Pathophysiological implications between chronic inflammation and the development of diabetes and obesity

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Abstract

The different theories about the mechanisms involved in the development of metabolic disease and its complications converge in the presence of an etiologic chronic proinflammatory state. Chronic inflammation is, at present, the central pathophysiological mechanism involved in the genesis of metabolic diseases. The multiple interactions between the immune system, adipose tissue, the vascular wall and the pancreas are the issues addressed in this review, focusing on specific intracellular and molecular aspects that may become new therapeutic targets. These lead to a proinflammatory, prothrombotic state as well as to proapoptotic endothelial damage that allows the development of atherosclerosis and, consequently, cardiovascular disease. The multiple immunopathological processes associated with the etiology and pathophysiology of different chronic diseases is still in the process of being fully elucidated, allowing the development of new therapeutic targets.

Key words: chronic inflammation, diabetes, obesity, innate immunity.

Introduction

Nowadays, different theories about mechanisms involved in the development of metabolic diseases and their complications agree that there is a chronic pro-inflammatory condition where metabolic alterations interact with the immune system and disturb anti-inflammatory, anti-thrombotic and anti-apoptotic pathways. By understanding these processes we will achieve a better therapeutic approach and strengthen the development of new therapeutic goals. During this review, we make reference to the main components of these pathways and their interactions. We also explain how a normally beneficial process can have severe consequences in the human body.

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Inflammation and Clinical Interpretation

Inflammation (from the Latin *inflammatio*: to ignite, to make fire) is a biological response against harmful stimuli. Egyptians described clinical data associated with this process about 3,000 B.C. Afterwards, Hippocrates, Galen and Celsus described four cardinal signs of inflammation and Virchow[1] added a fifth cardinal sign for this process:

- *Swelling*: Increase of interstitial liquid and edema
- *Rubor*: redness, chiefly associated with vasodilation phenomena
- *Heat*: temperature increases at inflammation area because of vasodilation and local consumption of oxygen
- *Pain*: appears as a consequence of released substances able to activate nociceptors such as prostaglandins.

This is the first sign of Celsus' tetrad (which includes the four signs here described).

- *Loss of function*: also known as Virchow's fifth sign and as *functio laesa* (Latin), describes functional changes in inflamed organ or region

Chronic and Acute Inflammation: Clinical and Molecular Approaches

It is important to highlight not only the clinical aspects of inflammation but also become familiar with and understand the relationships between each molecular and celular actor in accordance with this phenomenon. Although inflammation produces certain responses considered beneficial at the beginning, continuous inflammation produces adverse effects and generates chronic diseases. Understanding these processes has led to the development of new therapies and clinical approaches to these problems.

Inflammation can be classified as acute or chronic according to stimulus type and the effectiveness of initial response to end it. Whereas acute inflammation has an immediate onset and short duration, chronic inflammation has a long duration and is associated with lymphocyte and macrophage response because of blood vessel proliferation and endothelium dysfunction as well as fibrosis and tissue destruction. Chronic inflammation develops when acute inflammation is unable to palliate the harmful stimuli or when inflammatory response continues.

There has been strong evidence over the last two decades that chronic and subclinical inflammation produces, and is a consequence of, several metabolic diseases. An example of the above is the metabolic syndrome (MetS) where serum levels of inflammatory markers such as C-reactive protein (CRP), interleukin-6, tumor necrosis factor-alpha (TNF-α) and others have been proposed as part of its definition.[2,3]

Inflammation and Atherosclerosis

Atherosclerotic angiopathy is a metabolic disease with one of the highest morbimortality presentation rates having a clear immunopathological origin. This process starts when blood vessel walls are subjected to stress, which promotes the production of proteoglycans that can bond and retain lipoprotein particles, actually initiating atherogenesis. This results in endothelial dysfunction, which is reduced vasorelaxation ability from nitric oxide secreted by endothelial nitric oxide synthase (eNOS). Also, there is an increased adhesiveness of inflammatory cells regulated by an elevated expression of adhesion molecules. At the onset of atherosclerosis, there is an increased transcytosis of low-density lipoproteins (LDL), which build up fatty streaks at the lumen of the vessel. These fatty materials contain lipoproteins that lose contact with plasma antioxidant substances, producing their oxidized form (oxLDL) and inducing a local inflammatory response.[4] The oxLDL increase the expression of toll-like receptors (TLR)[5] as well as the activity of nuclear factor kappa-B (NF-κB) and concentration of monocyte chemoattractant protein-1 (MCP-1) and interleukin 8. This activates circulating monocytes that, together with an increased expression of adhesion molecules such as VCAM-1 and ICAM-1 mediated by endothelial dysfunction, increase their ability to infiltrate the vascular endothelium. Therefore, during atherogenesis:

1. Recruited monocytes differentiate into macrophages and then become foam cells after a defective response to subendothelial lipoproteins, especially oxLDL.[6]
2. Inflammatory mediators are produced with defective regulation. Cytokines, chemokines, eicosanoids and lipids such as platelet activating factor (PAF), which preserve a maladaptive response, are found.
3. Transformed macrophages are unable to eliminate debris and these accumulate in the vascular wall.[7]

The above, together with endothelial dysfunction, constitute the pathophyisiological basis for atherothrombotic or atheroembolic disease, which currently has become pandemic.

Onset of Inflammatory Process: Free Radicals

When we consider the interactions between inflammation and metabolic diseases we may wonder—what stimulus initiated this chronic inflammatory process? Several hypotheses have been proposed and several studies have been conducted; however, there is a fundamental theory that establishes that exogenous nutrients are the primary triggers of chronic inflammation. The first experimental evidence of the above was obtained when demonstrating that a dose of glucose administered to healthy persons increases the generation of reactive oxygen species (ROS) both by polymorphonuclear cells and monocytes,[8,9] and this reaction was controlled by administering a NADPH oxidase inhibitor.[10] This situation repeats when administering a fat load dose and in a smaller amount with a protein dose.[11] ROS have pathogenic implications by activating pro-inflammatory pathways where there are redox-sensitive transcription factors such as NF-κB, activator protein-1 (AP-1),

early growth response 1 factor (EGR-1) and thioredoxin (TRX) bond protein with an increasing prevalence. Once these pro-inflammatory factors are activated, they induce cytokines such as TNF-α, matrix metalloproteases 2 and 9 (MMP) and tissue factor (TF). All of the above initiate a pro-inflammatory, pro-thrombotic and pro-apoptotic cycle in response to oxidative stress that generates more free radicals after macrophage and lymphocyte reponse. This leads to a self-perpetuating cycle.[12,13]

Influence of Chronic Diseases

So far, we have considered the action of pro-inflammatory factors triggered by a physiological event: macronutrient ingestion. But, what happens when there are other external factors that influence this process such as concomitant diseases (rheumatoid arthritis, insulin resistance, etc.) where there is an already active chronic inflammatory process?

Inflammation triggered by hyperglycemia includes insulin as one of the actors involved in the process. Insulin is a pleiotropic hormone closely associated with an inflammatory swing partly triggered by food ingestion.[14] Its action involves a series of insulin-signaling cascades such as phosphatidylinositol 3-kinase (PI3K) pathway, chief regulator of glucose metabolism, among others. Ras-mitogen pathway involves migoten-activated protein kinase (MAPK) and protein serine/threonine kinase (PSK), and both modulate gene expression of growth factors and cellular differentiation. These pathways converge at insulin receptor substrate (IRS), which includes four families whose activation allows tyrosine substrate phosphorylation, triggering cellular signalling. Insulin is also modulated through ISR-4 receptor that phosphorylates tyrosine residues over an homologous receptor (Shc). In turn, this binds to growth factor receptor-bound protein 2 (Grb2) as well as to G protein-coupled receptor kinase 2 (GRK2), activating Cbl proto-oncogene and recruiting insulin receptor, allowing translocation of GLUT-4 independent of PI3K activity. However, ISR-1 inactivates when it phosphorylates in serine at position 307 through MAPK interaction or other factors that interact at that level such as NF-κB beta inhibitor (IκBβ) and C-Jun N-terminal kinase 1 (JNK-1) in JNK/AP-1 pathway. The latter has complex implications in macrophage pro-inflammatory function before external nociceptive stimuli. On the other hand, there are other negative regulators to insulin pathway that lead to an inflammatory deregulation such as suppressor of cytokine signaling proteins (SOCS). Both Socs-1 and Socs-3 induce inflammation per se and promote degradation of IRS proteins.[2,15,16]

Pro-inflammatory Molecules

So far, we have briefly reviewed mechanisms involved in creating a chronic inflammatory state. There are different studies that provide us with data to understand these interactions. We will now present other actors of this process that are closely associated with the pathophysiological basis of several metabolic alterations: insulin resistance.

TNF-α is a pro-inflammatory cytokine secreted chiefly by monocytes and macrophages with a strong influence over lipid metabolism, coagulation and endothelial function.[17] Its presence allows activation of NF-κB, which associates it proportionally with insulin resistance.[18] Nowadays, this has special importance because abdominal obesity increases this inflammatory process through blocking IRS-1 proteins at the cellular level.[19,20]

Other implied factors are JNK-1, JNK-2[21] and IKκB. When they are activated by any mechanism, they lead to the development of metabolic alterations by increasing insulin resistance.[23] Induced nitric oxide synthase (iNOS) enzyme located in the endothelium produces nitric oxide whose absence leads to vasoconstriction and favors insulin resistance. Free fatty acids, inflammatory cytokines and oxidative stress inactivate iNOS, which reduces the activity of IRS-1 and PSK.[24-27]

Another important aspect of chronic inflammation is the role of macrophages, especially those of adipose tissue adjacent to adipocytes. According to results from current studies, these macrophages allow deletion of IKκβ in myeloid cells, which increases sensitivity to insulin. Macrophages are attracted by MCP-1 and its chemokine receptor 2 (CCR-2),[28] which are found in endothelial cells and perpetuate the inflammatory cycle by attracting more monocytes to inflammed tissues.[29,30] Therefore, both macrophages and chemokines have been established as potential targets for new therapeutic approaches.

Macrophages also contain the peroxisomal proliferator-activated receptor gamma (PPARγ), which regulates this inflammatory complex negatively through repression of genes.[31] It is an important regulator of scavenger receptor CD 36 and therefore plays an important role in building fatty streaks. It also regulates nitric oxide synthase, gelatinase B, IL-1β, IL-6 and TNF-α.[32-34] It demonstrates anti-inflammatory activities that make PPARγ an attractive therapeutic target. Its activity also inhibits CCR2 expression, which reduces monocyte/macrophage recruitment towards the vascular wall. On the other hand, there is direct inference of LXRα expression control. This is a nuclear hepatic receptor that controls the expression of some genes including adenosine triphosphate-binding cassette protein (ABCA)-1, which is associated with control of apolipoprotein A1 (Apo

A-1) that regulates cholesterol efflux as high-density lipoproteins (HDL).[35]

TLRs are receptors involved in fighting infectious agents because they recognize certain elements in bacteria and viruses that trigger immune system activity.[36] Nevertheless, they have recently been shown to play an important role in the development of atherosclerosis.[37] Eleven receptors have been described in mammals and, of these, nine are present in humans. TLR-4 has a special affinity with lipopolysaccharides present in gram-negative bacteria and activates pro-inflammatory signaling pathways IKκβ/NFκB and JNK/AP-1 that in turn express different inflammatory cytokines. However, we can also observe it binding internally to ligands that include minimally modified low-density lipoproteins (mm-LDL)[38] and the heat shock protein (HSP).[60] The latter is a highly preserved evolutionary protein that expresses when the cell is subjected to a constant stress as well as when it is exposed to oxLDL, initiating the activation of autoimmunity and a pro-inflammatory state.[39] HSP60 and HSP70 are proteins considered as TLR-2 endogenous ligands that, once activated, induce the development of atherosclerosis through endothelial damage mediated by IL-6, IL-8 and MCP-1. The relationship between TLR and the development of atherosclerosis may include the involvement of infectious agents, e.g., the association of *Chlamydia pneumonie* in atheromatous plaques through serologic and histopathological evidence.[40,41]

The Role of Adipose Tissue and Leptin

Obesity involves deregulation of adipose tissue, which is an endocrine organ that secretes adiponectin and may play an important role in generating a pro-inflammatory condition. Leptin has an essential role that connects the nutritional state with the immune response (both innate and adaptive). Leptin modulates activation and proliferation of T-cells, has anti-apoptotic effects over T-cells, activates polymorphonuclear cells, promotes neutrophil chemotaxis, boosts production of cytokines such as IL-2, IL-12 and INF-γ, stimulates Th1 response when inhibiting IL-10 and IL-4 and stimulates monocyte proliferation and production of IL-6 and TNF-α. All this stimulates a proinflammatory environment.[42]

Inflammasome and Thioredoxin

The inflammasome[43] is still under study to explain the interactions between inflammatory processes and the development of metabolic alterations. This multiprotein oligomer involves Nod-like receptor family 3, containing pyrin domain (NLRP3), which is one of the chief regulators of innate immune response and thioredoxin-interacting protein (TxNIP),[44] which is one of the proteins associated with redox state and insulin resistance. The importance of this pro-inflammatory pathway lies in its potential therapeutic applications and its multiple activators including ROS particles, endotoxins and potassium-channel activators, although the latter do not interact directly with the inflammasome (in contrast with TxNIP). Even though multiple actions have been identified for TxNIP, its first acknowledged function was as TRX inhibitor and, therefore, promoting ROS generation. TxNIP mutations have been associated with hypertriglyceridemia. When TxNIP is active in pancreatic β cells, it is infraregulated by insulin.

Hyperglycemia indicates ROS generation, which triggers activation of NADPH oxidase in the pancreas. This acts as a buffer to cellular oxidative stress because NADPH accepts electrons. In turn, the NADPH system activates TRX reductase, which reduces TRX, producing a bond with TxNIP. The ultimate effect is NLRP3 activation with consequent production and maturation of IL-1β, activating NLRP3. Its interaction with TxNIP initiates secretion of IL-1β, which generates insulitis, perpetuating hyperglycemia and an inflammatory state. IL-1β is produced in response to different stimuli including bacterial toxins and pathogen-associated molecular patterns (PAMPs), as well as in response to cell signaling markers of oxidative stress such as the presence of minimal ROS concentrations. ROS also induce conformational changes in proteins yet to be identified that actívate the inflammasome. On the other hand, TxNIP overexpresses in macrophages as a response to certain external factors and participates in activation of natural cytocidal lymphocytes and dendritic cells.[44,45]

This pro-inflammatory pathway is important because TRX binding with TxNIP activates JNK, which favors apoptosome building and, therefore, insulitis. In pancreatic β cells, regulation of TxNIP expression is mediated by insulin. Patients with type 2 diabetes mellitus present an overexpression of such protein, especially in pancreatic cells mediated by MLX transcriptor factor (which promotes a response to carbohydrates). The TxNIP-NLRP3 complex or inflammasome secondary to hyperglycemia as well as other activators such as ROS, oxidative stress and cellular response secondary to immune response activation trigger production and secretion of IL-1β from pancreatic cells. Therefore, it is understandable that current studies focus interest on the underlying chronic inflammatory state in diabetic patients.[46]

Cellular Aspects

Another important aspect when dealing with chronic inflammation is the cellular impact produced by activation of previously described pro-inflammatory pathways. The most frequently studied organelles in this sense are mitochondria and endoplasmic reticulum (ER) that participate in synthesis, transportation and release of proteins as well as in lipid and glucose metabolism. Specialized cells modify the ER to fulfill their purposes according to protein synthesis requirements.[47] One of the functions of the ER is to determine bioavailability of glucose and allow the development of adaptive mechanisms such as unfolded protein response (UPR), which activates cellular inflammatory response and triggers JNK, IKκβ/NF-κB and ROS pathway. ER stress stimulates activation of three PERK receptors ([RNA-dependent protein kinase]-like endoplasmic reticulum kinase), transcription factor 6-activated and inositol-requiring enzyme-1 (IRE-1) involved in UPR response. If there is a sufficient response, it can promote cell survival; otherwise the cell dies.[48,49]

On the other hand, ER stress activates JNK, which phosphorylates to a Bcl-2 protein family, suppressing its anti-apoptotic effects. It also releases BH3 protein from the cytoskeleton through phosphorylation that unrestrains apoptotic effects of Bax and Bak proteins, inducing β-cell apoptosis.[50]

Insulitis

If we consider that cellular damage to β cells is secondary to these inflammatory processes, we should explain more in-depth another phenomenon that is extremely important because of its pathogenic and therapeutic implications: insulitis.

In general, cells respond to stress in different ways, ranging from activation of pathways for survival to initiating programmed cell death in order to eliminate damaged cells that may cause a deficiency of an affected organ. In the case of pancreatic β cells, hyperglycemia generates ER stress by inducing sustained hyperinsulinemia. Both oxidative stress with large ROS quantities and generation of inflammatory cytokines (such as IL-1β, TNF-α, IFN-γ) as well as ER stress eventually lead to functional failure of pancreatic β cells and insulin deficiency. On the other hand, β-cell apoptosis favors a chronic inflammatory state generated by inflammatory cytokines released by macrophages. IL-1β induces manganese-dependent superoxide dismutase (MnSOD) enzyme, which increases O_2 transformation to H_2O_2 within mitochondria, therefore increasing β-cell toxicity. Excessive cellular ROS production primary affects mitochondria, which is regarded as the leading trigger of this disease[50,51] (Figure 1).

In conclusion, cellular response to metabolic stress mediated by mitochondrium and ER as well as immune response to harmful stimuli are physiological defense mechanisms. However, known metabolic risk factors interact with the immune system, resulting in an inflammatory process triggered by ROS that become noxious if perpetuated. Therefore, it is a priority for physicians to study these processes that, during a hyperfunctional state, lead to generate pro-inflammatory cytokines that initiate atherosclerosis and all its clinical presentations. Oxidative and metabolic stresses triggered by ingesting caloric nutrients may lead to insulitis and β-cell apoptosis. At the present time, there are several immunopathological processes being investigated, which will allow the development of new therapeutic goals in order to reduce the pro-inflammatory signaling cascade. Some examples of these goals are IL-1β receptor antagonists, TLR antagonists and TRX. There are also studies on the therapeutic potential of active and passive immunization against molecules that trigger an inflammatory process at the endothelial level such as oxLDL. Among these therapeutic approaches, IL-1β antagonists appear to have a special importance because of the role this cytokine plays with the inflammasome during insulitis. At any rate, these studies are the bases to develop a target-oriented, more effective therapy with less collateral effects that will provide greater benefits for our patients.

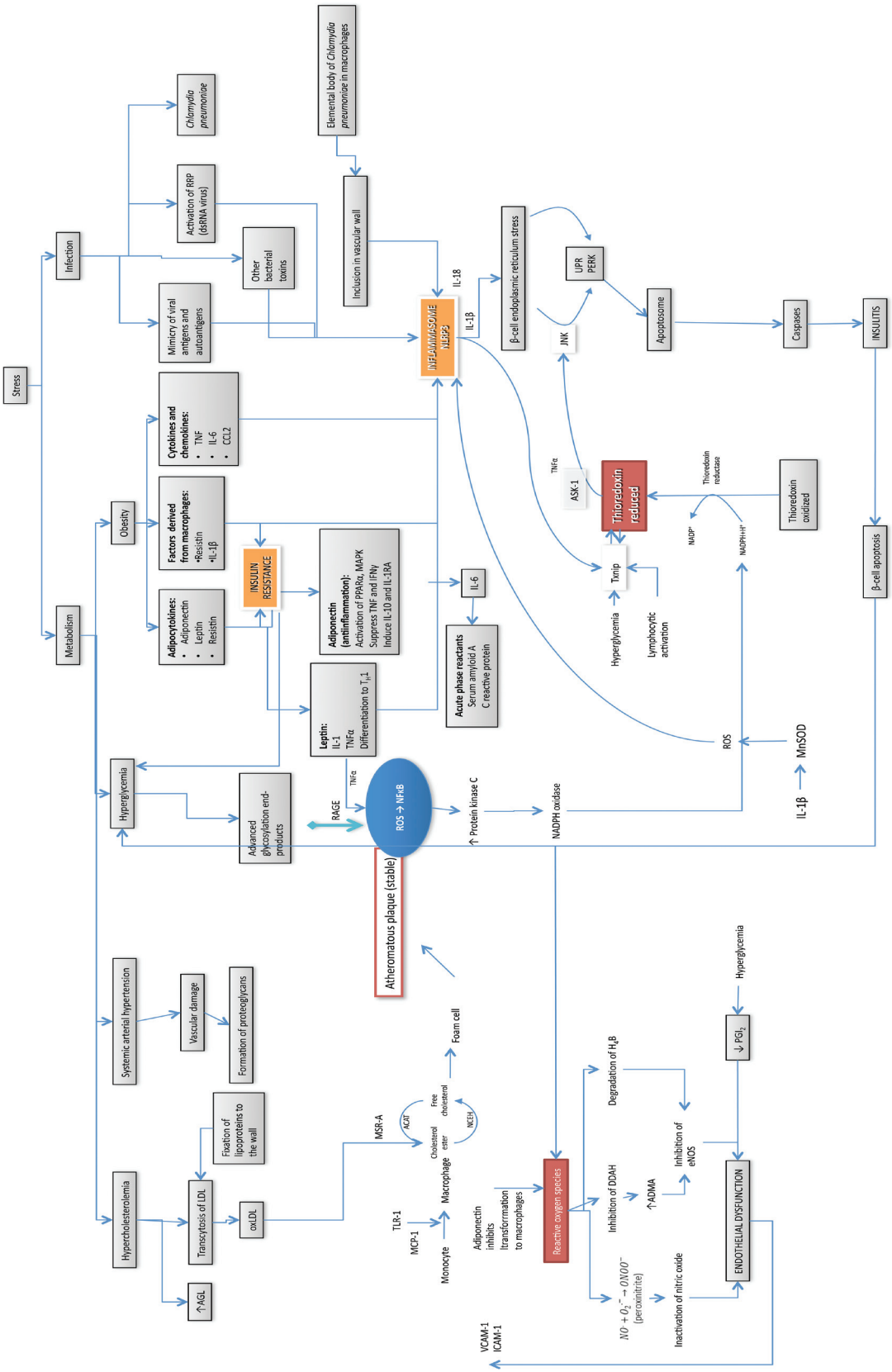

Figure 1. Overview of chronic inflammatory process and its interaction with different metabolic processes, immune system, adipose tissue, blood vessel wall and pancreas. TLR-1, toll-like receptor 1; MCP1, monocyte chemoattractant protein-1; ACAT, acyl-CoA cholesterol acyltransferase; NCEH, neutral cholesterol ester hydrolase; MSR-A, macrophage scavenger receptor; PRR, pattern recognition receptors; ARNdc, double-chain ribonucleic acid; TNF, tumor necrosis factor; IL, interleukin; CCL2, CC-chemokine-2 ligand; PPAR, peroxisomal proliferator-activated receptor; AMPK, AMP-activated kinase; IFN, interferon; IL-1RA, IL- receptor antagonist; JNK, C-Jun N-terminal kinase; LDL, low-density lipoproteins; oxLDL, oxidized LDL; VCAM-1, vascular cell adhesion molecule 1; ICAM-1, intercellular adhesion molecule-1; DDAH, dimethylarginine dimethylaminohydrolase; ADMA, asymmetric dimethylarginine; BH4, tetrahydrobiopterin; eNOS, endothelial nitric oxide synthase; RAGE, receptor for advanced glycosylation end products; ROS, reactive oxygen species; NADPH, nicotinamide adenine dinucleotide phosphate reduced; TxNIP, thioredoxin-interacting protein; ASK, apoptosis signal-regulating kinase; NLRP3, Nod-like receptor family; pyrin domain containing 3; MnSOD, manganese-dependent superoxide dismutase.

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