

EDITORIAL

How Does Interferon- α Insult the Vasculature? Let Me Count the Ways

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Systemic lupus erythematosus (SLE) is associated with a very significant increase in atherosclerotic cardiovascular (CV) complications (1) that are not explained by traditional risk factors (2). Although corticosteroids and cytotoxic agents can be used to effectively manage and control various lupus-related complications, to date, no drug has been proven to prevent the development of premature atherosclerosis in SLE. As such, establishing the key drivers of vascular insult and atherosclerosis progression in lupus is a priority, in order to identify therapeutic targets that could play an important role in the prevention of CV damage in SLE.

Although the etiology of premature vascular damage in lupus remains unclear and is likely multifactorial, recent evidence indicates that type I interferons (IFNs) could play a prominent role in endothelial cell damage and, by extension, could contribute to the development of atherosclerosis in SLE (3,4). Accumulating evidence from multiple research groups supports the concept that broad activation of the type I IFN pathway in lupus is associated with clinical manifestations and disease activity and suggests that this pathway plays an important role in disease pathogenesis (5,6). More recently, a link between type I IFNs, vascular damage, and progression of atherosclerosis in SLE has emerged.

In patients with SLE, a profound imbalance between endothelial cell damage and repair develops. This imbalance is characterized by accelerated endothelial cell apoptosis (7) and aberrant phenotypes and

functions of cells that are critical to vasculogenesis: bone marrow–derived endothelial progenitor cells (EPCs) and myeloid circulating angiogenic cells (CACs) (3,8,9). The alteration in EPC/CAC phenotype and function in patients with SLE and some animal models of lupus is profound (3,10) and comparable to that observed in patients with diabetes mellitus, the prototypic condition characterized by aberrant vasculogenesis. The notion that type I IFNs play a prominent role in the induction of decreased vascular repair is supported by the observations that abrogation of type I IFN signaling in lupus EPCs/CACs leads to restoration of a normal phenotype, and that EPCs/CACs isolated from healthy controls and exposed to IFN α develop the phenotypic and functional characteristics of lupus cells (3). Furthermore, high levels of type I IFN are associated with impaired endothelial function in patients with SLE (8).

The basis for decreased vascular repair and the antiangiogenic signature in EPCs and CACs induced by IFN α appears to be repression of interleukin-1 (IL-1) pathways, up-regulation of the IL-1 receptor antagonist (IL-1Ra), and down-regulation of the proangiogenic molecule vascular endothelial growth factor (VEGF) (4). Such an antiangiogenic pathway is present *in vivo* in patients with SLE who demonstrate vascular rarefaction, repression of VEGF, and increases in IL-1Ra in renal blood vessels and serum (4). Although it is possible that decreased IL-1 and increased IL-1Ra represent a phenotype that protects the vasculature, a cytokine profile that enhances antiangiogenic responses might also be considered to be vasculopathic and accelerate atherosclerosis in SLE. Indeed, vascular insults in SLE, in conjunction with increased levels of type I IFNs, may lead to periods of endothelial damage, followed by aberrant repair due to decreased levels of IL-1 and VEGF-A and increased levels of IL-1Ra. Such cyclic injury and failed repair would allow initiation and expansion of vascular lesions during these flares (4).

Recent evidence indicates that IFN α may additionally contribute to the development of acute vascular events through an effect on platelet function (11). Gene

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array expression studies of platelets from patients with lupus revealed increased expression of type I IFN-regulated genes, confirmed at the protein level, which is paired to increased platelet activation. Indeed, platelets from SLE patients with a history of vascular disease have increased levels of type I IFN-regulated proteins and increased activation when compared to those from SLE patients without a history of vascular disease (11). Conversely, platelets from patients with lupus that are activated by circulating immune complexes form aggregates with antigen-presenting cells, such as monocytes and plasmacytoid dendritic cells (pDCs), leading to enhancement of IFN α secretion through CD154-CD40 interactions (12). A feed-forward loop then develops, wherein type I IFNs induce platelet activation, which triggers platelets to synthesize IFN α and potentially leads to an increased risk of thrombosis.

Although the IFN α link with abnormal vascular repair and an enhanced potential for vascular injury has been firmly established, the transformation of recruited monocytes into lipid-laden macrophages, or foam cells, which are central to the development of atherosclerotic lesions (13), was not known to be related to IFN α . The scavenger receptors (SRs) SR class A (SR-A) and CD36 have been implicated in foam cell formation and in the regulation of inflammatory signaling pathways leading to lesional macrophage apoptosis and plaque necrosis (14).

In this issue of *Arthritis & Rheumatism*, Li et al provide key evidence that IFN α plays a direct role in the development of accelerated atherosclerosis in SLE (15). They report that IFN α priming increased the uptake of oxidized low-density lipoprotein (ox-LDL) by macrophages, thereby enhancing foam cell formation. Enhanced ox-LDL uptake by IFN was induced by the selective up-regulation of SR-A through an effect on its promoter activity, which required the phosphatidylinositol 3-kinase/Akt pathway. Li and colleagues provide evidence that this phenomenon is operational *in vivo* in patients, because SR-A messenger RNA expression was increased in peripheral blood mononuclear cells from patients with SLE compared to those from healthy control subjects and was positively correlated with the levels of type I IFN-inducible genes. Importantly, the levels of SR-A in mononuclear cells have been linked to acute coronary events in other patient populations (16).

It is important to note that the diverse deleterious effects of type I IFNs on the vasculature may not apply to lupus only. Indeed, recent evidence indicates a role for type I IFNs in the pathogenesis of other autoimmune conditions, including Sjögren's syndrome,

psoriasis, inflammatory myopathies, and progressive systemic sclerosis. Because vascular damage is also accelerated in these diseases, it would be important to assess the prevalence and correlates of atherosclerosis in these disease populations and the contribution of type I IFNs to this complication.

Furthermore, studies in the atherosclerotic arteries of individuals without systemic autoimmune diseases demonstrated that plaque-residing pDCs produce excess IFN α that sensitizes antigen-presenting cells toward pathogen-derived Toll-like receptor 4 ligands. Thus, local production of IFN α leads to enhanced synthesis of the proinflammatory cytokines and matrix metalloproteinases implicated in atherosclerotic plaque destabilization. IFN α expressed within the plaque stimulates cytotoxic T cells in blood vessels, augmenting vascular damage. These studies indicate that pathogens or nucleosome-containing immune complexes that induce synthesis of IFN α may threaten the stability of inflamed atherosclerotic plaques (17,18).

Identifying a newly described role for type I IFNs as enhancers of foam cell formation expands the pleiotropic effects of this cytokine on the vasculature from early endothelial cell damage and dysregulated repair of the damaged vasculature, to the development of atherosclerotic plaque, its destabilization, and the development of acute coronary syndromes through thrombosis enhancement.

With expanded understanding of the IFN pathway in SLE, identification of associations between type I IFNs, endothelial dysfunction and atherosclerosis in lupus, and the development of new biologic agents that block IFN α that are currently in preclinical and clinical trials (19,20), we are poised to perform studies to address the causality of IFN α and development of atherosclerosis in SLE. Given compelling evidence that IFN α is an appropriate target to modulate the CV risk in SLE, it is the responsibility of investigators and industry partners who design lupus trials with inhibitors of IFN α to include biomarkers of vascular damage and functional studies of vascular health as end points in their efficacy analyses. This should be the case not only in SLE but also in other autoimmune diseases in which anti-IFN α therapies are currently being tested. It is hoped that use of these drugs may translate into improved patient care in SLE, not only through abrogation of disease activity but also through decreased end-organ damage and fatal vascular complications that afflict so many patients with SLE.

AUTHOR CONTRIBUTIONS

Drs. Kaplan and Salmon drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

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