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GENERAL INFORMATION

Low-grade systemic inflammation and the development of metabolic diseases: From the molecular evidence to the clinical practice☆

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Low-grade systemic inflammation;
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Arteriosclerosis;
Macrophages

Abstract
Background: Systemic inflammation is characterised by high circulating levels of inflammatory cytokines and increased macrophage infiltration in peripheral tissues. Most importantly, this inflammatory state does not involve damage or loss of function of the infiltrated tissue, which is a distinctive feature of the low-grade systemic inflammation. The term ''meta-inflammation'' has also been used to refer to the low-grade systemic inflammation due to its strong relationship with the development of cardio-metabolic diseases in obesity.
Objective: A review is presented on the recent clinical and experimental evidence concerning the role of adipose tissue inflammation as a key mediator of low-grade systemic inflammation. Furthermore, the main molecular mechanisms involved in the inflammatory polarisation of macrophages with the ability to infiltrate both the adipose tissue and the vascular endothelium via activation of toll-like receptors by metabolic damage-associated molecular patterns, such as advanced glycation-end products and oxidised lipoproteins, is discussed. Finally, a review is made of the pathogenic mechanisms through which the low-grade systemic inflammation contributes to develop insulin resistance, dyslipidaemia, atherogenesis, type 2 diabetes, and hypertension in obese individuals.

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Conclusions: A better understanding of the molecular mechanisms of low-grade systemic inflammation in promoting cardio-metabolic diseases is necessary, in order to further design novel anti-inflammatory therapies that take into consideration clinical data, as well as the circulating levels of cytokines, immune cells, and metabolic damage-associated molecular patterns in each patient.

PALABRAS CLAVE
Inflamación sistémica de grado bajo;
Tejido adiposo;
Enfermedades metabólicas;
Resistencia a la insulina;
Diabetes mellitus tipo 2;
Arterioesclerosis;
Macrófagos

Inflamación sistémica de grado bajo y su relación con el desarrollo de enfermedades metabólicas: de la evidencia molecular a la aplicación clínica

Resumen
Antecedentes: La inflamación sistémica se caracteriza por la elevación en los niveles circulantes de citocinas inflamatorias; así como aumento en la infiltración de macrófagos en tejidos periféricos. Este escenario inflamatorio no induce lesión o pérdida de la funcionalidad en el tejido infiltrado, rasgo distintivo de un estado de inflamación sistémica de grado bajo. La inflamación sistémica de grado bajo posee una estrecha relación con el desarrollo de enfermedades cardiometabólicas en el paciente con obesidad, por lo que este estado de alteración inmune también ha recibido el nombre de metainflamación.
Objetivo: En esta revisión presentamos la evidencia clínica y experimental más reciente en torno al papel de la inflamación del tejido adiposo como detonante de la metainflamación. Además, revisamos a nivel molecular los mecanismos de polarización inflamatoria de macrófagos invasores del tejido adiposo y el endotelio vascular a través de la activación de receptores tipo toll por patrones moleculares asociados a daño metabólico, tales como proteínas glucosiladas y lipoproteínas oxidadas. Por último, revisamos los mecanismos fisiopatogénicos de la inflamación sistémica en el desarrollo de resistencia a la insulina, dislipidemia, aterogénesis, diabetes mellitus tipo 2 e hipertensión en el paciente obeso.
Conclusiones: Un entendimiento más detallado de los mecanismos moleculares a través de los cuales la inflamación sistémica de grado bajo promueve el desarrollo de enfermedades cardiometabólicas podría ser útil en el diseño de terapias antiinflamatorias que tengan en cuenta datos clínicos, así como el nivel circulante de citocinas, células inmunes y patrones moleculares asociados a daño metabólico en el paciente.

Background

Recent experimental and clinical evidence suggests that metabolic syndrome and cardiovascular disease could be the consequence of a systemic inflammatory process.[1] Systemic inflammation has major differences to a classic inflammatory response (Table 1). Specifically, systemic inflammation is characterised by high circulating levels of acute-phase proteins and active inflammatory cytokines, including C-reactive proteins (pCr), tumour necrosis factor alfa (TNF-α) and interleukins (IL) 1β, 6 and 17, in addition to an increase in immune cell infiltration including that of macrophages and t lymphocytes in insulin-dependent tissue.[2,3] Furthermore, there is a consensus of opinion that systemic inflammation does not cause damage in immunologically infiltrated tissue; this distinctive trait has led to the term low-grade systemic inflammation.[3,4] In other words, during a state of low-grade systemic inflammation tissues express high levels of inflammatory factors and immune cell infiltration whilst simultaneously not expressing any structural changes or loss of primary functions. By contrast, due to its close relationship with the development of cardio-metabolic diseases in obese patients, low-grade systemic inflammation has recently been referred to as meta-inflammation or metabolic inflammation.[5]

However, despite the fact that the relationship between low-grade systemic inflammation and cardio-metabolic diseases has considerably increased during the last decade, many elements are yet to be researched and discussed in this regard. For example, which cellular mechanisms drive the start and perpetuation of meta-inflammation? Which molecular events are involved in the clinical outset of systemic inflammation? Is there any existing evidence to suggest that low-grade systemic inflammation is the backdrop to pathologies such as insulin resistance, dyslipidaemia, high blood pressure and diabetes mellitus type 2?

Our approach in this review is to tackle each of the before-mentioned points, exposing the most recent