Viewpoint

Interpreting interest in interferon-α

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Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that affects approximately 0.1% of the population, with most afflicted individuals being young women. SLE is characterized by inflammatory destruction of skin, blood elements, joints, kidneys, serosa, central nervous system, and other tissues [1]. Despite intensive efforts by many investigators, the cellular and molecular mechanisms governing inflammation in connective tissue diseases such as SLE remain uncertain, although cytokines are believed to play an important role.

The group of cytokines known as interferons was first characterized in 1957. Interferons were named for their ability to 'interfere' with viral replication, conferring resistance to infection transferred from virally infected chick cells into uninfected cells [2]. The therapeutic potential of interferon in viral infection was first demonstrated through its ability to inhibit respiratory virus infection [3]. Interferons have since been proven clinically effective antiviral and antineoplastic therapeutic agents for a variety of disorders (for review [4]).

There are two groups of interferons: type I interferons (IFN-α, IFN-β, IFN-ω) and type II interferon (IFN-γ). Human IFN-α was cloned in 1980, and was found to represent a mixture of several closely related proteins expressed from distinct genes [5]. A second type of interferon, IFN-β, is produced mainly by fibroblasts, is a single protein species, and was cloned around the same time [6]. A third species of human type I interferon is known as IFN-ω [7]. IFN-γ is produced by activated T cells and has been found to be a single protein in all animal species [8]. Induction of interferon synthesis at high levels is triggered by viruses, and is also induced by a variety of nonviral agents such as bacteria and synthetic polymers [9,10]. The production of IFN-α and IFN-β by virally infected cells induces resistance to viral replication, enhances MHC class I expression, increases antigen presentation, and activates natural killer cells to kill virus-infected cells [11]. Thus, type I interferons are active in both innate and adaptive immunity. The actions of IFN-γ include macrophage activation, increased expression of MHC and antigen processing components, immunoglobulin class switching, and suppression of T-helper-2 responses [11].

Many historical studies have indicated a role for the type I interferon system in both human and murine SLE. Although controversial, some studies have shown that serum derived from lupus patients contains elevated levels of IFN-α [12,13]. The levels of IFN-α in serum correlate with disease severity, as measured by the number of organs involved and the presence of anti-DNA antibodies [12,14]. Additionally, the role of IFN-α as a causative agent in the pathogenesis of SLE is suggested by the finding that patients who are treated with IFN-α for disorders such as chronic hepatitis C infection and malignancy occasionally develop antinuclear antibodies, anti-double-stranded (ds)DNA, and autoimmune disorders [15–18]. The recent studies described below have added significantly to this body of literature, strongly implicating IFN-α and IFN-α inducible proteins as potential targets of therapeutics and diagnostics, respectively, in SLE.

A study conducted by Blanco and colleagues [19] has shown that serum derived from patients with SLE has the ability to induce the differentiation of monocytes into dendritic cells (DCs). The induction of DC differentiation was dependent on IFN-α, as demonstrated by addition of IFN-α to autologous serum (which induced differentiation into DCs) and addition of IFN-α neutralizing antibodies to SLE serum (which prevented differentiation into DCs). Monocytes that had been cultured with SLE sera developed the capacity to process and present antigens derived from apoptotic cells to $CD4^+$ T lymphocytes. The report concluded that SLE is characterized by a major defect in DC homeostasis, and that IFN-α is likely to be the main cytokine contributing to this defect.

DC = dendritic cell; ds = double-stranded; IFN = interferon; PBL = peripheral blood lymphocyte; SLE = systemic lupus erythematosus.

Second, it has been shown that the serum of SLE patients contains a factor that has the ability to induce the production of IFN-α in normal blood leukocytes *in vitro* [20]. Subsequently, this interferon inducing factor was identified as small immune complexes. Immune complexes containing anti-dsDNA antibodies and immunostimulatory plasmid DNA in combination acted as potent inducers of IFN-α in natural interferon-producing cells [21]. Priming natural interferon-producing cells with type I interferons and granulocyte macrophage-colony stimulating factor greatly enhanced the ability of these complexes to induce the production of IFN-α. This study suggests that IFN-α works through a positive feedback loop in SLE, mediated by immune complexes containing anti-DNA antibodies and DNA.

In a third report [22], expression profiling of peripheral blood lymphocytes (PBLs) derived from C57BL/6 mice congenic for the Nba2 non-MHC lupus susceptibility locus identified only two differentially expressed genes, both of which were induced by interferon. These interferon-inducible proteins, termed Ifi202 and Ifi203, were upregulated both at the mRNA and at the protein level in splenocytes. Two other murine studies have recently examined the effect of genomic deletion of one of the type I interferon receptor (IFNAR) chains on disease manifestations in lupus models [23,24]. Both studies demonstrated that interferon signaling plays a significant role in the generation of autoantibodies directed against red blood cells and DNA, and in mediating renal pathology.

More recently, two studies used DNA microarray technology to profile mRNA transcripts from PBLs obtained from SLE patients. Baechler and colleagues [25] performed transcript profiling of PBLs from 48 different SLE patients and 42 healthy control individuals. A 'biosignature' was identified that accurately differentiated between these two groups. A striking finding in this study was the observation that many of the upregulated transcripts in PBLs from SLE patients encoded interferon-inducible proteins. A correlation was found between the number of SLE criteria (particularly central nervous system and renal disease) and the number of interferon-inducible transcripts. In the second study, Bennett and colleagues [26] noted that interferon-inducible genes, as well as granulopoiesis-related genes, were overexpressed in blood leukocytes of patients with active lupus. Importantly, a correlation between disease activity according to the SLE Disease Activity Index and the expression of 10 of these genes was demonstrated. This 'interferon signature' disappeared when patients were treated with glucocorticoids. Interestingly, a similar result in pediatric dermatomyositis was obtained when transcript profiles from muscle biopsies were analyzed [27].

In summary, IFN-α probably plays an important role in the pathogenesis of connective tissue diseases such as dermatomyositis and SLE. The studies described above raise several important questions for future experiments. What cells are the main source of IFN-α, and what are the triggers that lead to its secretion? Are there other stimuli in target cells that can bypass the need for IFN-α, ultimately triggering the synthesis of IFN-α inducible genes? Can interferon-inducible gene or protein expression serve as a biosignature that can be used to categorize patients, to guide clinical decision making, or to follow patients enrolled in clinical trials? Finally, can development of inhibitors of IFN-α signaling effectively treat patients with connective tissue diseases? In humans, the type I interferons consist of 14 subtypes of IFN-α, IFN-β, and IFN-ω, arguing that development of specific therapeutics that can target all of the relevant type I interferons may be difficult. Nevertheless, it has been over 25 years since a new therapeutic agent for SLE was approved by the US Food and Drug Administration. Our 'interpretation' of the 'interest in interferons' is that disruption of type I interferon signaling holds great promise to 'interfere' with this disease.

Competing interests

None declared.

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Note

* These papers have been highlighted by Faculty of 1000, a web-based literature awareness service. F1000 evaluations for these papers are available on our website at http://arthritis-research.com/viewpoints/reflinks5_05.asp

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