Commentary

The role of IFN-γ in systemic lupus erythematosus: a challenge to the Th1/Th2 paradigm in autoimmunity

Argyrios N Theofilopoulos, Stefanos Koundouris, Dwight H Kono and Brian R Lawson

The Scripps Research Institute, Department of Immunology/IMM3, La Jolla, CA, USA

Correspondence: Argyrios N Theofilopoulos, MD, Professor, Department of Immunology, The Scripps Research Institute, 10550 North Torrey Pines Road/IMM3, La Jolla, CA 92037, USA. Tel: +1 (858) 784 8135; fax: +1 (858) 784 8361; e-mail: argyrio@scripps.edu

Abstract

The classification of T helper cells into type 1 (Th1) and type 2 (Th2) led to the hypothesis that Th1 cells and their cytokines (interleukin [IL]-2, interferon [IFN]-γ) are involved in cell-mediated autoimmune diseases, and that Th2 cells and their cytokines (IL-4, IL-5, IL-10, IL-13) are involved in autoantibody(humoral)-mediated autoimmune diseases. However, this paradigm has been refuted by recent studies in several induced and spontaneous mouse models of systemic lupus erythematosus, which showed that IFN-γ is a major effector molecule in this disease. These and additional findings, reviewed here, suggest that these two cross-talking classes of cytokines can exert autoimmune disease-promoting or disease-inhibiting effects without predictability or strict adherence to the Th1-versus-Th2 dualism.

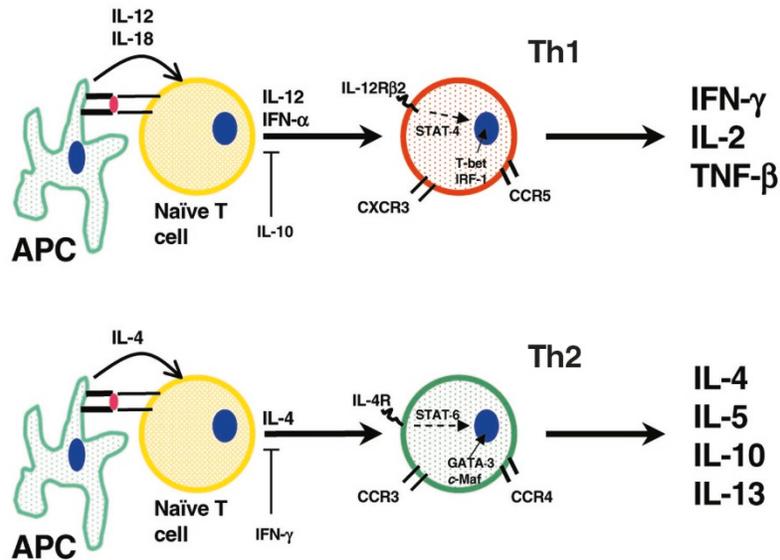**Keywords:** cytokines, IFN-γ, lupus, Th1, Th2

Introduction

Cytokines play a critical role in regulating lymphoid cell responses to most antigenic stimuli, and it is therefore very likely that these molecules profoundly affect the pathogenesis of autoimmune diseases. Consequently, investigations of the role of cytokines as effectors or predisposing elements in these diseases have received prominent attention for many years. Early findings from such studies, however, were frequently contradictory and, more importantly, difficult to incorporate into a conceptual framework. A new impetus in this area was provided by the discovery of Mosmann and colleagues that T cells could be conveniently divided into two main subsets, ie Th1 and Th2, with distinct arrays of cytokine secretion patterns and functions [1,2]. A hypothesis was subsequently formulated according to which cell-mediated autoimmune diseases, such as insulin-dependent diabetes mellitus, are induced by Th1 cells and their cytokines, and humorally-mediated autoimmune diseases, such as systemic lupus erythematosus, are induced by Th2 cells and their cytokines. As reviewed below, findings on the primary role of IFN-γ in the pathogenesis of murine lupus and other observations clearly refute this hypothesis.

Type 1 and Type 2 cells and their cytokines

Many studies have now clearly established that, after antigen recognition, cytokines at the priming site, together with other factors such as the type of antigen-presenting cell, antigen dose, expressed costimulatory molecules, affinity, and duration of exposure, direct a polarized differentiation of a T helper cell clone into either the Th1 or the Th2 type [2–5] (Fig. 1). Th1 cells secrete IL-2, IFN-γ, and TNF-β, while Th2 cells secrete IL-4, IL-5.

Be = B effector (cells); IFN = interferon; IL = interleukin; NF = nuclear factor; sIFNγR = soluble recombinant IFNγR; STAT = signal transducer and activator of transcription; Th = T helper (cells); TNF = tumor necrosis factor.

Figure 1

Schematic representation of Th1/Th2 differentiation. Modes of induction, important transcription factors and acquisition or markers are depicted (for details, see text).

IL-10, and IL-13. Th1 cells protect against intracellular pathogens, activate phagocytes, induce IgG_{2a} antibodies, and promote delayed-type hypersensitivity responses, whereas Th2 cells protect against extracellular pathogens, activate eosinophils, induce IgE-mediated allergic reactions, and promote other humoral responses in which IgG_1 predominates. Certain cell-surface molecules have been reported to be differentially expressed in these two subsets, including the chemokine receptors CCR5, CXCR3, and CCR1 on Th1 cells and CCR3 and CCR4 on Th2 cells [6]. Some of these markers are not specific, since they are not exclusive to one or the other subset. For example, CCR5 and CXCR3 are also expressed by Th2 cells, albeit at lower levels than by Th1 cells [7]. Moreover, a recently identified unique T-cell subtype does not fit either the Th1 or Th2 definition, and yet it expresses CXCR5 and preferentially localizes in B-cell follicles, where it provides help for antibody responses [8,9]. In addition to certain chemokine receptors, both IL-12Rβ2 [10–12] and IL-18R [13] are selectively expressed by Th1 cells.

Similar Th1- and Th2-like polarized cytokine secretion patterns have now been described for CD8+ and γ T cells, natural killer cells, dendritic cells, macrophages, mast cells, eosinophils, and even B cells [14]. With regard to the latter, it was recently found that naïve B cells that were stimulated in an antigen-dependent fashion with polarized, cytokine-secreting T effector cells could be induced to differentiate into two types of B effector cells, ie Be1, secreting IFN-γ (and other cytokines), and Be2, secreting IL-4

(and other cytokines) [15]. Moreover, IFN-γ secreted by Be1 cells and IL-4 secreted by Be2 cells, while presenting antigen to naïve T cells, regulated Th1 and Th2 development, respectively. In recognition of the fact that specific patterns of cytokine production are now applicable to many cell types, the main types of cytokine polarization are now defined as type 1 or type 2 rather than Th1 and Th2 [14]. Apparently, the immune system employs the same overall pattern of cytokine production regardless of the cell type involved in a particular response or setting. Therefore, the assumption that effects observed in a particular disease after treatment with cytokine agonists or antagonists are mediated by the corresponding subset of T cells is an oversimplification. In fact, a variety of other cellular components might be engaged, either directly or indirectly.

The molecular events associated with type 1 or type 2 cytokine polarization have not been fully elucidated. It is known that Th1 differentiation driven by IL-12 (a product of activated macrophages and dendritic cells) requires the IL-12-responsive signal transducer and activator of transcription (STAT)4, while Th2 differentiation requires the IL-4-responsive transcription factor STAT6 (Fig. 1) [16]. IL-18 acts synergistically with IL-12 in inducing IFN-γ production, but signalling by IL-18 is mediated by the IL-1 receptor-associated kinase pathway, not STAT4, leading to the nuclear translocation of the NF-κB complex selectively in Th1 cells [17]. Additional proto-oncogenes, kinases, and transcription factors have been implicated in Th1/Th2 differentiation, including the interferon regulatory

factor 1 and the T-box expressed in T cell protein for Th1 cells, and the *c-Maf* proto-oncogene and the GATA3 zinc finger protein for Th2 cells [16]. Moreover, the JNK/MAP kinase pathway is induced in Th1 but not Th2 effector cells [18].

IFN-γ in lupus immunopathology

We and others have used a variety of techniques to measure cytokine levels in lymphoid organs and affected tissues of mice predisposed to lupus and have catalogued a variety of perturbations, with some cytokines upregulated and others downregulated compared with controls [19]. The most consistent result was high levels of IFN-γ, particularly at the late stages of the disease, with the most abundant levels being observed in the MRL-*Fas^lpr* lupus strain [20–25]. These increases in IFN-γ were documented at both the RNA and protein levels, as well as by ELISPOT assays and by cloning kidney-infiltrating T cells. Increased expression of IL-12 in kidney-infiltrating mononuclear cells and tubular epithelial cells of MRL-*Fas^lpr* mice have also been reported [26–28].

In addition to spontaneous mouse models of lupus, transgenic mice with a normal background overexpressing IFN-γ in the epidermis (under the involucrin promoter) developed inflammatory skin disease, as well as a T-cell-dependent lupus-like syndrome with antinuclear autoantibodies and kidney deposits of immune complexes [29,30].

Concentrations of IFN-γ and IL-12 are also increased in the serum of lupus patients, particularly those in the active stages of the disease [31,32]. Moreover, in such patients, increases in the Th1/Th2 ratio have been detected in the peripheral mononuclear cells, and a predominance of Th1 cells is particularly evident in the blood and kidneys of patients with diffuse proliferative nephritis [33]. Mutations in the IFN-γR1 and R2 have been identified in some lupus patients, and a combination of the IFN-γR1 Met14/Val14 with the IFN-γR2 Gln64/Gln64 genotypes has been suggested to be a risk factor for this disease [34]. Nonetheless, *in vitro* experiments have shown higher IFN-γ expression in peripheral blood mononuclear cells of lupus patients than in controls after mitogenic stimulation [35]. Of interest is the observation that severe lupus-like disease was induced in some patients treated with IFN-γ for unrelated autoimmune diseases or myeloproliferative disorders [36,37].

The importance of IFN-γ in lupus pathogenesis (Table 1) was first suggested by the earlier studies of Jacob *et al* [38], who found accelerated disease in [New Zealand Black (NZB) × New Zealand White (NZW)]F$_1$ (B × W) lupus mice receiving IFN-γ or its inducers, while those receiving anti-IFN-γ antibody at an early stage had significantly delayed onset. Extending these initial observations, Ozmen *et al* [39] treated B × W mice with soluble recom-

Table 1

Studies documenting the detrimental effects of IFN-γ in murine systemic lupus erythematosus

Strain	Experimental manipulations	References
(CBA × C57/BL10)F1	trIFN-γ	[29,30]
B × W	IFN-γ	[38,39]
B × W	Anti-IFN-γ mAb	[38]
B × W	sIFN-γR	[39]
B × W	IFN-γR$^{-/-}$	[43]
MRL-*Fas^lpr*	sIFN-γR/Fc	[47]
MRL-*Fas^lpr*	IFN-γ$^{-/-}$	[41,42]
MRL-*Fas^lpr*	IFN-γR$^{-/-}$	[44]

binant IFN-γR (sIFN-R) or IFN-γ, or with anti-IFN-γ antibody commencing at 4 months of age. All the mice treated with sIFN-γR or anti-IFN-γ antibody were alive at approximately 9.5 months, with reduced serologic and histologic disease parameters, while those receiving IFN-γ exhibited earlier mortality than controls. Treatments with sIFN-γR or anti-IFN-γ antibody were effective only if initiated early in the disease process, perhaps because of the lack of adjustments in dosage, which might have been inadequate to neutralize the very high levels of the ligand attained at later disease stages. In contrast to the studies just mentioned, other studies showed that treatment with monoclonal antibody to IFN-γ did not affect the severity of disease or the survival of MRL-*Fas^lpr* mice [40], perhaps because of an inadequate dose of the antibody or its inability to reach inflammatory sites.

Definitive evidence that IFN-γ is required for pathogenesis in murine lupus was provided in a series of studies with MRL-*Fas^lpr* or B × W mice in which the *IFN-γ* or *IFN-γR* gene had been deleted [41–44]. These studies uniformly reported significant reduction of histologic and serologic disease characteristics and extended survival. The authors of one of these studies [42] made two notable observations. First, they found that hypergammaglobulinemia was maintained in MRL-*Fas^lpr* mice in which the IFN-γ gene had been deleted, with a switch from IgG$_{2a}$ to IgG$_1$ predominance, but that the dramatic decrease in levels of the predominant IgG$_{2a}$ anti-dsDNA autoantibodies was not associated with a compensatory increase in IgG$_1$ anti-dsDNA subclass autoantibodies. A second, remarkable, finding was that glomerulonephritis and early death were prevented even in mice heterozygous for this deletion (IFN-γ$^{+/-}$; that is, with about 50% reduction in IFN-γ concentrations), even though autoantibody levels and renal deposits of immune complexes were the same as those in the wild-type MRL-*Fas^lpr* mice [42]. These important find-

ings suggest that therapeutic interventions to reduce IFN-γ levels in lupus may selectively affect certain autoimmune responses without significantly compromising the capacity to respond to exogenous antigens. Further, even partial reduction in IFN-γ might curtail its deleterious effects locally in the afflicted organs. Similar uncoupling phenomena between autoantibody production and local inflammatory responses have been described in B × W mice in which the gene for the FcRγ-chain had been deleted [45]. Moreover, our genome-wide studies have shown that some loci associated with glomerulonephritis or mortality do not cosegregate with those associated with the production of anti-dsDNA autoantibody [46], indicating that other autoantibody specificities or additional locally acting mechanisms may be necessary for the development of glomerulonephritis. Overall, the findings suggest that IFN-γ may exert disease-promoting effects at both a systemic, humorally-mediated axis and a local, cell-mediated axis.

Treatment of murine lupus with cDNA encoding IFN-γR/Fc

Encouraged by the beneficial effects of experiments blocking IFN-γ in murine lupus, we developed a new strategy to intercept the activity of this molecule by intramuscular injections of a nonviral vector containing cDNA encoding the IFN-γR/IgG$_1$Fc fusion protein [47]. We used this inhibitor instead of the truncated receptor alone, because fusion molecules secreted as disulfide-linked homodimers have been shown to have much longer half-lives than the truncated IFN-γR (40 vs 1–3 h, respectively) [48,49], and dimeric IFN-γR/Fc fusion protein shows higher ligand avidity than single-chain receptors [50]. This therapy significantly reduced serum levels of IFN-γ and all disease parameters in MRL-Fas^{lpr} mice when it was initiated before appearance of the disease, particularly when expression of this biomolecule was enhanced by electroporation at the injection site. Remarkably, this treatment arrested and often ameliorated disease even when the treatment was initiated when the disease was at an advanced stage, an unprecedented result. It is impressive that inhibition of a single molecule has such a profound effect on this multifactorial disease.

Because of the highly pleiotropic properties of IFN-γ, it is very difficult to identify the exact mechanism(s) by which blockade of this molecule curtails the development of murine lupus. The most likely possibility is reduced expression of MHC class I and II molecules on both mononuclear and tubular epithelial cells, leading to inefficient self-peptide presentation and responses [42]. Additional mechanisms may include reduced expression of other inflammatory molecules, such as intercellular adhesion molecule 1 and monocyte chemoattractant protein-1 [47].

The delivery of IFN-γ inhibitory molecules by intramuscular injection of plasmid vectors is simple, and appears to be nontoxic and safe. This approach for gene therapy of lupus circumvents several problems encountered with viral vectors [51], and may have advantages over the use of sIFN-γR, such as provision of a depot of genetic material for long-term expression of a biomolecule as well as its expression in afflicted organs due to migration of the injected DNA to distant sites [52].

Th2 cytokines in lupus

Although demonstrations of the primary role of IFN-γ in the pathogenesis of murine lupus challenge the Th1/Th2 paradigm in autoimmunity, this finding should not be taken as evidence that Th2 cytokines are without influence in this disease. On the contrary, several studies have shown that manipulation of IL-4, IL-6, or IL-10 can also affect the progression of murine lupus. For example, treatment of B × W or MRL-Fas^{lpr} mice with IL-4R or anti-IL-4 antibody resulted in reduced mortality and disease [53,54]. Conversely, IL-4 was shown not to be a necessary component in the BXSB male lupus disease [55] and, as a further complication, transgenic high expression of IL-4 under the influence of an immunoglobulin promoter in (NZW × C57B/6.Yaa)F$_1$ mice was protective [56]. In addition, administration of IL-6 promoted, and anti-IL-6 inhibited, the B × W and MRL-Fas^{lpr} disease [57,58]. Finally, anti-IL-10 treatment ameliorated disease in B × W mice, presumably by upregulating TNF-α [59].

Conclusion

The discovery of the Th1-vs-Th2 dichotomy provided the paradigm according to which cell-mediated autoimmune diseases engage Th1 cells and their respective cytokines, while humorally mediated autoimmune diseases engage Th2 cells and their respective cytokines. Evidence reviewed above, primarily on the role of IFN-γ in lupus pathogenesis, appears to contradict this paradigm. Challenges to this hypothesis have also been provided by evidence from other autoimmune diseases. For example, IFN-γ was also shown to be required in the classic autoantibody-mediated disease myasthenia gravis, whereas IL-4 was not [60,61]. Furthermore, both Th1 and Th2 reportedly affect the severity of disease in the cell-mediated autoimmune diabetes of nonobese diabetic mice. Thus, depending on the experimental conditions, IFN-γ was both detrimental and beneficial [62,63], pancreatic IL-4 expression was protective [64], islet-specific expression of IL-10 accelerated disease [65] while systemic treatment with IL-10 prevented it [66], and deletion of the IL-10 gene was without effect [67] in this model. It appears, therefore, that both Th1 and Th2 cytokines can modify a given autoimmune disease depending on various factors, such as stage of the disease and timing of treatment, local vs systemic expression, and genetic background. Overall, it seems that the effects of cytokines in autoimmune syndromes cannot be dogmatically predicted, and their effects can be much more complex than the simplistic Th1-vs-Th2 definition dictates.

Acknowledgements

References

1. Mosmann TR, Cherwinski H, Bone MW, Giedlin MA, Coffman RL: **Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins**. *J Immunol* 1986, **136**:2348–2357.
2. Seder RA, Mosmann TR: **Differentiation of effector phenotypes of CD4+ and CD8+ T cells**. In: *Fundamental Immunology*. Edited by Paul WE. Hagerstown: Lippincott Williams & Wilkins; 1998: 879–908.
3. Abbas AK, Murphy KM, Sher A: **Functional diversity of helper T lymphocytes.** *Nature* 1986, **383**:787–793.
4. O'Garra A: **Cytokines induce the development of functionally heterogeneous T helper cell subsets.** *Immunity* 1998, **8**: 275–283.
5. Lanzavecchia A, Sallusto F: **Dynamics of T lymphocyte responses: intermediates, effectors, and memory cells.** *Science* 2000, **290**:92–97.
6. Sallusto F, Mackay CR, Lanzavecchia A: **The role of chemokine receptors in primary, effector, and memory immune responses.** *Ann Rev Immunol* 2000, **18**:593–620.
7. Sallusto F, Lenig D, Mackay CR, Lanzavecchia A: **Flexible programs of chemokine receptor expression on human polarized T helper 1 and 2 lymphocytes.** *J Exp Med* 1998, **187**:875–883.
8. Breitfeld D, Ohl L, Kremmer E, Ellwart J, Sallusto F, Lipp M, Forster R: **Follicular B helper T cells express CXC chemokine receptor 5, localize to B cell follicles, and support immunoglobulin production.** *J Exp Med* 2000, **192**:1545–1552.
9. Schaerli P, Willimann K, Lang AB, Lipp M, Loetscher P, Moser B: **CXC chemokine receptor 5 expression defines follicular homing T cells with B cell helper function.** *J Exp Med* 2000, **192**:1553–1562.
10. Rogge L, Barberis-Maino L, Biffi M, Passini N, Presky DHY, Gubler U, Sinigaglia F: **Selective expression of an interleukin-12 receptor component by human T helper 1 cells.** *J Exp Med* 1997, **185**:825–831.
11. Szabo SJ, Jacobson NG, Dighe AS, Gubler U, Murphy KM: **Developmental commitment to the Th2 lineage by extinction of IL-12 signaling.** *Immunity* 1995, **2**:665–675.
12. Rogge L, Papi A, Presky DH, Biffi M, Minetti LJ, Miotto D, Agostini C, Semenzato G, Fabbri LM, Sinigaglie F: **Antibodies to the IL-12 receptor beta 2 chain mark human Th1 but not Th2 cells in vitro and in vivo.** *J Immunol* 1999, **162**:3926–3932.
13. Xu D, Chan WL, Leung BP, Hunter D, Schulz K, Carter RW, McInnes IB, Robinson JH, Liew FY. **Selective expression and functions of interleukin 18 receptor on T helper (Th) type 1 but not Th2 cells.** *J Exp Med* 1998, **188**:1485–1492.
14. Mosmann T: **Complexity or coherence? Cytokine secretion by B cells.** *Nature Immunol* 2000, **6**:465–466.
15. Harris DP, Haynes L, Sayles, PC, Duso DK, Eaton, SM, Lepak, NM, Johnson LL, Swain SL, Lund FE: **Reciprocal regulation of polarized cytokine production by effector B and T cells.** *Nature Immunol* 2000, **6**:475–482.
16. Rengarajan J, Szabo SJ, Glimcher LH: **Transcriptional regulation of Th1/Th2 polarization.** *Immunol Today* 2000, **21**:479–483.
17. Robinson D, Shibuya K, Mui A, Zonin F, Murphy E, Sana T, Hartley SB, Menon S, Kastelein R, Bazan F, O'Garra A: **IGIF does not drive Th1 development but synergizes with IL-12 for interferon-gamma production and activates IRAK and NFkappaB.** *Immunity* 1997, **7**:571–581.
18. Yang DD, Conze D, Whitmarsh AJ, Barrett T, Davis RJ, Rincon M, Flavell RA: **Differentiation of CD4+ T cells to Th1 cells requires MAP kinase JNK2.** *Immunity* 1998, **9**:575–585.
19. Theofilopoulos AN, Lawson BR: **Tumour necrosis factor and other cytokines in murine lupus.** *Ann Rheum Dis* 1999, **58 (suppl 1)**:I49–I55.
20. Prud'homme GJ, Kono DH, Theofilopoulos AN: **Quantitative polymerase chain reaction analysis reveals marked overexpression of interleukin-1 beta, interleukin-1 and interferon-gamma mRNA in the lymph nodes of lupus-prone mice.** *Mol Immunol* 1995, **32**:495–503.
21. Fan X, Wuthrich RP: **Upregulation of lymphoid and renal interferon-gamma mRNA in autoimmune MRL-Fas(lpr) mice with lupus nephritis.** *Inflammation* 1997, **21**:105–112.
22. Shirai A, Conover J, Klinman DM: **Increased activation and altered ratio of interferon-gamma: interleukin-4 secreting cells in MRL-lpr/lpr mice.** *Autoimmunity* 1995, **21**:107–116.
23. Murray LJ, Lee R, Martens C: **In vivo cytokine gene expression in T cell subsets of the autoimmune MRL/Mp-lpr/lpr mouse.** *Eur J Immunol* 1990, **20**:163–170.
24. Umland S, Lee R, Howard M, Martens C: **Expression of lymphokine genes in splenic lymphocytes of autoimmune mice.** *Mol Immunol* 1989, **26**:649–656.
25. Manolios N, Schrieber L, Nelson M, Geczy CL: **Enhanced interferon-gamma (IFN) production by lymph node cells from autoimmune (MRL/1, MRL/n) mice.** *Clin Exp Immunol* 1989, **76**:301–306.
26. Schwarting A, Tesch G, Kinoshita K, Maron R, Weiner HL, Kelley VR: **IL-12 drives IFN-gamma-dependent autoimmune kidney disease in MRL-Fas(lpr) mice.** *J Immunol* 1999, **163**:6884–6891.
27. Fan X, Oertli B, Wuthrich RP. **Up-regulation of tubular epithelial interleukin-12 in autoimmune MRL-Fas(lpr) mice with renal injury.** *Kidney Int* 1997, **51**:79–86.
28. Huang FP, Fend GJ, Lindop G, Stott DI, Liew FY: **The role of interleukin 12 and nitric oxide in the development of spontaneous autoimmune disease in MRL/Mp-lpr/lpr mice.** *J Exp Med* 1996, **183**:1447–1459.
29. Seery JP, Carroll JM, Cattell V, Watt FM: **Antinuclear autoantibodies and lupus nephritis in transgenic mice expressing interferon gamma in the epidermis.** *J Exp Med* 1997, **186**: 1451–1459.
30. Seery JP, Wang EC, Cattell V, Carroll JM, Owen MJ, Watt FM: **A central role for alpha beta T cells in the pathogenesis of murine lupus.** *J Immunol* 1999, **162**:7241–7248.
31. Tokano Y, Morimoto S, Kaneko H, Amano H, Nozawa K, Takasaki Y, Hashimoto H: **Levels of IL-12 in the sera of patients with systemic lupus erythematosus (SLE) – relation to Th1- and Th2-derived cytokines.** *Clin Exp Immunol* 1999, **116**:169–173.
32. al-Janadi M, al-Balla S, al-Dalaan A, Raziuddin S: **Cytokine profile in systemic lupus erythematosus, rheumatoid arthritis and other rheumatic diseases.** *J Clin Immunol* 1993, **13**:58–67.
33. Akahoshi M, Nakashima H, Tanaka Y, Kohsaka T, Nagano S, Ohgami E, Arinobu Y, Yamaoka K, Niiro H, Shinozaki M, Hirakata H, Horiuchi T, Otsuka T, Niho Y: **Th1/Th2 balance of peripheral T helper cells in systemic lupus erythematosus.** *Arthritis Rheum* 1999, **42**:1644–1648.
34. Nakashima H, Inoue H, Akahoshi M, Tanaka Y, Yamaoka K, Ogami E, Nagano S, Arinobu Y, Niiro H, Otsuka T, Hiho Y: **The combination of polymorphisms within interferon-gamma receptor 1 and receptor 2 associated with the risk of systemic lupus erythematosus.** *FEBS Lett* 1999, **453**:187–190.
35. Gerez L, Shkolnik T, Hirschmann O, Lorber M, Arad G, Kaempfer R: **Hyperinducible expression of the interferon-gamma (IFN-gamma) gene and its suppression in systemic lupus erythematosus (SLE).** *Clin Exp Immunol* 1997, **109**:296–303.
36. Machold KP, Smolen JS: **Interferon-gamma induced exacerbation of systemic lupus erythematosus.** *J Rheumatol* 1990, **17**: 831–832.
37. Wandl UB, Nagel-Hiemke M, May D, Kruezfelder E, Kloke O, Kranzhoff M, Seeber S, Niederle N: **Lupus-like autoimmune disease induced by interferon therapy for myeloproliferative disorders.** *Clin Immunol Immunopathol* 1992, **65**:70–74.
38. Jacob CO, van der Meide PH, McDevitt HO: **In vivo treatment of (NZB×NZW)F1 lupus-like nephritis with monoclonal antibody to gamma interferon.** *J Exp Med* 1987, **166**:798–803.
39. Ozmen L, Roman D, Fountoulakis M, Schmid G, Ryffel B, Garotta G: **Experimental therapy of systemic lupus erythematosus: the treatment of NZB/W mice with mouse soluble interferon-gamma receptor inhibits the onset of glomerulonephritis.** *Eur J Immunol* 1995, **25**:6–12.
40. Nicoletti F, Meroni P, DiMarco R, Barcellini W, Borghi MO, Gariglio M, Mattina A, Grasso S, Landolfo S: **In vivo treatment with a monoclonal antivody to interferon-gamma neither affects the survival nor the incidence of lupus-nephritis in the MRL/lpr-lpr mouse.** *Immunopharmacol* 1992, **24**:11–16.
41. Peng SL, Moslehi J, Craft J: **Roles of interferon-gamma and interleukin-4 in murine lupus.** *J Clin Invest* 1997, **99**:1936–1946.

42. Balomenos D, Rumold R, Theofilopoulos AN: **Interferon-gamma is required for lupus-like disease and lymphoaccumulation in MRL-lpr mice.** *J Clin Invest* 1998, **101**:364–371.
43. Haas C, Ryffel B, Le Hir M: **IFN-gamma receptor deletion prevents autoantibody production and glomerulonephritis in lupus-prone (NZB×NZW)F1 mice.** *J Immunol* 1998, **160**:3713–3718.
44. Schwarting A, Wada T, Kinoshita K, Tesch G, Kelley VR: **IFN-gamma receptor signaling is essential for the initiation, acceleration, and destruction of autoimmune kidney disease in MRL-Fas(lpr) mice.** *J Immunol* 1998, **161**:494–503.
45. Clynes R, Dumitru C, Ravetch JV: **Uncoupling of immune complex formation and kidney damage in autoimmune glomerulonephritis.** *Science* 1998, **279**:1052–1054.
46. Kono DH, Theofilopoulos AN: **Genetics of systemic autoimmunity in mouse lupus.** *Int Rev Immunol* 2000, **19**:367–387.
47. Lawson BR, Prud'homme GJ, Chang Y, Gardner HA, Kuan J, Kono DH, Theofilopoulos AN: **Treatment of murine lupus with cDNA encoding IFN-gammaR/Fc.** *J Clin Invest* 2000, **106**:207–215.
48. Kurschner C, Ozmen L, Garotta G, Dembic Z: **IFN-gamma receptor-Ig fusion proteins. Half-life, immunogenicity, and in vivo activity.** *J Immunol* 1992, **149**:4096–4100.
49. Ozmen L, Gribaudo G, Fountoulakis M, Gentz R, Landolfo S, Garotta G: **Mouse soluble IFN gamma receptor as IFN gamma inhibitor. Distribution, antigenicity, and activity after injection in mice.** *J Immunol* 1993, **150**:2698–2705.
50. Kurschner C, Garotta G, Dembic Z: **Construction, purification, and characterization of new interferon gamma (IFN gamma) inhibitor proteins. Three IFN gamma receptor-immunoglobulin hybrid molecules.** *J Biol Chem* 1992, **267**:9354–9360.
51. Mulligan RC: **The basic science of gene therapy.** *Science* 1993, **260**:926–932.
52. La Cava A, Billetta R, Gaietta G, Bonnin DB, Baird SM, Albani S: **Cell-mediated DNA transport between distant inflammatory sites following intradermal DNA immunization in the presence of adjuvant.** *J Immunol* 2000, **164**:1340–1345.
53. Nakajima A, Hirose S, Yagita H, Okumura K: **Roles of IL-4 and IL-12 in the development of lupus in NZB/W F1 mice.** *J Immunol* 1997, **158**:1466–1472.
54. Schorlemmer HU, Dickneite G, Kanzy EJ, Enssle KH: **Modulation of the immunoglobulin dysregulation in GvH- and SLE-like diseases by the murine IL-4 receptor ((L-4-R).** *Inflamm Res* 1995, **44**:S194–S196.
55. Kono DH, Balomenos D, Park MS, Theofilopoulos AN: **Development of lupus in BXSB mice is independent of IL-4.** *J Immunol* 2000, **164**:38–42.
56. Santiago ML, Fossati L, Kacquet C, Muller W, Izui S, Reininger L: **Interleukin-4 protects against a genetically linked lupus-like autoimmune syndrome.** *J Exp Med* 1997, **185**:65–70.
57. Ryffel B, Car BD, Gunn H, Roman D, Hiestand P, Mihatsch MJ: **Interleukin-6 exacerbates glomerulonephritis in (NZB×NZW)F1 mice.** *Am J Pathol* 1994, **144**:927–937.
58. Finck BK, Chan B, Wofsy D: **Interleukin 6 promotes murine lupus in NZB/NZW F1 mice.** *J Clin Invest* 1994, **94**:585–591.
59. Ishida H, Muchamuel T, Sakaguchi S, Andrade S, Menon S, Howard M: **Continuous administration of anti-interleukin 10 antibodies delays onset of autoimmunity in NZB/W F1 mice.** *J Exp Med* **179**:305–310.
60. Balasa B, Deng C, Lee J, Bradley LM, Dalton DK, Christadoss P, Sarvetnick N: **Interferon gamma (IFN-gamma) is necessary for the genesis of acetylcholine receptor-induced clinical experimental autoimmune myasthenia gravis in mice.** *J Exp Med* 1997, **186**:385–391.
61. Balasa B, Deng C, Lee J, Christadoss P, Sarvetnick N: **The Th2 cytokine IL-4 is not required for the progression of antibody-dependent autoimmune myasthenia gravis.** *J Immunol* 1998, **161**:2856–2862.
62. Wogensen L, Molony L, Gu D, Krahl T, Zhu S, Sarvetnick N: **Postnatal anti-interferon-gamma treatment prevents pancreatic inflammation in transgenic mice with beta-cell expression of interferon-gamma.** *J Interferon Res* 1994, **14**:111–116.
63. Gu D, Arnush M, Sawyer SP, Sarvetnick N: **Transgenic mice expressing IFN-gamma in pancreatic beta-cells are resistant to streptozotocin-induced diabetes.** *Am J Physiol* 1995, **269**:E1089–E1094.
64. Mueller R, Krahl T, Sarvetnick N: **Pancreatic expression of interleukin-4 abrogates insulitis and autoimmune diabetes in nonobese diabetic (NOD) mice.** *J Exp Med* 1996, **184**:1093–1099.
65. Balasa B, Sarvetnick N: **The paradoxical effects of interleukin 10 in the immunoregulation of autoimmune diabetes.** *J Autoimm* 1996, **9**:283–286.
66. Nitta Y, Tashiro F, Tokui M, Shimida A, Takei I, Tabayashi K, Miyasaki J: **Systemic delivery of interleukin 10 by intramuscular injection of expression plasmid DNA prevents autoimmune diabetes in nonobese diabetic mice.** *Hum Gene Ther* 1998, **10**:1701–1707.
67. Balasa B, Van Gunst K, Jung N, Katz JD, Sarvetnick N: **IL-10 deficiency does not inhibit insulitis and accelerates cyclophosphamide-induced diabetes in the nonobese diabetic mouse.** *Cell Immunol* 2000, **202**:97–102.

commentary

review

reports

primary research