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Cytokine-Induced Autoimmune Disorders

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Summary

Cytokines are now commonly used in the treatment of many conditions, especially cancer, haematological malignancies and chronic viral hepatitis. With some of these cytokines, clinical induction and/or exacerbation of autoimmune manifestations have been observed. This has been the case with interferon-α and interferon-γ, interleukin-2 and some colony-stimulating factors. All known biological and clinical autoimmune features have been observed but thyroid abnormalities have been particularly frequent. Some of these manifestations appear to be related to the effect of these exogenous cytokines on the T helper cell (T_H) $1/T_H2$-cytokine balance and the regulatory properties of these cells. Patients with a history of underlying autoimmune disease or baseline serological abnormalities should be monitored for autoimmunity when treated with certain T_H1 or T_H2-inducing cytokines.

Cytokines are now used in the treatment of an increasing number of diseases. This has been possible because of rapid progress in the discovery of different cytokines and in the biotechnology techniques allowing their production to be of high quantity and purity.

In the early stages of the development of cytokine treatment, diseases were selected as targets based on the limitations of current treatment rather than a scientific rationale. Thus, cancer and haematological malignancies were selected first. Unpredicted adverse effects were observed. Indeed, the therapeutic administration of cytokines has assisted in clarifying some concepts regarding their role in host defence. In a number of cases, autoimmunity was detected. With time, the situation has been clarified and various explanations for this observation have emerged. In particular, the classification of cytokines according to their regulatory properties has been useful to explain some of these manifestations.

1. Spontaneous or Acquired Autoimmune Diseases

Lesions seen in human autoimmune conditions have many features in common. Lesions are under the control of endogenous cytokines and, as such, are able to respond to exogenous cytokines.

1.1 Common Features of Autoimmune Lesions

Endothelial cell swelling leading to the formation of high endothelium venules is one of the earliest pathological findings of autoimmune lesions (fig. 1). *In vivo*, these changes are seen with interleukin-2 and are associated with an increased expression of adhesion molecules leading to increased cell migration.[1] Inflammatory cells, predominantly CD4+ T lymphocytes with a memory phenotype, accumulate around vessels. Persistence of the infiltrate is associated with progressive changes in the organ structure and function. Disease secondary to function failure becomes clinically apparent only when a large proportion of the organ has been destroyed. When the target organ has been eliminated, active inflammation slowly disappears. Conversely, persistence of chronic inflammation is associated with waves of clinical activity where the release of cytokines is implicated.

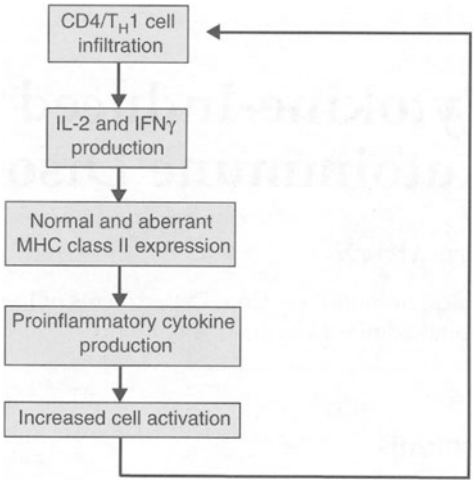

Fig. 1. Early features of T cell–mediated autoimmune reaction. *Abbreviations:* IFN = interferon; IL = interleukin; MHC = major histocompatibility complex; T_H = T helper cell.

1.2 Contribution of the Underlying Disease

The lack of an identified causative agent in spontaneous autoimmune diseases remains the major limitation for early diagnosis and treatment before organ dysfunction occurs. Although major progress has been made in defining risk factors, such as genetic background, often the precise aetiology of the autoimmunity remains an unresolved clinical problem.

Treatment with some, but not all, cytokines can lead to autoimmunity. However, the contribution of the disease itself must be considered. For example, hepatitis C is often associated with Sjögrens syndrome and lymphocytic infiltration of the salivary glands;[2] this infection is also a common cause of cryoglobulinaemia.[3,4] The association of autoimmune disorders with autoantibodies of various specificities is frequent and includes rheumatoid factors, and antinuclear and antithyroid autoantibodies.[5] Spontaneous autoimmune diseases are more frequent in women and in those with pre-

existing autoantibodies and/or an increased frequency of human leucocyte antigen (HLA)-DR_4 and DR_3 phenotypes. Similar findings are observed with cytokine-induced thyroid abnormalities.[6,7] Thus, in a pre-existing, multifactorial background, exogenous cytokines may play the role of a cofactor in the development of an autoimmune disorder.

Clinical observations in line with those described above, such as the improvement of rheumatoid arthritis during pregnancy, have indicated that even long-standing inflammatory disease can improve and go into remission, presumably under the action of nonspecific factors such as cytokines.[8] Such concepts may lead to new therapeutic approaches to controlling chronic inflammation and autoimmunity without a specific action at the level of the antigen. Conversely, some cytokines described below have the opposite effect, inducing chronic inflammation and autoimmunity. These adverse effects could be explained by examining the balance of regulatory cytokines.

2. T Cell Subsets and Cytokine Production

CD4+ T cells represent the major cell population involved in an autoimmune reaction. The cytokine patterns of T cell clones have been examined. More recently, the results of such studies have been extended to determine the cells infiltrating the lesion itself.

2.1 T Helper Cell (T_H) Subsets and Diseases

Studies with murine T cell clones established that interleukin-4 and interleukin-5 are mostly produced in conjunction with interleukin-6, interleukin-10 and interleukin-13 by T helper cell (T_H) 2 clones, whereas interleukin-2 and interferon-γ are produced by T_H1 clones[9] (fig. 2). Results in animal models have indicated the role of T_H1 cells in delayed-type hypersensitivity and that of T_H2 cells in allergy and some parasitic infections. The same dichotomy was later applied to human T cells.[10] However, in the human system, the classification is not as clear since monocytes represent a major source of interleukin-10.[11]

With respect to allergy, CD4+ T cells infiltrating the conjunctiva of patients with vernal conjunctivitis or allergen-specific T cell clones obtained from atopic patients were essentially of the T_H2 type.[12]

In chronic inflammation, CD4+ T cells infiltrating the thyroid gland of patients with autoimmune thyroid disease are mostly of the T_H1 type. Similar observations have been made in diabetes mellitus, at least in the mouse model.[13] In situations where the antigen is known, such as tuberculosis or leprosy, T cell clones specific to the bacterial antigens, but also for heat shock proteins (HSP), produce large amounts of interferon-γ with no interleukin-4.[14]

T_H1 cytokine-producing cells are implicated in chronic allograft rejection mediated by the activation of cytotoxic T cells by T_H1 cytokines. Administration of exogenous cytokines may lead to termination of tolerance to both normal organ cells and tumour cells.[15]

2.2 Control of the T_H1/T_H2 Balance

An important feature of T_H1 and T_H2 cells is the ability of one subset to regulate the activities of the other. The balance between these cells can

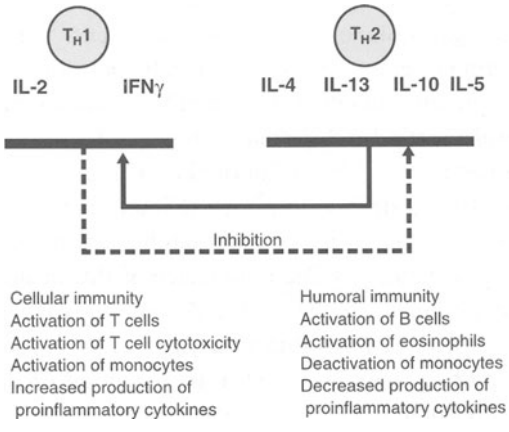

Fig. 2. T helper cell (T_H) 1 and T_H2 cytokines and immune regulation. *Abbreviations:* IFN = interferon; IL = interleukin.

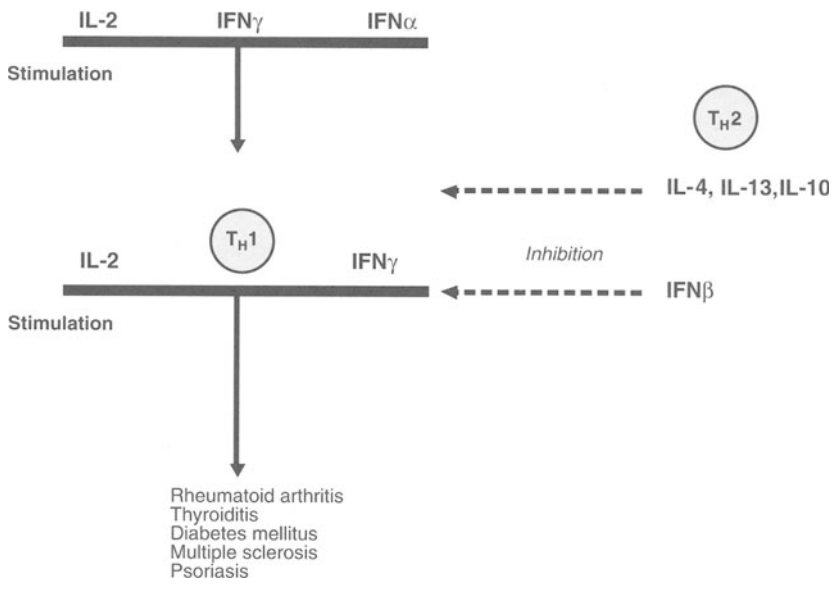

Fig. 3. Exogenous cytokines and disease. *Abbreviations:* IFN = interferon; IL = interleukin; T_H = T helper cell.

play a major role in the type of disease manifestation observed. The establishment of this balance depends on many factors including the antigen structure, the antigen-presenting cells and the cytokine environment.[16] This feature is critical for the understanding of adverse effects induced by cytokines.

T cells from healthy individuals produce T_H1 cytokines in response to mycobacterial antigens and T_H2 cytokines in response to allergens.[17] Furthermore, culture of normal T cells performed in the presence of either interferon-γ or interleukin-4 results in the development of clones of T_H1 or T_H2, respectively.[17] Both interleukin-4 and interleukin-10 are strong inhibitors of interferon-γ production whereas interferon-γ inhibits interleukin-10 production.[11] The importance of this balance can be demonstrated by the disease associations observed when a dysfunction occurs (fig. 3). More importantly, the persistence or induction of this dysfunction by some exogenous cytokines may further contribute to the induction or exacerbation of certain diseases.

3. Consequences of Cytokine Imbalance

T cell cytokines have major regulatory functions. Increased T_H2 activity has been associated with allergic conditions and increased T_H1 activity with chronic inflammation (fig. 3).

3.1 Imbalance Toward T_H1

T cell–derived cytokines such as interleukin-2 and interferon-γ contribute to the induction of autoimmunity and chronic inflammation.[18] Interleukin-2 appears to interfere with T cell tolerance, reversing functional non-responsiveness and enabling non-deleted T cells that bear a potentially autoreactive T cell repertoire to cause autoimmunity.[19] When considering the early phases of an autoimmune disease, interferon-γ is critical for the induction of HLA-DR expression and antigen presentation, for the production of proinflammatory cytokines and for the inhibition of interleukin-10 production by monocytes.[11,20] Later in the disease process, cytokines such as tissue necrosis factor (TNF) α and granulocyte-macrophage colony-

stimulating factor (GM-CSF) contribute to the persistence of the increased major histocompatibility complex (MHC) class II expression (fig. 1).

The T_H1 cytokines activate the production of high levels of proinflammatory cytokines such as interleukin-1, TNFα and interleukin-6. These cytokines, mainly produced by monocytes/macrophages, then activate endothelial cells and mesenchymal cells, such as fibroblasts, leading to the production of growth factors and proinflammatory cytokines. Such soluble factors include leukaemia inhibitory factor (LIF), interleukin-6, granulocyte colony-stimulating factor (G-CSF), GM-CSF and interferon-α.[21] When combined, these factors play a major role in chronic inflammation and organ degradation. Such cytokines enhance T cell–mediated immunity, contributing to autoreactivity and allograft rejection as well as thrombosis.[22]

As a consequence, administration of these cytokines will induce T cell–mediated immune reactions with a T_H1 and proinflammatory pattern.[23] This will either induce autoimmune features and/or activate ongoing or latent diseases (fig. 3).

3.2 Imbalance Toward T_H2

Increased levels of immunoglobulin E (IgE) and allergy are the major conditions associated with T_H2 imbalance.[12] In addition, the T_H2 cytokines interleukin-4, interleukin-13 and interleukin-10 can be considered as anti-inflammatory cytokines as they inhibit interleukin-1, interleukin-6, TNFα, interleukin-8 and prostaglandin E_2 production by monocytes. Interferon-β shares some of these effects *in vitro* and in patients by inhibiting some of the effects of interferon-γ.[24,25] These inhibitory effects on the production of destructive cytokines provide a strong rationale for the use of interleukin-4, interleukin-13 and interleukin-10 in chronic inflammatory diseases. Studies in animal models have confirmed this; these T_H2 cytokines were able to not only prevent but, more importantly, control ongoing disease in models of multiple sclerosis, rheumatoid arthritis and diabetes mellitus.[13]

In clinical studies with T_H2 cytokines, no autoimmune features have appeared in patients with malignancies treated with interleukin-4 and no such tendency has been seen in ongoing studies with interleukin-10 in inflammatory bowel diseases. However, T_H2-related adverse effects could be expected. Conversely, T_H2 cytokines could be useful to control some T_H1-induced adverse effects.

4. Treatment with Cytokines and their Autoimmune Adverse Effects

The list of cytokines ready for clinical use has been growing quickly but concern remains over their autoimmune adverse effects. As with any adverse effect observed with a new compound, the interpretation of the underlying mechanisms is often difficult. The frequency of adverse effects is obviously related to the properties of the molecule itself, dosage regimen and mode of administration but also to the underlying disease and the size of the population which has been treated. Among the cytokines already in clinical use, interferon-α has been the most widely used, particularly in patients with chronic viral hepatitis. Because of its widespread use, among other reasons, interferon-α in chronic viral hepatitis has been associated with the largest number of adverse effects of any of the cytokines.

4.1 Interferon-α

The major indications for the use of interferon-α have been the treatment of cancer, mostly renal cell carcinoma and melanoma, haematological malignancies and type B and C chronic viral hepatitis.[26] Currently, interferon-α is the only drug of documented efficacy in the treatment of viral hepatitis. Interferon-α has also been used in many other conditions. The large number of patients with various diseases who have been treated, now in the range of over 10 000,[27] allows a good estimation of the adverse effects of interferon-α and a better interpretation of their incidence (table I).

Induction of autoimmune events, including the entire list of all manifestations of autoimmunity and associated diseases,[85] appears to be frequent with interferon-α treatment.[86] This has led to the

Table I. Adverse effects of interferon-α therapy

Autoreactivity against blood cells: haemolytic anaemia;[28,29] thrombocytopenia[30-34]
Autoreactivity against blood factors: acquired factor VIII inhibition,[35] induction of lupus anticoagulant,[36] induction or exacerbation of cryoglobulinaemia[37,38]
Skin diseases: vitiligo (alone or with scleroderma),[39] flare of psoriasis,[40,41] induction of anti-epidermis antibodies,[42,43] paraneoplastic pemphigus,[44] induction of sarcoid nodules[45]
Autoimmune diseases: thyroid diseases[46-53] (e.g. thyroid autoantibodies, hypothyroidism, hyperthyroidism and Graves' disease and thyroiditis; diabetes mellitus[54,55] caused by induction of anti-insulin antibodies, induction of anti–glutamic acid decarboxylase antibodies, insulin-dependent diabetes mellitus and insulin allergy
Connective tissue diseases: induction of anti-nuclear and anti-DNA antibodies;[36,56-58] induction or flare of rheumatoid, psoriasis, lupus, spondylarthropathy or other unclassified arthritis,[59-61] systemic lupus erythematosus,[36,56-58] Sjögren's syndrome,[2] dermatomyositis or polymyositis,[62,63] myasthenia gravis with anti–acetylcholine receptor antibodies,[64-67] Guillain-Barré syndrome[68]
Hepatic diseases: accentuation of viral hepatitis,[7] induction or accentuation of autoimmune hepatitis,[69-75] induction of anti–smooth muscle autoantibodies,[76,77] induction or exacerbation of primary biliary cirrhosis[78,79]
Graft survival:[80-84] graft-versus-host disease after bone marrow transplantation, allograft rejection

recommendation to exclude patients with concomitant, clinically overt autoimmune disease when considering the use of interferon-α for the treatment of viral hepatitis.

These autoimmune adverse effects range in severity from the mere presence or induction of autoantibodies with no clinical consequence to the most severe autoimmune disease. The pathogenicity of autoantibodies is often unclear and is far from being always associated with disease manifestations, as with the spontaneous autoimmune diseases. The targets of these antibodies include blood cells (red cells, leucocytes, platelets), coagulation factors (factor VIII, lupus anticoagulant), immunoglobulins (rheumatoid factor with or without cryoglobulin activity), intracellular components (nucleus, enzymes), hormones (thyroid, insulin) and skin (epidermis).[42,43] In particular, exacerbation of hepatitis C–related cryoglobulinaemia has been described as leading to severe clinical consequences including polyneuritis and even death.[37,38] Although treatment with interferon-α is usually helpful,[87,88] this has to be taken into account when considering treatment since an association with hepatitis C is found in almost 50% of all cases of mixed cryoglobulinaemia.[3]

Blood cells and coagulation factors are frequent targets of autoantibodies and manifestations include idiopathic or autoimmune haemolytic anaemia[28,29] and thrombocytopenia.[30-34] Some patients with haemophilia A and hepatitis C receiving treatment with interferon-α have developed antibodies to factor VIII.[35] Induction of lupus anticoagulant has been implicated in the development of thrombotic events during treatment with interferon-α.

Thyroid abnormalities appear to be the most common of the organ-specific diseases;[46,47] the exact incidence remains unclear. In a survey of 11 241 patients with hepatitis, 71 developed autoimmune thyroid disease during interferon-α treatment.[27] During combined interferon-α and interleukin-2 therapy, this figure was even higher. Various thyroid abnormalities have been observed[48] with around 50% of patients developing hypothyroidism, 30% hyperthyroidism and 20% a biphasic (hyperthyroidism followed by hypothyroidism) pattern.[49] These patterns include the 2 ends of the spectrum of thyroid disorders, ranging from patients clinically and biochemically hypothyroid but negative for thyroid autoantibodies to patients remaining euthyroid but with thyroid autoantibodies.[50] Patients developing hyperthyroidism with Graves' disease may require long term antithyroid medications.[51,52]

Idiopathic thyroiditis is a very common autoimmune disease, often associated with Sjögren's syndrome and resulting in the lymphocytic infiltration of the exocrine glands. It is important to keep in mind that such features are commonly found in patients with hepatitis C in the absence of any treatment with cytokines.[2]

Induction of insulin antibodies and onset of insulin-dependent diabetes with increased anti–glutamic acid decarboxylase antibody levels have been observed during interferon-α therapy.[54] This

occurred in 10 of the 11 241 patients included in the survey described above.[27] In a patient already receiving insulin, induction of insulin antibodies and insulin allergy have been observed during treatment of renal cell carcinoma with interferon-α.[55]

Among other autoimmune disorders, interferon-α has been found to be responsible for the induction or flare of various types of inflammatory arthritis associated either with rheumatoid arthritis, psoriasis, lupus, spondylarthropathy or as yet unclassified arthritis.[56-61] Cases of interferon-α–induced dermatomyositis and polymyositis have been described, mostly in patients with chronic hepatitis C.[62,63] Similarly, cases of myasthenia gravis with anti–acetylcholine receptor antibodies[64-67] and Guillain-Barré syndrome have been observed.[68]

Interferon-α treatment has been reported to induce features of systemic lupus erythematosus, including severe cases involving nephropathy, cerebral vasculitis and chorea.[56-58] Vitiligo, either alone or associated with scleroderma, has been observed in patients treated with interferon-α and interleukin-2.[39] Flare of psoriasis has also been cited as a reason for discontinuation of interferon-α treatment[40,41] and rare cases of paraneoplastic pemphigus have been described.[44] Although not fully classified as an autoimmune disease, induction of sarcoidosis and sarcoid nodules have been observed with interferon-α.[45]

Interference with graft survival has been a major consequence of interferon-α treatment. Graft-versus-host disease following therapy for relapsed leukaemia post-allogeneic bone marrow transplantation has been reported, as well as allograft rejection following treatment of hepatitis C after liver, and after renal, transplantation.[80-84]

An area of major concern is the possible induction or accentuation of autoimmune hepatitis which can lead to liver failure.[69-71] In this case, the contribution of the viral and autoimmune components is particularly difficult to dissociate;[72,73] some serological markers may be useful.[74,75] Indeed, interferon-α therapy has been associated with the induction of high titres of smooth muscle autoantibodies which became negative after discontinuation of therapy;[76] the same adverse effect has been observed in patients treated for haematological disorders.[77] Induction or exacerbation of primary biliary cirrhosis with specific autoantibodies has also been described in patients with hepatitis C.[78,79]

4.2 Interleukin-2

This cytokine was the first factor used as a recombinant product. In early clinical studies, interleukin-2 was used for the *ex vivo* culture of autologous peripheral blood lymphocytes before re-injection; these are referred to as lymphokine activated killer (LAK) cells. Tumour-infiltrating lymphocytes have been cultured the same way. Treatment with interleukin-2 has resulted in reduction of metastases in patients with extensive melanoma and renal cell carcinoma.[89] Most recent studies have used interleukin-2, either alone or combined with other cytokines, mainly interferon-α.

One of the major adverse effects of interleukin-2 is the acute accumulation of body fluid related to a capillary leak syndrome.[90] *In vivo* studies showed activation of complement and skin vascular endothelial cells by proinflammatory cytokines, the production of which was stimulated by interleukin-2.[1,91,92] When interleukin-2 is used on a long term basis, such an effect may contribute to the migration of inflammatory cells, mostly lymphocytes, to the perivascular site. A number of adverse effects observed with interferon-α have also been described with interleukin-2,[93] including the induction of chronic arthritis,[94] myositis,[63,95] thyroid manifestations[96] and induction of various antibodies.[50,97]

Carpal tunnel syndrome has been observed in patients treated with interleukin-2 and interferon-α in combination, most probably in association with accumulation of body fluid.[98] Skin manifestations are very common in patients treated with interleukin-2[99] and include allergic reactions with angioneurotic oedema and urticaria associated

with activation of neutrophils and complement,[100] and local[101] and systemic hypersensitivity reactions, in particular to iodinated contrast products and antineoplastic therapy drugs.[102-104] Rapid exacerbation of scleroderma was observed in a patient treated for renal cell carcinoma with interleukin-2 and LAK cells.[105]

4.3 Interferon-β

Interferon-β is currently used for the treatment of multiple sclerosis.[106] Although the clinical experience is not as large as with interferon-α, autoimmune manifestations do not appear to be a frequent concern.[106]

4.4 Interferon-γ

The experience with interferon-γ indicates its autoimmune potential.[36] In patients with hepatitis C, thyroid dysfunction was uncommon in comparison with the induction of antinuclear antibodies.[107] Induction of sarcoidosis has been observed with interferon-γ therapy.[108] In patients with lepromatous leprosy, prolonged treatment with interferon-γ induced erythema nodosum.[109] In patients with psoriasis arthritis or spondylarthropathy, increased arthritis activity was observed. In patients with rheumatoid arthritis, no benefit was demonstrated from interferon-γ therapy but in some cases induction of antinuclear antibodies was seen.[110,111] In some patients with multiple sclerosis, treatment with interferon-γ led to increased disease activity.[112]

4.5 Colony-Stimulating Factors

The family of CSFs includes interleukin-3 or multi-CSF, G-CSF and GM-CSF. Such cytokines are used for the stimulation of bone marrow precursors after spontaneous or antineoplastic therapy–induced bone marrow depression.

Most autoimmune manifestations were observed with G-CSF or GM-CSF. These have been used in the treatment of patients with rheumatoid arthritis, particularly Felty's syndrome, defined as the combination of rheumatoid factor–positive destructive rheumatoid arthritis, severe neutropenia and splenomegaly. Improvement of the neutropenia was observed, sometimes with increased thrombocytopenia and anaemia.[113] Some patients showed increased arthritis activity.[114-120] However, such flare-ups were not a constant observation.[121]

5. Conclusion

Some of the autoimmune manifestations induced with cytokines could have been predicted with the current knowledge regarding their role in the regulation of normal homeostasis. The presence of a history of underlying autoimmune disease or baseline serological abnormalities in these patients suggests that such treatment can lead to the exacerbation of an underlying subclinical autoimmune process. Such patients should therefore be either excluded or closely monitored for autoimmunity when treated with some T_H1-derived or T_H1-inducing cytokines[122] (fig. 3). Conversely, T_H2-derived or T_H2-inducing cytokines may prove helpful to treat some of the cytokine-induced autoimmune disorders.[123]

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