

## Review Article

# Activation of Type I Interferon Pathway in Systemic Lupus Erythematosus: Association with Distinct Clinical Phenotypes

Theophanis P. Karageorgas,<sup>1,2</sup> Dimitrios D. Tseronis,<sup>1</sup> and Clio P. Mavragani<sup>2</sup>

<sup>1</sup> Department of Rheumatology, General Hospital of Athens "G. Gennimatas", Mesogion St 154, 11527 Athens, Greece

<sup>2</sup> Department of Experimental Physiology, School of Medicine, University of Athens, M. Asias 75, 11527 Athens, Greece

Correspondence should be addressed to Clio P. Mavragani, kmauragan@med.uoa.gr

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Growing evidence over the last few years suggests a central role of type I IFN pathway in the pathogenesis of systemic autoimmune disorders. Data from clinical and genetic studies in patients with systemic lupus erythematosus (SLE) and lupus-prone mouse models, indicates that the type I interferon system may play a pivotal role in the pathogenesis of several lupus and associated clinical features, such as nephritis, neuropsychiatric and cutaneous lupus, premature atherosclerosis as well as lupus-specific autoantibodies particularly against ribonucleoproteins. In the current paper, our aim is to summarize the latest findings supporting the association of type I IFN pathway with specific clinical manifestations in the setting of SLE providing insights on the potential use of type I IFN as a therapeutic target.

## 1. Introduction

Systemic lupus erythematosus (SLE) is the prototype of systemic autoimmune disorders, affecting virtually any organ system of mainly young women of child-bearing age, at an incidence ranging from 2 to 5 cases per 100,000 persons. It is characterized by remarkable heterogeneity in regard to the spectrum and severity of clinical and laboratory manifestations, with disease activity fluctuating considerably during the course of the disease. While genetic susceptibility along with environmental interactions contributes significantly to the immune dysregulation that characterizes SLE, the exact etiopathogenesis remains elusive [1].

In the late 1970s, increased serum levels of interferon (IFN) were shown for the first time to be significantly associated with SLE and to correlate with disease activity [2]. Later reports showing that chronic treatment with recombinant IFN $\alpha$  in patients affected with malignancies induces autoimmune manifestations [3] coupled by subsequent studies documenting heightened serum levels of type I IFN and type I IFN-inducible genes [4] in patients with SLE reinforced the hypothesis that type I IFN has a major role

in the pathogenesis of SLE. Although the exact triggers of type I IFN activation in SLE are unknown, exogenous viral agents or endogenous nucleic acids seem to be potential candidates through sensing of pattern recognition membrane and cytosolic receptors of specialized IFN $\alpha$ -producing cells such as plasmacytoid dendritic cells (pDCs), while genetic contributors in generation of type I IFN in SLE have been also implicated [5]. Of note, recent data have shown that mature neutrophils from lupus patients undergo apoptosis upon exposure to SLE-derived anti-ribonucleoprotein antibodies releasing neutrophil extracellular traps (NETs) that contain DNA and neutrophil-derived proteins. The SLE NETs efficiently activate the pDCs to produce type I IFNs, thus, acting as an endogenous stimulus for the type I IFN pathway [6, 7].

In the current paper, our aim is to summarize the latest findings previously shown to support the association of type I IFN pathway with specific clinical manifestations of SLE particularly those characterized by renal, skin, neurological involvement, as well as concomitant atherosclerosis providing insights on the potential use of type I IFN as a biomarker and/or therapeutic target in these patients. To the best of our

knowledge, no data to date support the association of type I IFN activation with other lupus-related manifestations such as serositis or arthritis.

## 2. Type I IFN and Lupus Nephritis

Lupus nephritis and the progression to end-stage renal disease represent one of the major causes of morbidity and mortality in SLE patients. Almost half of the patients with SLE present with clinical lupus nephritis, and up to 90% of patients have some degree of histological renal damage. Different interacting pathogenetic mechanisms such as immune complex deposition, renal infiltration by T cells, macrophages, and dendritic cells, activation of toll-like receptors (TLRs), and a variety of cytokines as well as end-organ responses to immune injury contribute to the pathogenesis of lupus nephritis [15].

Despite data deriving both from murine lupus models and patients with SLE supporting a pathogenetic role for type II IFN (IFN $\gamma$ ), there is ever increasing evidence indicating type I IFNs as one of the major players in the pathogenesis of lupus nephritis. In 1979, Hooks et al. noticed for the first time a significant association of type I IFN serum levels with active lupus [2]. Two years later, Rich reported that typical lupus inclusions (detected in the glomerular endothelium in almost all lupus patients and in the peripheral blood lymphocytes of more than two-thirds) were induced by type I IFN in the Raji cells, a human B-lymphoblastoid cell line of Burkitts lymphoma origin [16]. Since then, several studies in patients with SLE have demonstrated a significant association between both type I IFN serum levels and IFN-induced gene expression in peripheral blood mononuclear cells (PBMCs)—the so-called interferon signature—[2, 8–14] with disease activity and other disease-related features including lupus nephritis (Table 1). It should be noted that the largest so far study performed by Weckerle et al., which included 1089 patients from 3 different ancestral backgrounds, showed a strong association between certain autoantibodies and high IFN $\alpha$  activity but failed to detect significant association with clinical features of the disease. However, disease activity was not assessed in this study. In addition to the aforementioned studies associating type I IFN and clinical and serological features of SLE, cDNA microarray analysis of gene expression in glomeruli, isolated by laser-capture microscopy from kidney biopsies of lupus patients with focal/diffuse proliferative glomerulonephritis, revealed increased expression of type I IFN-inducible genes, thus, implying a possible pathogenetic role for type I IFN in these patients [17]. Glomerular expression of TLR-9, an endosomal sensor of CpG DNA leading to type I IFN production, was reported in patients with lupus nephritis but not in healthy controls and was associated with anti-dsDNA and higher activity index of lupus nephritis [18].

Moreover, recent genetic association studies have identified many lupus-associated genetic variants in genes encoding transcription factors and various molecular components involved in the type I IFN pathway [19–37]. Studies investigating a possible association between genotype and

phenotype in lupus patients have brought to light conflicting results regarding the association with lupus nephritis. A case-control study by Taylor et al. in a large cohort of North American patients of European descent showed a significant association between the single nucleotide polymorphism (SNP) rs7574865 of the STAT4 gene and lupus nephritis, anti-dsDNA and early disease onset [38]. Accordingly, SNPs of the STAT4 gene was associated with lupus nephritis and anti-dsDNA in a cohort of 695 Swedish patients [24]. Similar results, although not statistically significant probably due to small sample size, were reported in a Japanese study for the SNP rs7574865 of STAT4 gene [39]. In contrast, the same SNP of STAT4 was not associated with any specific clinical manifestation of lupus in a Northern Han Chinese case-control study. This may be attributed to differences in immune pathways influenced by this polymorphism among different populations. An alternative explanation could derive from the fact that rs7574865 with nearby SNPs can form different haplotype blocks each one conferring a distinct risk for SLE and for specific SLE manifestations. Therefore, the diverse effect of this risk SNP in SLE subphenotypes could be explained by the presence of distinct risk haplotypes among different ethnic groups. In the same study, 2 more SNPs, rs4963128 and rs2246614 of the interferon-regulatory factor 7 (*IRF7*) gene, were tested for association with SLE. In contrast to what was observed in a European women cohort [20], no association with increased susceptibility for SLE in northern Han Chinese was reported. However, these 2 SNPs were associated with different subphenotypes of SLE. In particular, the rs4963128 was associated with the production of anti-SSA/B antibodies and lupus nephritis. The authors suggest that particular variants of the *IRF7/KIAA1542* region may induce the generation of certain autoantibodies [32]. A recent small study of 190 Chinese patients with lupus nephritis reported a significant association of the rs2004640 polymorphism of the interferon-regulatory factor 5 (*IRF5*) gene with lupus nephritis but showed no association with any specific histological or clinical manifestation of lupus kidney disease [40]. However, a Swedish study, consisting of 272 SLE patients, investigating several SNPs related to *IRF5* (including the rs2004640 polymorphism tested in the aforementioned Chinese study), as well as risk SNPs of STAT4 and TNF receptor-associated factor-1 complement component-5 (*TRAF1-C5*) demonstrated no association with lupus nephritis [41]. However, it should be noted that this was a study primarily investigating a possible overlap in genetic susceptibility between IgA nephropathy and lupus nephritis. Moreover, the small sample size of this study does not offer sufficiently powered results to contradict the positive association between risk alleles in *STAT4* gene and lupus nephritis demonstrated in other studies. Taken together, the data provided by genetic studies further support the association of the type I IFN pathway with SLE susceptibility and possibly with lupus nephritis at least in some ethnic groups (Table 2).

This association between type I IFN and lupus nephritis in humans, which per se does not define a direct cause-effect relationship, has been put to test in many experimental murine lupus models in order to clarify the pathogenetic role

TABLE 1: Studies in patients with SLE showing statistical significant associations ( $P < 0.05$ ) between peripheral type I IFN activity and clinical and serological features.

Author	No. of patients	Type I IFN levels	Type I IFN-inducible genes	Clinical associations	Serological associations
Hooks et al. [2]	28	High	NM	Disease activity	Anti-dsDNA Low C3
Kanayama et al. [8]	25	High	NM	Fever	NM
Bengtsson et al. [9]	30	High	NM	Disease activity Fever Skin	Anti-dsDNA Low C1q Low C3 Leucopenia
Baechler et al. [10]	48	NM	High	Renal and/or NPSLE Hematologic	NM
Dall'era et al. [11]	65	High	NM	Disease activity Skin	Anti-dsDNA Low C3
Kirou et al. [12]	77	NM	High	Renal	Anti-dsDNA Anti-Ro Anti-U1 RNP Anti-Sm Low C3 Low C4
Feng et al. [13]	48	NM	High	Renal NPSLE (weak association)	Anti-dsDNA Anti-Sm Anti-Ro/La Low C3
Weckerle et al. [14]	1089	High	NM	NS	Anti-dsDNA Anti-Ro

NM: not measured, NS: not statistically significant. All abbreviations are explained in the text.

of type I IFN in lupus renal disease. Studies in autoimmune prone mice that were treated with polyinosinic : polycytidylic acid (poly I : C), a synthetic double-stranded RNA ligand for TLR-3 that strongly induces type I IFN response, showed higher titers of anti-dsDNA antibodies, increased immune complex deposition, accumulation of activated lymphocytes and macrophages, and increased metalloproteinase activity that led to accelerated lupus nephritis and death [43–45]. Similar results supporting the pathogenetic effect of type I IFN in lupus glomerulonephritis were obtained from murine models injected with adenovirus expressing IFN $\alpha$  that leads to sustained release of that cytokine [45–49]. Moreover, recent studies in healthy (not lupus-prone) mice treated with 2,6,10,14-tetramethylpentadecane (pristane), an inducer of type I IFN through TLR-7 signaling, resulted in lupus-like nephritis, possibly through recruitment of inflammatory cells by type I IFN-inducible chemokines. Interestingly, different strains of mice under the effect of pristane develop histological lesions of diverse severity probably due to yet unknown genetic factors [50]. These data demonstrate that increased levels of type I IFN are able to induce lupus nephritis both in lupus-prone and healthy mice.

Additional evidence supporting the pivotal role of type I IFN in lupus glomerulonephritis derives from studies in New Zealand Black (NZB), New Zealand, mixed 2328 as well as pristane-treated mice deficient of the receptor of type I IFN (IFNAR $^{-/-}$ ). The defective signaling through

IFNAR in IFNAR $^{-/-}$  mice conferred protection from kidney disease and was associated with a decrease in the titers of lupus-specific autoantibodies and disease severity. In these models, a decrease in the proliferation and activation of dendritic cells as well as B and T cells was documented [51–53]. However, one study conducted in congenic MRL/lpr mice, a lupus-prone model that develops severe crescentic glomerulonephritis, reported that IFNAR deficiency caused a significant deterioration of renal disease. In contrast, deficiency of the type II IFN (IFN $\gamma$ ) receptor had beneficial effects on kidney disease, thus, suggesting a protective role for type I IFN pathway at least in this mouse model [54].

The role of TLRs and especially of TLR-7, responsive to ssRNA, and TLR-9, responsive to hypomethylated CpG-rich DNA, in type I IFN production in lupus is well established. Studies in mice that overexpress TLR-7 (Y-linked autoimmune accelerating locus mice—Yaa mice) or that were treated with pristane demonstrate the importance of type I IFN and TLR-7 signaling in accelerating and aggravating kidney injury [55–57]. Interestingly a study by Thibault et al. using the pristane-induced mouse model of SLE showed that upregulation of TLR-7 receptors in B cells and effective activation through TLR-7 and TLR-9 of B cells to produce lupus-specific autoantibodies require an intact type I IFN signaling pathway, thus, suggesting that type I IFN is upstream of TLR signaling in the activation of autoreactive B cells in SLE [58]. Moreover, activation

TABLE 2: Genetic studies investigating the association between several SNPs and both lupus nephritis and specific auto-antibodies in different ethnic populations.

Author	No. of SLE patients	No. of healthy controls	Ethnic origin	Gene/SNP studied	Associations	
					Nephritis	Autoantibodies
Taylor et al. [38]	1396	2560	North Americans (European descent)	<b>STAT4/</b> rs7574865	$P < 10^{-11}$ *	Anti-dsDNA/ $P < 10^{-19}$
Kawasaki et al. [39]	308	306	Japanese	<b>STAT4/</b> rs7574865	$P = 1.0 \times 10^{-5}$ **	Anti-dsDNA/ $P = 4.9 \times 10^{-5}$ **
Qin et al. [40]	190	182	Chinese	<b>IRF5/</b> rs2004640T	$P = 0.002$ ***	NS
Vuong et al. [41]	272	307	Swedish	<b>-STAT4/</b> rs10181656	-NS	-NM
				<b>-IRF5/</b> rs729302 rs4728142 rs2004640 rs3807306	-NS	-NM
				rs10954213 rs11770589 rs2280714		
				<b>-TRAF1-C5/</b> rs3761847	-NS	-NM
				<b>-TGFB1 /</b> rs6957 rs2241715 rs1982073 rs1800469	-NS	-NM
Li et al. [32]	748	750	Chinese (Northern Han)	<b>-STAT4 /</b> rs7574865 <b>- IRF7/</b> <b>KIAA1542</b> rs2246614†	$-P = 3.78 \times 10^{-8}$ -NS	-Anti-SSB/ $P = 9.63 \times 10^{-6}$ -NS
Luan et al. [42]	675	678	Chinese	<b>STAT4/</b> rs7582694	-NS	-NS
Sigurdsson et al. [24]	695	—	Swedish	<b>STAT4/</b> rs7582694	0.04	Anti-dsDNA/ $P = 5.3 \times 10^{-7}$

\* Severe nephritis (ESRD or severe progressing renal disease in renal biopsy),  $P < 10^{-4}$ . \*\* Statistical significance found only in the case-control arm of the study, whereas, in the case-only arm of the study, results both for nephritis and anti-dsDNA reached no statistical significance.

\*\*\* While a statistically significant association with lupus nephritis was detected, no association was found with any specific clinical finding or histological type of nephritis.

† These 2 SNPs of the *IRF7/KIAA1542* gene were not associated with SLE but only with specific SLE subphenotypes such as nephritis and anti-SSB.

NS: not statistically significant association. NM: not measured.

The rest of the abbreviations used are explained in the text.

of TLR-9 signaling pathway through CpG-rich DNA was shown to induce severe lupus nephritis in lupus-prone mice [59]. Additional confirmation was obtained from a study that tested a dual inhibitor of TLR-7 and TLR-9 (known to inhibit IFN $\alpha$  production by pDCs) in lupus-prone mice. A significant improvement of proteinuria, glomerulonephritis, and survival as well as a reduction of serum levels of nucleic acid-specific autoantibodies was observed [60].

Further evidence emphasizing the central role of type I IFN in lupus nephritis came from studies investigating the cellular source of type I IFN in lupus nephritis. pDCs are well known to be the main type I IFN-producing cells

and potentially responsible for the systemic increase of type I IFN levels. Tucci et al. showed that peripheral pDCs were decreased in SLE patients and that this was associated with lupus nephritis. Moreover, this study demonstrated the presence of pDCs in the glomeruli of patients with severe lupus nephritis [61]. Interestingly, other studies suggest that immature monocytes recruited in the kidneys [62, 63] as well as resident renal cells [64] represent the main source of type I IFN in the kidney, thus, promoting end-organ disease in murine lupus nephritis models.

Finally a recent study by Ichii et al. showed that over-expression of the IFN-activated gene 202 (*Ifi202*) positively

correlated with the progression of lupus nephritis in the B6.MRLc1 (82–100) mice. *Irf202* is an IFN-stimulated gene localized on the murine chromosome 1, and its overexpression in the kidneys and in the immune organs was confirmed in many lupus-prone mouse models such as BXSB, NZB/WF1 and MRL/lpr. This further supports the role of this IFN-stimulated gene in the pathogenesis of lupus nephritis and lupus susceptibility in general [65].

Taken together, these data highlight the importance of the IFN system in lupus nephritis creating exciting new perspectives both at diagnostic and clinical levels. Interferon-induced chemokines, like macrophage chemoattractant protein 1 (MCP-1) and others, seem to be highly sensitive biomarkers in the assessment of current disease activity and in the early detection of lupus nephritis flare [66, 67]. Moreover, inhibition of MCP-1 in a murine model of lupus nephritis showed significant amelioration of disease symptoms suggesting a new therapeutic approach to lupus kidney disease [68]. Zagury et al. successfully used an IFN $\alpha$  immunogen (termed IFN $\alpha$  kinoid) in mice with nephritis that transiently induces anti-IFN $\alpha$  antibodies resulting in net improvement of lupus nephritis [69]. On the other hand, MRL-*Fas*<sup>lpr</sup> mice treated with IFN $\beta$  showed a significant amelioration of lupus nephritis in these mice suggesting that IFN $\beta$  exerts a local (rather than systemic) anti-inflammatory effect [70]. Additionally, phase I human clinical trials using anti-IFN $\alpha$  monoclonal antibody in patients with mild to moderate SLE showed promising results including suppression of type I IFN-inducible genes overexpression in whole blood and skin lesions, profound effects on signaling pathways such as BAFF, TNF $\alpha$ , IL-1 $\beta$  and consistent trends toward improvement in disease activity, reduced number of flares, and decreased requirement for new or increased immunosuppressive treatments. Preliminary data regarding the safety profile especially viral infections and major adverse events support further clinical development [71–73]. However, more data regarding the efficacy and safety of this treatment are awaited.

### 3. Type I IFN and Cutaneous Lupus Erythematosus (CLE)

Cutaneous lupus erythematosus (CLE) is one of the most common autoimmune-associated skin diseases worldwide. In most cases, the disease is localized and limited to the skin area, without multisystemic involvement characteristic of SLE. While approximately 10%–40% of CLE—depending on the clinical subset of CLE—may transit to systemic disease, skin lesions in the setting of SLE can occur in up to 70% of patients during the disease course [74, 75]. While the pathogenesis of the CLE remains still unclear, a number of contributors—among them type I IFNs—have been proposed. In line with this hypothesis, lupus-like skin lesions have been previously reported at the site of injection of recombinant IFN $\alpha$  and IFN $\beta$  in patients with malignancy and multiple sclerosis respectively, while patients with generalized CLE features often experience flu-like symptoms [76, 77]. In patients with lupus, upregulation

of the IFN-inducible antiviral protein Myxovirus A (MxA) in CLE has been first reported by Fah et al. [78], a finding which has been later confirmed in discoid (DLE), subacute cutaneous (SCLE), as well as other lupus-associated rashes [74, 79, 80]. Of interest, MxA expression was mainly seen in the epidermis and the upper dermis in DLE and SCLE, while, in rarer cases of lupus tumidus and lupus profundus, MxA was mainly detected in perivascular and subcutaneous areas, respectively, reflecting the distribution of the inflammatory infiltrate in different subsets of CLE [74].

Intracellular IFN $\alpha$  itself has been detected at mRNA and protein level in all lesional and more than half of not involved skin specimens from 11 lupus patients compared to only one out of 11 healthy controls [81]. The overexpression of IFN-related genes in nonpathological skin might be the result of genetically determined IFN pathway activation in these patients. Despite the enhanced expression of the IFN $\alpha$ -inducible *IRF7* gene in CLE lesions reported by Meller et al. IFN $\alpha$  mRNA expression has been reported not significantly different in CLE skin compared to normal skin [82]. Subsequent studies detected the accumulation of pDCs—the classical IFN $\alpha$  producing cells—in lesional skin from patients with DLE, SLE, and lupus tumidus, providing an explanation for the previously reported reduced pDC numbers in lupus patients [79, 82–85]. Two pDC subsets have been identified according to their distribution pattern in CLE skin biopsies: a dermal pDCs subset (D-pDC) surrounding dermal vessels associated with Th1 responses and a second subset at the dermoepidermal junction zone (J-pDC) in association with cytotoxic T lymphocytes and subsequent local epithelial damage [84]. In the same study, a positive association was found between the pDC numbers and the density of the infiltrate, suggesting that IFN $\alpha$  production could regulate the degree of inflammation in the affected skin areas. Of note, a higher density infiltrate has been shown in DLE compared to SLE patients [84].

As a result of the locally produced IFN $\alpha$ , recruitment of lymphocytes in the CLE lesion occurs through the production of IFN $\alpha$ - and  $\gamma$ -inducible chemokines CXCL9, CXCL10, CXCL1, which share a common lymphocytic CXCR3 receptor. Compared to IFN $\gamma$ , IFN $\alpha$  has been shown to induce earlier production of these chemokines by keratinocytes, dermal endothelial cells, and dermal fibroblasts, ensuring a first wave of CXCR3+ lymphocytic migration—at the site of the CLE lesion [82]. These findings provide an explanation for the peripherally decreased number of CXCR3+—lymphocytes in these patients [86].

Serum type I IFN activity or expression of IFN-inducible genes in PMBCs from lupus patients was found to be associated with the presence of lupus-associated rashes in some but not all studies so far performed. Of interest, a positive trend between a history of photosensitivity and type I IFN-induced gene expression has been reported by Kirou et al. [9–13].

While the initial trigger for pDC activation in CLE remains elusive, observations of cutaneous lupus flares after sun exposure coupled with experimental evidence suggests UV irradiation as a central player in initiation of the lupus-associated skin injury. UV irradiation has been shown to

exaggerate the already enhanced apoptosis of keratinocytes in CLE leading to generation of RNA and DNA fragments with subsequent secondary necrosis, production of a variety of IFN $\alpha$ -induced chemokines which in turn lead to lymphocytic recruitment and subsequent local inflammatory tissue injury [82, 87]. In accord with the proposed mechanism, inhibitors of TLR7 and TLR9 signaling in a lupus-prone murine model of interface dermatitis attenuated the skin lesions [88].

Moreover, a recently identified IFN $\alpha$ - and  $\gamma$ -induced protein—the GTPase human guanylate binding protein-1 (GBP-1)—is expressed by keratinocytes and endothelial cells in primary and ultraviolet- (UV-) induced skin lesions from patients with various subtypes of CLE compared to nonlesional skin [89]. It has also been recently demonstrated that the IFN $\alpha$ -inducible IFI16 protein—normally localized in the nucleus—translocates in the cytoplasm of affected skin cells from lupus patients and in UV irradiated keratinocytes—leading to generation of antibodies against the IFN $\alpha$ -inducible *IFI16* recently detected in sera of lupus patients [90].

#### 4. Type I IFN and Neuropsychiatric Systemic Lupus Erythematosus (NPSLE)

Neuropsychiatric systemic lupus erythematosus (NPSLE)—among the most severe manifestations of SLE—includes a variety of manifestations involving central, peripheral, and autonomic nervous system as well as psychiatric disorders after other underlying causes have been carefully excluded. The prevalence of neuropsychiatric manifestations in the setting of SLE varies at a range approximately between 15% and 75%, depending of the ascertainment method used [91].

Several mechanisms have been so far implicated in the etiopathogenesis of NPSLE, including antibody-mediated vascular and parenchymal brain injury, concomitant atherosclerotic disease, or the effect of various inflammatory cytokines, including among others interleukin 1 $\beta$  (IL1 $\beta$ ), tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), IFN $\gamma$ , and IFN $\alpha$ . These cytokines have been shown to induce peripheral depletion of tryptophan—previously implicated in the pathogenesis of depression—through stimulation of the enzyme indoleamine 2,3-dioxygenase [92]. IFN $\alpha$  has been also shown to induce the IFN $\gamma$ -inducible protein 10 (IP-10) and interleukin-6 (IL6) previously implicated in pathogenesis of CNS abnormalities [93].

Induction of SLE-like syndromes and neuropsychiatric manifestations have been reported after therapeutic use of IFN $\alpha$  approximately in one-third of patients mainly with hepatitis C or certain malignancies giving potential insights of type I IFN implication in lupus-related clinical syndromes [94–96]. While depression seems to be among the most common IFN $\alpha$ -related neuropsychiatric side effects and a main contraindication for IFN $\alpha$  administration, psychotic features, confusion, bipolar disorders, and seizures can also occur [92]. IFN $\alpha$  production by astrocytes in transgenic mouse models revealed structural and functional abnormalities ranging from seizures and severe behavioral

disorders with high mortality to more subtle learning disabilities depending on high or low intrathecal levels of IFN $\alpha$ , respectively [97]. Notably, calcium and phosphorus deposition in the brain in this experimental model resembled the mineral deposition observed in basal ganglia from patients with the Aicardi-Goutieres syndrome, an early-onset encephalopathy with elevated CSF IFN $\alpha$  levels. The Aicardi-Goutieres syndrome is an autosomal recessive disease related to mutations in 5 genes, including among others the 3-repair DNA exonuclease 1 (*TREX1*), recently associated with lupus [98].

The first evidence of type I IFN implication in NPSLE pathogenesis comes from an early small study in the 1980s, in which elevated CSF levels of IFN $\alpha$  were detected in 2 out of 15 patients with SLE and CNS involvement but not in 20 non-NPSLE individuals. Both of these patients suffered from psychosis and were characterized by the presence of CSF oligoclonal IgG [99].

In accord with the above findings, elevated IFN $\alpha$  levels have been subsequently detected in CSFs of five out of 6 lupus patients with psychosis but with no other NP manifestations. In the brain autopsy of one of the study participants who died from generalized seizures, the presence of IFN $\alpha$  in neurons and microglia has been demonstrated by immunohistochemistry [100]. However, elevated IFN $\alpha$  levels—measured by immunoassay—were detected in approximately one-fifth of CSFs of both 28 NPSLE and 14 non-NPSLE patients, suggesting a limited diagnostic role for IFN $\alpha$  in clinical grounds [101]. While no significant differences have been observed in serum levels of interferogenic activity—measured by bioassay—between SLE patients with and without neuropsychiatric involvement, CSF interferogenic activity has been found to be elevated in NPSLE patients compared to controls with other autoimmune disorders and CNS features. Of note, remarkably lower levels of interferogenic activity have been observed in sera compared to CSFs of NPSLE patients. This was partially attributed to an inhibitory effect of serum IgG, providing a potential explanation for the success of intravenous immunoglobulin (IVIG) treatment in some cases of NPSLE [102] and other neurological diseases [103, 104]. In a recent study, involving 59 NPSLE patients, it was observed an association between acute flares of NP manifestations and elevated IFN $\alpha$  activity in the CSF [105].

The CSF interferogenic activity seems to result from pDC stimulation by CSF-containing immunocomplexes formed by autoantibodies and antigens released by neurocytotoxic Abs or other injured brain cells [93]. While pDCs have not been studied in the NPSLE patients brain cells, elevated number of pDC cells has been isolated from the CSF of other neuroinflammatory diseases [106].

In regard to peripherally detected type I IFN activity in NPSLE, in a cohort of 48 SLE patients reported by Feng et al., significantly higher IFN-inducible gene expression in peripheral mononuclear cells has been demonstrated in 9 patients, who ever suffered from psychosis or seizures, compared to those without those manifestations [13]. Such an association was not, however, observed in a larger cohort of 77 SLE patients by Kirou et al. (Table 1). Moreover, in

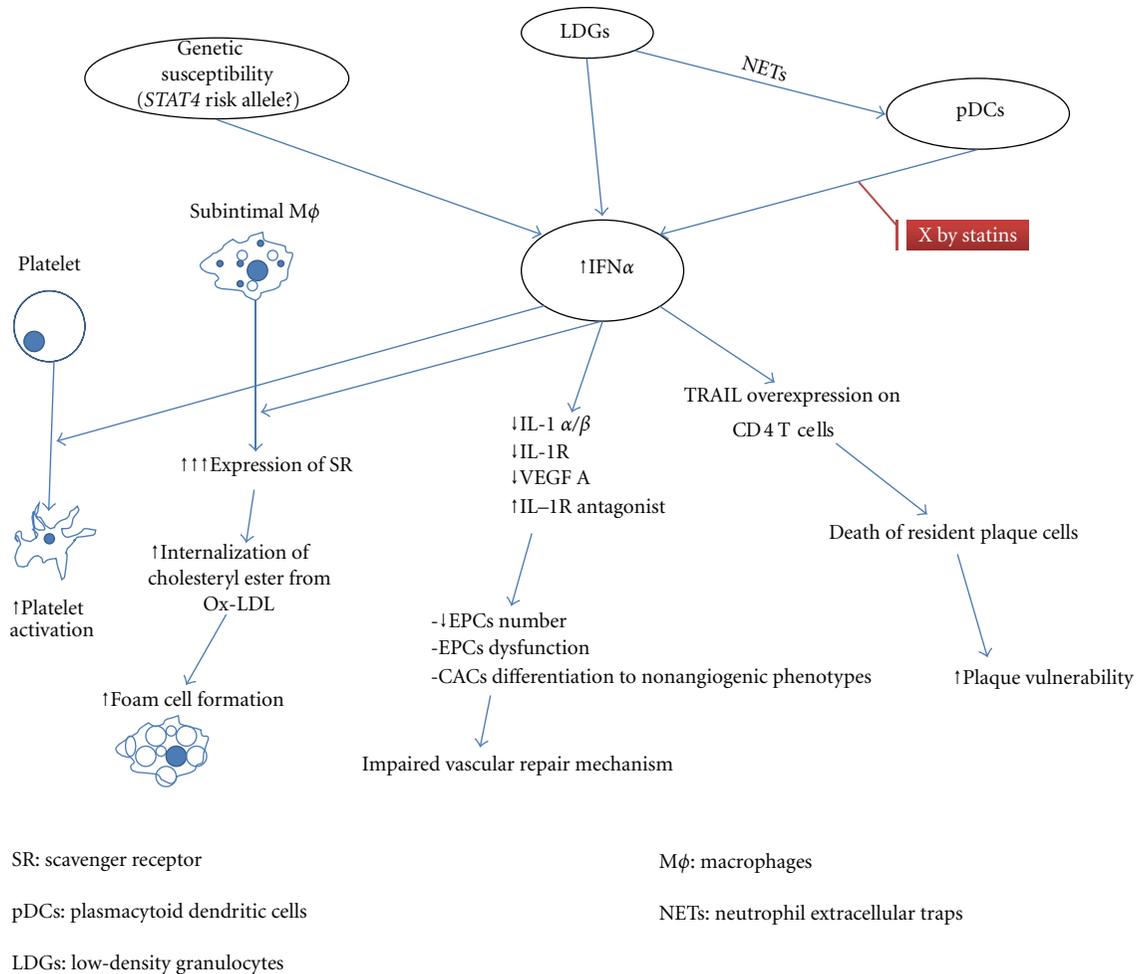


FIGURE 1

a recent cross-sectional study including 58 SLE patients, no correlation between depression scores and type I IFN-induced gene expression in PBMC has been detected [107].

Taken together, these data imply a potential involvement of type I IFN system in pathogenesis of lupus-related CNS features. Prospective studies with larger number of patients and careful collection of clinical, serological, and imaging data are required to further understand its contribution in pathogenesis of NSPLE.

## 5. Type I IFN and Atherosclerosis in SLE Patients

Extensive epidemiological studies in SLE patients demonstrate a bimodal distribution in mortality rates with the earlier peak attributed to infections and complications from kidney disease and/or neuropsychiatric lupus and a later peak mainly linked to atherosclerotic cardiovascular (CV) events [1]. A population-based case-control analysis, using general practice database data, found a relative CV disease risk of 2 for women with SLE [108, 109]. Strikingly, a fifty-fold increased risk of myocardial infarction was reported

among premenopausal women with SLE [110]. While several traditional risk factors for atherosclerosis are more prevalent among SLE patients, they cannot fully explain their increased CV burden [111]. Additionally, the effect on CV risk of SLE is more pronounced comparing to the impact of other inflammatory diseases like rheumatoid arthritis [108]. These observations support the hypothesis that accelerated atherosclerosis and premature CV disease are significantly enhanced by factors inherent to the pathogenesis of SLE. Among these, increasing evidence designates type I IFN as a major player in promoting both the pathogenesis of SLE and atherosclerosis (Figure 1).

It is widely believed that atherosclerosis results from chronic endothelial injury paired with a defective vascular repair mechanism leading to invasion of inflammatory cells, lipid deposition, vascular smooth muscle proliferation, and neointima formation. Several studies suggest that circulating myeloid-derived endothelial progenitor cells (EPCs) and myelomonocytic circulating angiogenic cells (CACs) are the key players in the vascular repair mechanism [112, 113].

Interestingly, reduced number and/or functional abnormalities of EPCs/CACs have been documented in patients with SLE [114–118]. Moreover, heightened type I IFN

levels were associated with EPCs depletion and endothelial dysfunction in SLE patients possibly through IFN $\alpha$ -mediated apoptosis of EPCs/CACs and induction of differentiation of myeloid cells to nonangiogenic phenotypes. Neutralizing the type I IFN pathway redressed the abnormal EPC/CAC phenotype [119, 120]. In accord with the human studies, in a lupus-prone murine model, elevated levels of type I IFN led to reduced number and EPCs dysfunction [121]. Moreover, the presence of IFN $\alpha$  inhibited EPCs from nonlupus-prone mice to differentiate into mature endothelial cells. Thacker et al. showed that IFN $\alpha$  represses the transcription of the proangiogenic factors IL1  $\alpha$  and  $\beta$  and vascular endothelial growth factor A (VEGF) and upregulates the antiangiogenic IL1 receptor antagonist. In vivo confirmation of this antiangiogenic pathway of IFN $\alpha$  interfering with IL1 pathways was established by examining renal biopsies of patients with lupus nephritis [122].

Furthermore, studies investigating the cellular source of type I IFN add supporting evidence to the effects of type I IFN in vascular injury. pDCs have been implicated in the pathogenesis of atherosclerosis and in particular in the destabilization of the atherosclerotic plaque which leads to acute vascular events through upregulation of TNF-related apoptosis-inducing ligand (TRAIL) on CD4<sup>+</sup> T cells which enhance them to kill plaque-resident cells, thus, rendering the plaque vulnerable [123]. However, depletion of pDCs does not reverse the abnormal EPC/CAC phenotype in vitro. A recently studied subset of proinflammatory neutrophils, termed low-density granulocytes (LDG), was identified in the blood of SLE patients. LDGs exert cytotoxic effects on the endothelium and produce sufficient type I IFN to prevent EPCs from differentiating into mature endothelial cells. Depletion of LDGs restores the functional capacity of the EPCs/CACs in vitro, therefore, supporting a role of these abnormal cells and of type I IFN in the pathogenesis of vascular damage in SLE [124].

Interestingly a recent study investigating the immunomodulatory effects of statins in SLE demonstrated that simvastatin and pitavastatin significantly inhibit type I IFN production both from pDCs isolated from lupus patients and from healthy pDCs treated with sera from SLE patients. The inhibitory effect on type I IFN production was shown to be attributable to inactivation of Rho kinases (a family of downstream kinases of the TLR pathway) that results in inhibition of the p38 MAPK and Akt as well as prevention of IRF7 nuclear translocation. These findings imply that statins exert a beneficial effect in the atherosclerotic process not only due to its lipid-lowering properties but also through inhibition of the type I IFN production. It also provides a rationale for a potential therapeutic use of statins in IFN-mediated autoimmune diseases such as SLE [125].

An additional pathway by which type I IFN may be implicated in CV disease is through platelet activation. In a recent study, Lood et al. demonstrated that, in patients with lupus, platelets are activated and overexpress type I IFN-regulated proteins comparing to platelets from healthy controls. Given that the same platelet phenotype has been observed in patients with a history of vascular disease, they hypothesized that type I IFN-induced platelet activation

could be implicated in the development of vascular disease in SLE [126].

Further supporting evidence for the role of type I IFN in atherosclerosis and especially in the formation of foam cells came from a study by Li et al. [127]. Foam cells derive from infiltrating monocytes in the subintima where they differentiate into macrophages. Upon exposure to oxidized-LDL (ox-LDL), macrophages expressing scavenger receptors (SR) internalize cholesteryl ester from ox-LDL and are transformed into foam cells which represent the primary components of the early atherosclerotic lesion. In this study, IFN $\alpha$  priming induced upregulation of SR in the macrophages and increased foam-cell formation. Furthermore, peripheral blood mononuclear cells from patients with SLE overexpressed SR which was positively correlated with increased type I IFN activity.

Finally, a recent Swedish study showed that SLE patients with the risk allele rs10181656(G) in the STAT4 gene had a significantly increased risk of ischemic cerebrovascular disease (ICVD), comparable in magnitude to that of hypertension. Moreover, this SNP was associated with the presence of two or more antiphospholipid antibodies (aPLs). This study indicates that a genetic predisposition involving the type I IFN pathway is an important and previously unrecognized risk factor for ICVD in SLE and that aPLs may be one underlying mechanism [128].

These data indicate that premature atherosclerosis in SLE patients can at least partially be attributed to increased activation of the type I IFN system. Current attempts to block the type I IFN activity in SLE patients may provide therapeutic approaches that achieve successful overall disease activity control and reduce the fatal vascular events that afflict these patients.

## 6. Concluding Remarks

Over the past years, the role of type I interferon system in generation of distinct lupus-related clinical phenotypes arising from skin, renal, and CNS involvement has been increasingly appreciated. Moreover, growing evidence suggests the implication of type I IFN pathway in the pathogenesis of atherosclerosis, a frequent comorbidity in these patients, often not fully explained by the presence of co-existing traditional CV risk factors. Careful characterization of clinical features associated with heightened IFN levels would further increase our insight into lupus pathogenesis allowing the potential use of type I interferon as a therapeutic target for lupus patients characterized by specific clinical and/or serological phenotypes.

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