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REVIEW ARTICLE

Nanotechnology, a new paradigm in atherosclerosis treatment☆

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Abstract Atherosclerosis, a known and prevalent disease, causes progressive deterioration of affected vessels, inducing a blood flow reduction with different complications, and its symptoms usually manifest in advanced stages of the disease. Therefore, the traditional therapeutic alternatives are insufficient because the damage they cause is often irreversible. For this reason, there is a need to implement intelligent forms of drug administration and develop new therapeutic targets that reduce the progression of the atherosclerotic lesion. The implementation of new tools for the prevention, diagnosis and treatment of this cardiovascular disease is of special interest, focusing on achieving a more effective control of the immune system. This review highlights the latest knowledge about nanotechnology as a powerful, modern and promising therapeutic alternative applied to atherosclerotic disease, as well as warning of the potential complications associated with its use.

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Nanotecnología, un nuevo paradigma en el tratamiento de la aterosclerosis

Resumen La aterosclerosis, una conocida enfermedad arterial prevalente, ocasiona el deterioro progresivo de los vasos afectados provocando reducción del flujo sanguíneo con diversas complicaciones, y los síntomas suelen manifestarse en estadios avanzados de la enfermedad. En este sentido, las clásicas alternativas terapéuticas resultan insuficientes debido al carácter muchas veces irreversible del daño provocado. Por lo tanto, emerge la necesidad de implementar novedosas formas más eficaces para administrar fármacos y también el desarrollo de nuevas dianas terapéuticas que reduzcan la progresión de la lesión aterosclerótica. Además, resulta de especial interés la implementación de nuevas herramientas para la prevención, diagnóstico y tratamiento de esta patología cardiovascular, focalizando la atención en lograr un mejor control sobre el sistema inmunológico. En esta revisión se pone en relieve el conocimiento actual sobre la nanotecnología como una alternativa terapéutica potencial, moderna y prometedora, aplicada a la patología aterosclerótica, pero se advierte también sobre posibles complicaciones de su uso.

Introduction

The prevalence of atherosclerosis has steadily increased worldwide due to population ageing. Economic development and urbanisation have led to habits of diets rich in saturated fats and scant physical exercise, both of which promote and aggravate atherosclerosis.[1] However, the development of atherosclerosis is not limited to patients with a western lifestyle characterised by the aforementioned factors. Recent studies have identified novel non-traditional risk factors for atherosclerosis that are all associated with activation of the immune system. These findings are consistent with studies showing inflammation as an essential element in the onset, progression and destabilisation of atherosclerotic plaques. This chronic disease is one of the main causes of serious cardiovascular events, such as myocardial infarction and stroke (responsible for 17 million deaths/year).[2,3] Recent research has shown how alterations in the inflammatory pathway can be associated with atherosclerosis.[4–9]

Atherosclerotic disease is characterised by arterial wall thickening and rigidity, deregulation of lipid metabolism, and the formation of the characteristic plaque. In this situation, restricted blood flow and the eventual rupture of the plaque itself can be life-threatening.[10] Plaque formation is a complex biological process that includes endothelial dysfunction, macrophage infiltration, inflammatory factor expression, intraplaque neovascularisation and intima-media thickness remodelling, among other phenomena.[11]

Atherosclerotic plaque is rich in macrophages, which, together with monocytes, participate in the initiation, progression and destabilisation of atherosclerotic plaques by activating various mechanisms.[2] M_1 and M_2 macrophages in particular play a crucial role in progressive atherosclerotic disease.[12] In the early stages of atherosclerosis, macrophages contribute to the clearance of reactive oxidised low-density lipoprotein (oxLDL) particles through scavenger receptor A (SR-A) and CD36-mediated uptake. In later stages, the phagocytic activity of macrophages becomes impaired due to intracellular accumulation of oxLDL. Foam cell macrophages undergo apoptosis due to oxidative stress and inflammatory responses, a process which ultimately contributes to the formation of the pro-thrombotic necrotic core that characterises mature atherosclerotic plaques.[2] Some studies have shown that vascular smooth muscle cells within atherosclerotic lesions can switch to a macrophage-like phenotype characterised by higher expression of inflammatory markers that may further contribute to disease progression.[13] Furthermore, altered molecular patterns accumulated in atherosclerotic plaques are a dangerous source of factors that can activate macrophages by binding to specific receptors such as Toll-like receptors (TLRs), scavenger receptors (SRs) and intracellular nucleotide-binding oligomerisation domain (NOD)-like receptors (NLRs). Macrophages, therefore, play a pivotal role and modulate the expression of multiple cellular mediators that can create a proinflammatory environment in the plaque (Fig. 1). In addition, lesional macrophages contribute to the remodelling of atherosclerotic plaques into a rupture-prone unstable phenotype by the production of proteases. The presence and proliferation of autoimmune B cells has also been observed within the diseased

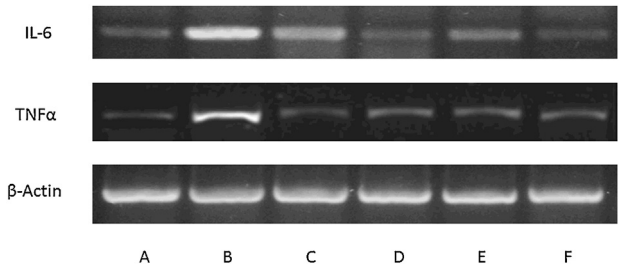

Figure 1 Expression of inflammatory mediators in culture of mouse glial macrophages. Blots showing expression in control macrophages (A), macrophages affected by lipopolysaccharides (BF) and incubated with: allicin (C), phenyl isothiocyanate (D), erucine (E) and indole-3-carbinol (F). The lipopolysaccharide-induced pro-inflammatory response and phytochemical modulation of this response are clearly seen (n = 3).