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Review

Mechanisms of atherosclerosis and cardiovascular disease in antiphospholipid syndrome and systemic lupus erythematosus. New therapeutic approaches☆

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ABSTRACT

Systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) are 2 highly related autoimmune-rheumatic diseases associated with an increased risk of developing cardiovascular (CV) diseases. Despite the great progresses made in understanding the pathological mechanisms leading to CV diseases in those pathologies, there is still the unmet need to improve long term prognosis. CV diseases in SLE and APS is thought to happen as the result of a complex interaction between traditional CV risk factors, immune deregulation and disease activity, including the synergic effect of cytokines, chemokines, adipokines, proteases, autoantibodies, adhesion receptors, oxidative stress and a plethora of intracellular signalling molecules. Genomic and epigenomic analyses have further allowed the identification of specific signatures explaining the proathero-thrombotic profiles of APS and SLE patients. This review examines the complex role of these heterogeneous factors, and analyses new therapeutic approaches under study to reduce the CV risk in these autoimmune disorders.

Mecanismos de aterosclerosis y enfermedad cardiovascular en el síndrome antifosfolípido y el lupus eritematoso sistémico. Alternativas terapéuticas

Palabras clave:
Lupus eritematoso sistémico
Síndrome antifosfolípido
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RESUMEN

La aterotrombosis en el síndrome antifosfolípido primario (SAF) y el lupus eritematoso sistémico (LES) constituye una enfermedad de carácter sistémico, en cuyo desarrollo interviene una compleja red de mediadores inmunológicos, procoagulantes, componentes inflamatorios y el estrés oxidativo, todos ellos conducentes a la activación del complemento, el daño endotelial y la activación leucocitaria. Estudios genómicos y epigenéticos han contribuido asimismo a identificar nuevos biomarcadores que, junto a factores de riesgo tradicionales, han permitido delinear nuevos mecanismos patogénicos implicados en el desarrollo de trombosis y enfermedad cardiovascular (CV) en estos pacientes. Actualmente se están estudiando nuevas herramientas terapéuticas para la prevención de la enfermedad CV, tales como las estatinas, los inhibidores del interferón α o la coenzima Q10, entre otros. Los nuevos anticoagulantes orales pueden suponer también avances importantes en el tratamiento de estos pacientes. El presente estudio examina aspectos moleculares y terapéuticos asociados al diagnóstico y el seguimiento de la enfermedad CV en SAF y LES.

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Introduction

Atherothrombotic vascular disease represents a global public health problem of increasing importance. Despite the advances that have been made in the treatment of the clinical manifestations of this disease (myocardial infarction, cerebrovascular accidents, aortic aneurysm, peripheral vasculopathy, etc.), relapses are frequent and morbidity and mortality continue to be high. An important aspect of the prevention and treatment of atherothrombosis is the early-stage identification of subjects with increased cardiovascular risk, susceptible to develop thrombotic episodes.

The new concepts related to the pathogenesis of atherothrombosis (AT), where the inflammation generated by an immunological mechanism is considered a determining factor, have suggested that an autoimmune process could be involved in its development and perpetuation.[1] The most studied autoimmune diseases related to AT are those with a higher incidence, such as systemic lupus erythematosus (SLE) and primary antiphospholipid syndrome (APS). The development of cardiovascular (CV) disease in these disorders involves genetic factors as well as other acquired risk factors (e.g. hypercholesterolemia, diabetes mellitus and hypertension). The prothrombotic and inflammatory components of the immune response (mainly tissue factor and various cytokines), oxidative stress, as well as autoimmune elements (e.g. autoantibodies, autoantigens and autoreactive lymphocytes) also appear to be involved in these processes.[2]

Cardiovascular disease in autoimmune diseases: autoantibodies as atherothrombotic risk factors

In autoimmune diseases like APS and SLE, acute coronary events occur without prior traditional risk factors which could justify them. The analysis of the mechanisms that lead to the development of premature and/or accelerated atherothrombosis in these diseases allows to establish similarities between atherogenesis and the chronic inflammatory processes that characterize these diseases: increase in the expression of adhesion molecules in the endothelium, increase proinflammatory cell recruitment and activation of macrophages, increased cytokine expression, growth factors and other inflammatory factors that interrelate the different cell types. Thus, the presence of an autoimmune disease constitutes a major atherogenic risk factor, since it increases the probability of a thrombotic episode in a greater degree and in a shorter time than the traditional risk factors.

Recent cellular and molecular studies have shown that proinflammatory and prothrombotic mechanisms are intimately associated within the atherosclerotic plaque. Numerous theories have been proposed in systemic autoimmune diseases to explain these mechanisms, although the pathogenesis appears to be multifactorial.

Monocytic activation induced by antiphospholipid antibodies (APA), present in APS patients and in a high percentage of those with SLE, is caused by a complex interaction between numerous intracellular effectors, which are largely responsible for the development of thrombosis (Fig. 1). Some years ago, our group described that an essential process is the induction of procoagulant activity, through the activation of the tissue factor (TF), the main trigger of blood clotting.[3] Intracellular signalling associated with such activation is mediated by protease-activated receptors (PAR, mediators of critical responses for thrombosis, haemostasis and inflammatory processes and participants in the development of atherosclerosis), whose expression is increased in the monocytes of APS patients.[4] Complementary studies have shown that such intracellular signalling, induced by APA, involves the constitutive activation of mitogen-activated protein kinases (MAPK)

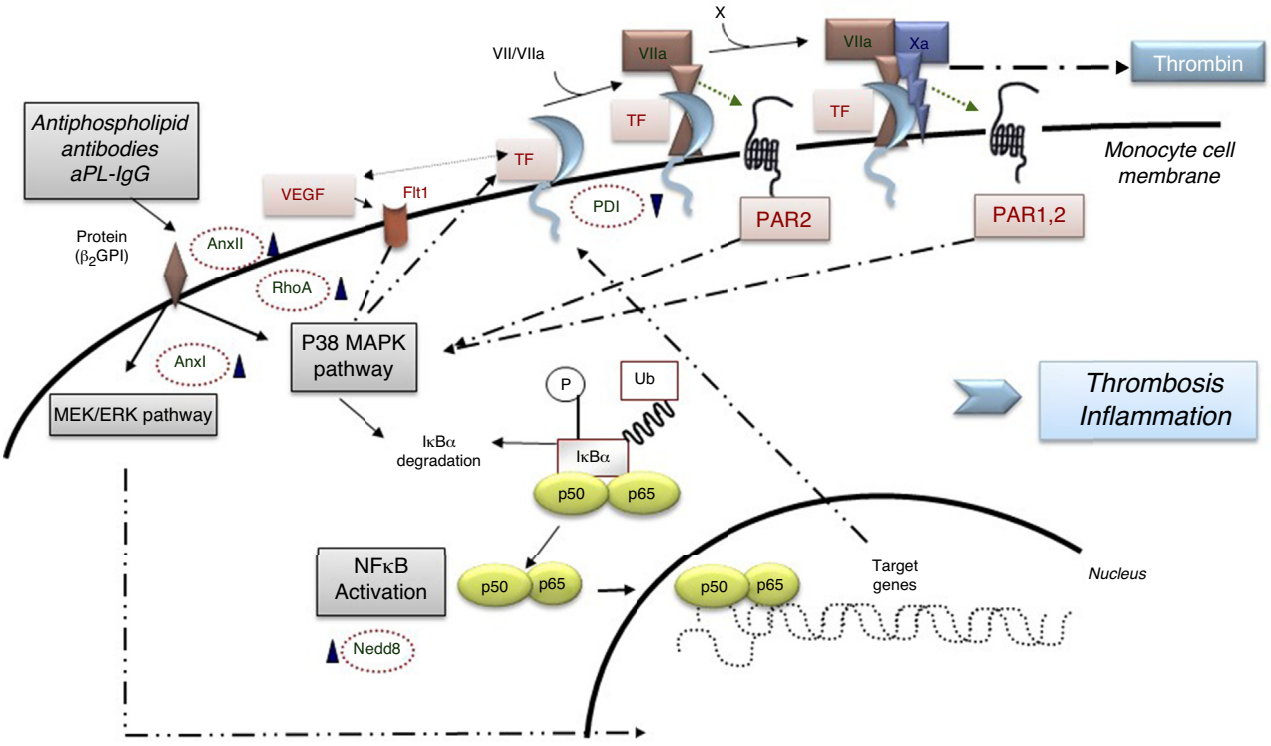

Fig. 1. Prothrombotic/proinflammatory mechanisms in antiphospholipid syndrome. AnxI: annexin I; AnxII: annexin II;APL: *antiphospholipid antibodies*; Flt1: *Fms-related tyrosine kinase 1* ("VEGF receptor 1"); MAPK: *mitogen-activated protein kinases*; NFκB: *Nuclear factor kappa-light-chain-enhancer of activated B cells*; PAR: *protease activated receptors*; PDI: protein disulphide isomerase; TF: *tissue factor*; VEGF: *Vascular endothelial growth factor*.