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REVISIÓN

The pleiotropic role of HDL in autoimmune diseases

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KEYWORDS
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Abstract As is widely known, the classic function of HDL is reverse cholesterol transport (RCT), thus removing cholesterol from peripheral tissues. Early epidemiological studies, such as Framingham's, stated that increased HDL levels were associated with a significant decrease in relative risk for cardiovascular disease (CVD) mortality. However, those with heightened expectations in recent years for the development of therapeutic targets to increase HDL levels have been disappointed, because efforts have demonstrated the opposite effect on cardiovascular and global mortality.

However, in contrast, studies have highlighted the complexity and the intriguing role of HDL in different pathological conditions, such as infections, neoplasms, and autoimmune diseases.

In this review an attempt is made to summarize some biological pathways that link HDL function with the immune system, and its possible clinical repercussions in autoimmune diseases.

PALABRAS CLAVE
HDL;
Enfermedades autoinmunes;
Lupus eritematoso sistémico;

El papel pleiotrópico de las partículas HDL en las enfermedades autoinmunes

Resumen La función clásica de las partículas de colesterol HDL en el transporte reverso de colesterol está ampliamente establecida. Estudios epidemiológicos clásicos, tales como Framingham ya establecieron la relación inversa entre el incremento de los niveles de HDL y la mortalidad por riesgo cardiovascular.

Abbreviations: RCT, reverse cholesterol transport; CVD, cardiovascular disease; CAD, coronary artery disease; ApoA1, apolipoprotein A1; APR, acute phase response; PON1, paraoxonase-1; ABCA1, ATP-binding protein A1; ABCG1, ATP-binding protein A1; PAF-AH, platelet-activating factor acetyl hydrolase; LCAT, lecithin: cholesterol acyltransferase; GSPx, glutathione selenoperoxidase; SAA, serum amyloid A; HDL, high density lipoprotein; LDL, low density lipoprotein; PTX3, pentraxin 3; IL-1, interleukin 1; TNF, tumoral necrotic factor; IL-6, interleukin 6; APC, antigen presentation cells; CE, cholesterol ester; TLR, toll-like receptor; BLR, B lymphocyte receptor; DC, dendritic cells; LPS, lipopolysaccharides; MHC, major histocompatibility complex; S1P, sphingosine 1-phosphate; ApoM, apolipoprotein M; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; MS, multiple sclerosis; LPL, lipoprotein lipase; β2-GLP1, beta2-glycoprotein-1; Apo H, apolipoprotein H.

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Respuesta de fase aguda

Las grandes expectativas para el desarrollo de terapias que incrementen los niveles de colesterol HDL han creado grandes decepciones en estudios relativamente recientes. A pesar de todo, estos estudios han destacado la complejidad de las partículas HDL en diferentes condiciones patológicas como infecciones, neoplasias y enfermedades autoinmunes.

En esta revisión intentamos resumir algunos mecanismos biológicos que unen las HDL con las funciones dentro del sistema inmune y sus posibles repercusiones clínicas en las enfermedades autoinmunes.

Introduction

As is widely known, the classic function of HDL is reverse cholesterol transport (RCT), removing cholesterol from peripheral tissues. Early epidemiological studies, such as Framingham's, stated that increased HDL levels were associated with a significant decrease in relative risk for cardiovascular disease (CVD) mortality.[1] However, those with heightened expectations in recent years for the development of therapeutic targets to increase HDL levels have been disappointed because efforts have demonstrated the opposite effect on cardiovascular and global mortality.[2]

In contrast, however, studies have highlighted the complexity and the intriguing role of HDL in different pathologic conditions, such as infections, neoplasms and autoimmune diseases. These heterogenic functions of HDL have not been well understood, but what appears to be clear is that not only HDL-c levels but also lipoprotein particle composition appear to be important for the function of this complex lipoprotein.[3,4]

The predominant lipoprotein content in the plasma of several species is HDL. The main apolipoprotein associated with HDL is Apolipoprotein A1 (ApoA1), which is associated with cholesterol transport in cell surfaces via ABCA1 and ABCG1.[5] ApoA1's structure is conserved throughout its evolution, and recent studies have associated HDL function not only with the homeostasis of cholesterol metabolism but also with immune system regulation,[6] the acute phase response after infections; environmental stresses, such as severe burns; autoimmune diseases; and cancer.[7–11]

The proper knowledge of the role of HDL particles in pathologic conditions other than atherosclerosis has increased interest in the development of new therapeutic strategies for clinical conditions beyond cardiovascular diseases.[4,12] In this review, we attempt to summarize the possible clinical relevance of HDL's functioning in the immune system in relation to its possible clinical implications in autoimmune diseases (Fig. 1).

HDL and the acute phase response

The potential protective nature of HDL has been primarily attributed to its role in RCT. However, the mechanisms by which HDL may impact cardiovascular health and disease remain complex and not fully understood.[3,4] HDL possesses a number of heterogenic functions that impact cardiovascular

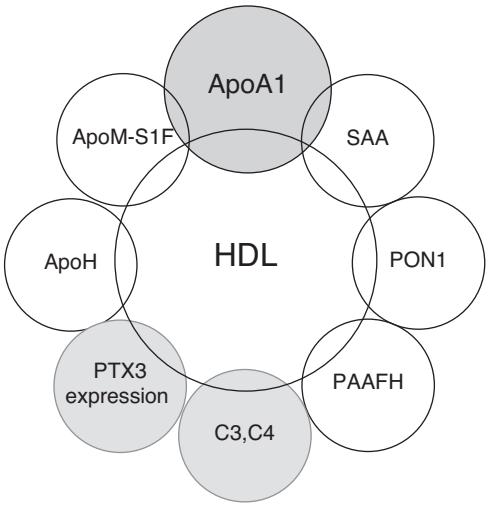

Figure 1 Main HDL-bounded proteins linked to immune system and acute phase response.

health. The heterogenic functions of HDL involve anti-inflammatory, antioxidant, antithrombotic, antiapoptotic and nitric oxide synthesis mechanisms. These different functions are related to the complex and heterogenic structure of HDL particles. This heterogeneity is the result of changes in the content of the apolipoproteins, lipids and proteins that are associated with HDL and are related not only to cholesterol metabolism but also to regulating the complement system and the acute phase response.[13–17]

The acute phase response (APR) is a systemic reaction to infectious and noninfectious tissue destruction. Multiple physiologic adaptations occur, including changes in the hepatic synthesis of a number of plasma proteins, termed acute-phase reactants.[18] Two acute-phase reactants, C-reactive protein (CRP) and serum amyloid A protein (SAA), are known to interact with lipoproteins.[19,20] CRP binds to apolipoprotein B, which is contained in atherogenic lipoproteins, whereas SAA circulates primarily with HDL.

Apolipoprotein A1(ApoA1) and enzymes associated with HDL with antioxidant properties such as paraoxonase-1 (PON1), platelet-activating factor acetylhydrolase (PAF-AH), lecithin: cholesterol acyltransferase (LCAT) and glutathione selenoperoxidase (GSPx) are replaced by SAA after the acute phase response.[21–28]

Under these pro-inflammatory conditions, the composition of HDL particles changes; they evolve into