remarkable alterations in HDL-associated proteins, including SAA, ApoA1, PON1, and CETP. Nevertheless, the accurate mechanism whereby inflammatory response reduced the serum HDL-C concentrations is still not elucidated. The alterations in HDL particle mediated by inflammatory response decrease the function of HDL particle in RCT and prevent the oxidation of LDL particles.

According to the findings mentioned above, it has been clearly indicated that inflammatory response could influence the structure and function of HDL particles. We could also make a reasonable speculation that these alterations were advantageous under the status of inflammatory response and acute/chronic impairments. For instance, under the condition of inflammatory status, the impaired process of RCT or elevated extent of LDL oxidation could up-regulate the serum cholesterol concentrations within macrophages where it could activate the host repair. Nevertheless, these alterations could increase the development of atherosclerosis over the long terms.

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Declarations

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