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COMMENTARY

INTERFERON-γ: MECHANISM OF ACTION AND THERAPEUTIC POTENTIAL

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Interferon-γ (IFN-γ) is a cytokine originally discovered by virtue of its ability to inhibit virus replication in cells. Although it shares this property with the other interferons (α and β), and it may play a role in nonspecific resistance to virus infections, its true role in physiology and pathology seems to extend far beyond this function as an interferon proper. At the cellular level, IFN-γ exerts its action through a membrane receptor different from that used by other interferons [1, 2]. Whether binding of IFN-γ to its receptor is sufficient to transfer its signal to the cell, or whether IFN-γ also needs to be internalized for biological activity, is not fully established [3]. Clearly, the presence of a high-affinity membrane receptor alone is not sufficient to render cells sensitive for IFN-γ since mouse cells transfected with the human IFN-γ receptor gene can bind human IFN-γ but fail to respond to it [4]. This means that other, yet to be defined, species-specific factors are required which assist the receptor in transduction of the IFN-γ message.

Although most cell types seem to possess receptors and can respond in some way to IFN-γ, the cells which have attracted most of the current interests as targets for this cytokine are macrophages and macrophage-like cells which are part of the immune system, e.g. endothelial cells, dendritic cells, Langerhans cells, and nursing cells. On such cells IFN-γ exerts a variety of effects which may be summarized under the heading "activation" [5]. Macrophages fulfill various regulatory and effector functions in the immune system. Therefore, an important role can be assigned to endogenous IFN-γ in the ontogenesis and phenomenology of the immune response. In addition, macrophage-like cells (sometimes designated by specific names) occur in various organs (e.g. pancreas, hypophysis, and liver) with specific functions other than mounting an immune response. It is possible that, by activating these cells, IFN-γ affects the physiology of these organs.

Another difference between IFN-γ and other interferons is the fact that the spectrum of cells which produce IFN-γ is more narrow, being limited to T-lymphocytes and NK-cells [6, 7]. Production of IFN-γ occurs only when these cells are activated, a process which is triggered by exogenous agents (e.g. bacteria, viruses, and antigens), and regulated by a large set of endogenous factors (see, for example, Refs. 8–10). Cytokines other than IFN-γ constitute an important group of factors able to regulate IFN-γ production: the other interferons, the interleukins, the lymphotoxins [including tumor necrosis factor (TNF)] and others. In addition, one aspect of the actions of IFN-γ on cells is that it directly synergizes with other cytokines, in particular TNF.

Table 1. Effects of IFN-γ on phagocytic and/or antigen-presenting cells (APC)

Induces increased expression of MHC/Class-II antigen
Induces production by macrophages of
IL-1 and TNF
H_2O_2
Platelet activating factor
Proteases (uPA)
Pterin
Enhances production of complement factors
B, C2 and C1-inhibitor
Enhances tumoricidal capacity
Inhibits growth of intracellular bacteria
(Rickettsia; Legionella; Mycobacterium; Chlamydia)
Inhibits growth of intracellular parasites *(Toxoplasma)*
Inhibits growth of intracellular molds *(Histoplasma capsulatum)*
Protects monocytes against lymphokine-activated killer (LAK) cell-mediated lysis
Induces APC properties in B-cells

It is clear, therefore, that the role of IFN-γ cannot be comprehensively conceptualized without taking into account its many interconnections with other cytokines. A classical example is the well-established fact that interleukin-2 (IL-2, a T-cell product) promotes the production of IFN-γ [11]. However, the production (as well as action) of IL-2 is itself regulated by other cytokines, e.g. IL-1 and IL-6 [12–14]. Remarkably, however, these cytokines are themselves products of macrophages and macrophage-like cells [15], and their production is regulated by exposure of these cells to IFN-γ. Thus, feed-back loops exist which govern the overall level of production of IFN-γ and, in fact, of all cytokines involved in the network.

Functions of IFN-γ

Table 1 summarizes the many effects of IFN-γ on macrophages and macrophage-like cells. Some of these effects may give us a hint for answering the question why IFN-γ is indispensable in the body.

IFN-γ seems to be the principal if not the only cytokine able to induce Class-II antigen expression [16]. Since Class-II major histocompatibility complex (MHC) antigen expression is considered to be necessary for antigen-processing cells to be able to

present antigenic epitopes to the immune system, we may conclude that antigen-specific immune responses would be impossible without IFN-γ.

Besides their antigen presenting function, necessary for initiation and regulation of the antigen-specific immune response, macrophages fulfill effector functions in host defenses, in particular killing of microorganisms (bacteria, viruses, parasites) and tumor cells. Some microorganisms enter the macrophage as part of their normal life cycle; other, intrinsically extracellular microorganisms are ingested by macrophages only to be killed. The mechanisms of intracellular killing are complex; suffice it to say that IFN-γ enhances the ability of the macrophage to ingest and to kill certain (but not all) species of microorganisms [5]. Macrophages also have the ability to kill other cells (e.g. cancer cells) by entering into contact with them or by secreting cytotoxic substances [17].

While performing these killing functions, or independently from them, IFN-γ-activated and duly triggered macrophages produce an array of substances (cytokines, arachidonic acid derivatives, histamine-like substances, complement factors) which trigger inflammation [18]. Inflammation is a complex, integrated tissue reaction, comprising vascular phenomena (vasodilatation, increased permeability, blood coagulation), cell movement (in particular leukocyte infiltration), tissue destruction (e.g. through protease release) and cell multiplication (granuloma formation, fibrosis, tissue remodelling and scar formation) [19]. In all these phenomena, the macrophage is generally considered to be the central player. Therefore, the principal activator of macrophages, IFN-γ, can also be considered to be the master key to inflammation (Fig. 1).

Two-sidedness of IFN-γ actions

The multiplicity and complexity of activities of IFN-γ (and of cytokines in general) imply that the net result on a particular physiological phenomenon or parameter will often go counter to expectation. Some of the activities may indeed counteract each other, and the net result will depend, therefore, on which activity predominates in the particular system being considered. Some examples are as follows.

Two-sided effects on the ontogenesis of specific immune responses. IFN-γ can boost as well as suppress antibody formation. Specifically, it causes a strikingly selective induction of IgG2a production by lipopolysaccharide (LPS)-stimulated resting B-cells *in vitro*. On the other hand, it inhibits expression of other Ig isotypes (IgG2b, IgG1, IgE) [20]. *In vivo* observations confirm this duality [21]. Production of IFN-γ, therefore, may explain the selective stimulation of certain Ig isotypes seen in infections with viruses or parasites.

IFN-γ may also have a net positive or negative effect on T lymphocyte proliferation and activity depending on the experimental system that is chosen. Accordingly, anti-IFN-γ antibody may suppress allograft reactivity by T lymphocytes [22] but may remove suppression of normal B and T cells from mice with graft-versus-host disease [23]. IFN-γ may inhibit *in vitro* proliferation of TH2 cells and immature thymocytes [24, 25] but may stimulate growth of T cells from other origins [26].

Two-sided effects through macrophage activation. Macrophage activation, one of the principal actions of IFN-γ, may in itself have two-sided repercussions on a variety of phenomena. A striking example is the outcome of an infectious disease. Failure of macrophages to be properly activated will be associated with inability of the body to eliminate the infectious agent. As a result the infectious agent either may overwhelm the body by massive multiplication, leading to death by anergy, or it may persist in relatively low numbers, causing chronic debilitating disease.

The other side of the coin is that excess macrophage activation, being the main pathway of inflammation, may cause excessive inflammation. In these instances, production of IFN-γ may be to the disadvantage of the host.

It is of relevance to note here that, although IFN-γ is probably the most complete and the most powerful macrophage activator, it is not the only one. Other mediators including TNF, colony-stimulating factors and certain hormones may trigger certain activities of macrophages as effectively as IFN-γ or even more effectively. For example, it has been found that macrophages stimulated *in vitro* with IFN-γ inhibit the replication of *Toxoplasma gondii* but not that of *Listeria monocytogenes* or *Salmonella thyphimurium*, whereas macrophages activated *in vivo* with bacillus Calmette-Guérin + purified protein derivative (BCG + PPD) do kill all named microbes [27]. IFN-γ may even inhibit antibacterial activity of macrophages: TNF-treated macrophages have been shown to have an increased capacity to kill *Mycobacterium avium* complex, whereas IFN-γ-treated macrophages are less effective killers than non-treated ones [28].

Protective and destructive effects on normal fibroblasts. IFN-γ, as its name implies, may interfere with viral infections of cells and protect cells against virus-induced cytopathic effect. This is also the case for normal mouse embryonic and adult tissue fibroblasts. However, at doses higher than those required for antiviral activity IFN-γ induces a suicide reaction in these cells [29]. This IFN-γ-induced cell death is enhanced in the presence of other cytokines (e.g. IL-1) or bacterial products.

Paracrine and endocrine effects may oppose each other. IFN-γ, as well as other cytokines, have local (so-called paracrine) effects. When released in a certain excess, their concentration in the general circulation may reach levels, such that they may affect the function of distant organs (endocrine effect). A generally recognized example is that of IL-1 which is considered a hormone as much as a cytokine. Low levels of IL-1 in the blood stream cause fever (by its effect on the anterior hypothalamus [30]), an acute phase response (by its direct and indirect effects on hepatocytes [30]), and ACTH release (by its direct and indirect effects on the anterior hypophysis [31]). Similar situations may occur with other cytokines, including IFN-γ, and local (paracrine) effects may be antagonized by

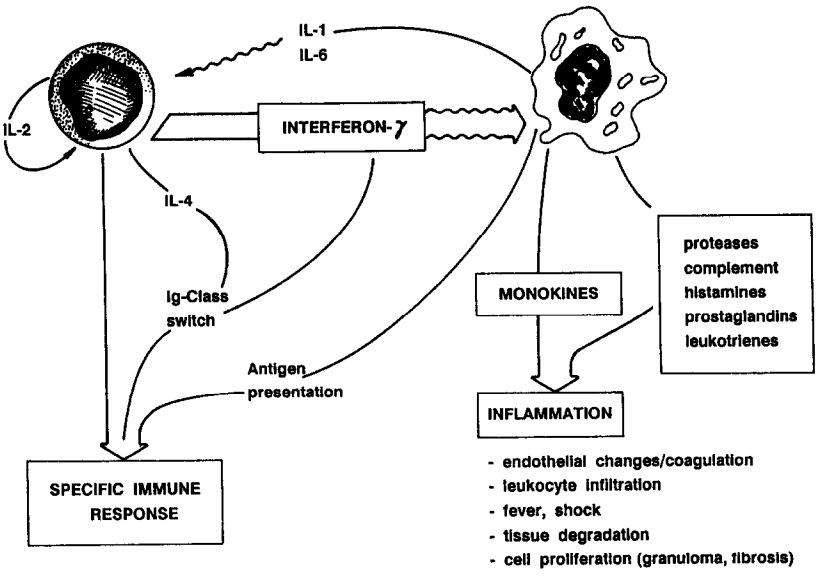

Fig. 1. Schematic representation of the key role of IFN-γ in inflammation and immunity. IFN-γ is produced by T lymphocytes after stimulation with antigen. Other cytokines (IL-1, IL-2, IL-6) may be required for optimal IFN-γ production. IL-4 is another product of T lymphocytes and, together with IFN-γ, this factor guides immunoglobulin isotype switch. B lymphocytes and mononuclear phagocytic cells represent a major group of target cells for IFN-γ. Activation of the latter cells results in more efficient killing of microbes and tumor cells, enhanced secretion of inflammatory mediators and monokines, and improved capacity to function as antigen presenting cells. Monokines (TNF, IL-1, IL-6), in turn, participate in the stimulation of T lymphocytes, thereby regulating IFN-γ production. In addition, they regulate a large number of processes that determine the onset and severity of inflammatory responses.

effects generated through the endocrine pathway. This mechanism has been proposed as one possible way to explain paradoxical observations regarding the role of IFN-γ in inflammation [32].

Hypo*reactivity may be a hallmark of* hyper*stimulation.* Early studies on *in vivo* production of interferon have revealed a phenomenon called hyporeactivity [33]. Typically, an experimental animal given two injections of LPS or virus within a time interval of 24–72 hr produces much less circulating interferon after the second than after the first injection. Despite many studies, the true mechanism(s) of hyporeactivity remains largely unknown (for a review see Ref. 34). An interesting suggestion is that an interferon controls its own synthesis by a negative feed-back loop. Another suggestion based on some exprimental support is that another factor, co-induced with interferon, causes the inhibition; perhaps this so-called "serum hyporeactive factor" [35] is to be identified with one of the cytokines that have since been fully characterized. One may also speculate that similar mechanisms which control production of type α/β interferons are operational to control the synthesis of IFN-γ. An implication of this may be that one may be misled when having to interpret an observed lack of production of IFN-γ (or other cytokines) in a given clinical entity such as a chronic infectious disease. One may easily be tempted to attribute failure of the host to overcome his disease to his lack of cytokine production, and to overlook the possibility that, independently and more importantly, this failure may be a hallmark of chronic overstimulation of the system. Whichever of the two possibilities outweighs the other will determine the best therapeutical approach.

Perspectives for therapy

Diseases characterized by defects in production of IFN-γ have been looked for; it is probably fair to say that diminished production of IFN-γ occurs in some rather common diseases, e.g. multiple sclerosis [36] or acquired immune deficiency syndrome (AIDS) (for review see Ref. 37), but that it does not constitute an essential pathogenetic element in these diseases. A similar situation has occurred in the case of IFN-α; nevertheless, at least one disease, hairy cell leukemia, has been identified in which this IFN has a therapeutical effect so distinctive that it suggests a specific defect in either production of, or sensitivity to, the cytokine. Therefore, we should not exclude the possibility that indiscriminate therapeutic trials will one day reveal the existence of one or more diseases that are essentially due to a lack of IFN-γ production.

Meanwhile, speculation and experimentation aimed at developing an IFN-γ-based therapy capitalize on the idea that a supplement of IFN-γ may afford benefit to patients with diseases in which the immune response is somehow involved. However, from the considerations outlined above, it should be clear that there is ample space for speculation that blocking IFN-γ may also help to control diseases,

Table 2. IFN-γ: Possible therapeutic perspectives

IFN-γ therapy
—Recovery from chronic infections (e.g. leishmaniasis)
—Adjuvant to vaccination
—Control of IgE allergy
—Adjuvant to TNF for cancer therapy
—Prevention of delayed type hypersensitivity (DTH) reactions
—Auto-immunity (lupus? arthritis? multiple sclerosis?)
—AIDS?
IFN-γ antagonists
—Septic shock
—Organ transplantation
—Inflammatory complications of acute infection
—Auto-immunity (lupus? arthritis? multiple sclerosis?)
—AIDS?

especially those with a strong inflammatory component (Table 2).

IFN-γ as an adjuvant to immunization. It has been shown that administration of IFN-γ during an immunization procedure can result in higher antibody titers [38]. This is a potentially important observation, as it is well recognized that certain vaccines, when administered without adjuvants, provide inadequate protection. Also, many adjuvants that are currently in use, have pharmacological disadvantages making them unsuitable for use in humans, so that their application remains confined to veterinary medicine.

Another potential field of application is desensitization of patients with allergy. Recently, cytokines, especially IFN-γ, have been recognized to steer Ig isotype switches, a process of paramount importance in the pathogenesis of IgE-mediated allergy [21]. It is probably naive to think that administration of IFN-γ will be helpful as such to desensitize allergic patients to particular antigens. However, the implication of the cytokine in allergy certainly merits further investigation.

IFN-γ as a panacea in cancer therapy? Clinical trials with classical (α/β) interferons and with TNF have taught that cytokines are *not* panaceas for cancer therapy. Nevertheless, efforts to insert IFN-γ into therapeutical trials are being continued. By itself it does not seem to exert much of an antitumor effect. However, when combined with other cytokines, in particular TNF, it enhances the *in vitro* anticellular effectiveness of these cytokines [39, 40]. A severe problem encountered in trials with TNF seems to be the generalized toxicity. The pervading idea is that one may succeed in designing combined-cytokine regimens which have limited toxicity, but are nevertheless effective [41].

An aspect of cytokine involvement in cancer that is often overlooked is the fact that certain tumors may continuously stimulate *in vivo* production of cytokines. These may be responsible for fever, malaise and cachexia. One cytokine, in particular, is held responsible for this effect, i.e. TNF [42]. However, IFN-γ, by itself or by synergizing with TNF, may also be instrumental in bringing about the general deterioration seen in cancer patients [43].

An IFN-γ-based therapeutic approach for auto-immunity? IFN-γ may be involved in auto-immune diseases in two possible ways. First, it may affect the specific immune responses to the auto-antigen(s) concerned; its net effect may be positive or negative, depending on which cells (suppressors, helpers, etc.) are predominantly involved. Second, by its activating potential for macrophages and other leukocytes, IFN-γ may regulate the aspecific inflammatory reaction resulting from auto-immunization.

The complexity of both disease pathogenesis and biological activities of IFN-γ precludes one from making educated predictions as to whether the disease will respond favorably to IFN-γ or, alternatively, to blocking of IFN-γ. Therefore, only experimentation can tell. However, such experimental evaluation is hampered by the lack of representative models in standard laboratory animals. In addition, most auto-immune diseases encountered in the clinic have a protracted, progressive course with many ups and downs; this unpredictability severely compounds the interpretation of clinical trials.

One model of acute auto-immunity is acute experimental allergic encephalomyelitis, which is elicited in rodents by injecting spinal cord homogenate or myelin basic protein (MBP). The pathogenesis of this disease is only partly understood, one aspect of it being that it is mediated by T-cells [44, 45]. One of the ways in which T cells may intervene in the pathogenesis is by secreting cytokines such as IFN-γ. In experiments with this model, administration of IFN-γ by systemic route had a mitigating effect on the course of the disease; treatment with antibody against IFN-γ, as a contrast, rendered the disease more severe [46]. These observations indicate that IFN-γ is produced in the course of the disease and exerts a mitigating effect, the mechanism of which remains merely a subject of speculation.

Another model of auto-immunity in which the effect of IFN-γ has been investigated to some degree is the spontaneous nephritis of NZB/NZW-F1 mice, a model for lupus erythematosus in humans [47]. In this case, the administration of antibody to IFN-γ alleviated the symptoms and delayed the fatal outcome. Obviously, IFN-γ is produced more or less continuously and is instrumental in bringing about the symptoms and organ destruction.

IFN-γ in infection. Endogenous IFN-γ is necessary for an efficient host response to infection with certain bacteria, parasites or viruses. The general idea is that macrophage activation by IFN-γ is necessary for effective ingestion and killing of organisms. However, in certain cases (e.g. in experimental listeriosis), augmentation of the killing potential by macrophages does not seem to be the mechanism whereby IFN-γ provides protection of the host [27, 48].

The potential of IFN-γ to augment host resistance to intracellular agents is already finding its way into medical practice, notably in the cases of therapy-resistant leishmaniasis [49]. Another related example of successful application of IFN-γ in the clinic is the favorable response of patients with X-linked chronic granulomatous disease, a disorder of host defense characterized by an impairment in the killing of

microbes that results from defective production of superoxide anion by phagocytes [50].

Organic and functional damage to organs during infections is often due to the inflammatory reaction rather than to direct destruction of cells or supracellular structures by the infectious agent. Therefore, one way in which IFN-γ may influence the course of infectious disease is by modulating inflammation. An illustrative example is the beneficial effect of anti-IFN-γ in experimental cerebral malaria (ECM). This disease is a model for the homonymous condition occurring in humans as a complication of natural plasmodium infection. The basic lesion of ECM consists of an occlusion of small brain vessels by infected macrophages and red cells. The pathogenesis of this lesion comprises stimulation of leukopoiesis in the bone marrow, alterations in the endothelia of certain blood vessels, activation of macrophages and secretion of TNF. Treatment of the animals with anti-IFN-γ antibody was found to prevent occurrence of the complication [51]. This is another demonstration of the fact that endogenous IFN-γ may not always be a favorable factor in the course of a disease.

IFN-γ in septic shock. Septic shock is a special example of functional and organic organ damage occurring as a result of infection. Although Gram-positive bacteria can cause shock (toxic shock syndrome due to *Staphylococcus aureus* is an example), classical septic shock is due to overwhelming multiplication in the body of any of a number of Gram-negative bacterial species. Fatal outcome of this condition is due to a lowering of blood pressure. Associated symptoms are diverse, including disseminated intravascular coagulation, endothelial damage, bleedings and renal involvement. The *primum movens* of Gram-negative septic shock is LPS released by disintegrating bacteria. Experimental models for septic shock (e.g. the generalized Shwartzman reaction) often rely on the use of LPS rather than live bacteria. LPS stimulates various leukocytes to produce mediators responsible for the dramatic inflammatory and vasomotoric changes. Virtually all categories of mediators have been found to be implicated (histamines, prostaglandins, complement factors, etc.), the most recently recognized category being the cytokines. A condition resembling septic shock can be elicited in mice by the administration of TNF, and LPS-induced shock can be prevented by anti-TNF antisera [52–54]. However, aside from TNF, other cytokines may be involved as demonstrated by studies focused on IFN-α/β and IFN-γ. In mice, treatment with monoclonal antibodies against IFN-γ was found to be effective in blocking LPS-induced shock [55].

These observations open a new perspective for the clinical management of septic shock.

IFN-γ in AIDS. A current hypothesis on AIDS holds that the virus (HIV) persists in a latent state in some cells and that it is occasionally activated to replicate when these cells are activated by cytokines [37]. One of the candidate cells in which the virus persists is the monocyte/macrophage [56, 57]. The (unproven) implication is that IFN-γ, being the macrophage-activating cytokine by excellence, may in certain instances activate virus replication [37]. Since IFN-γ is by definition an *anti-* rather than a *pro-*viral factor, this may seem a rather unconventional view. Nevertheless, for a variety of reasons it may prove a useful view to be considered. First, there are reasons to believe that in AIDS patients the production of IFN-γ is being stimulated continuously [58]. While it is correct that mononuclear cells from AIDS patients produce less IFN-γ than those of controls, this may be interpreted as hyporeactivity due to over-stimulation (see above). More importantly, spontaneous IFN-γ production has been found to occur in a mouse model of AIDS [59].

Second, activation of latently infected monocytes/macrophages to produce the virus has been proposed to lead to massive presentation of the viral envelope antigen to all $CD4^+$ cells (irrespective of their idiotype specificity) [37, 60]. Such presentation may, in fact, be responsible for continuous stimulation of IFN-γ production, but also for polyclonal proliferation of lymphocytes characteristic of the early stages of AIDS. Hence, endogenous IFN-γ may be involved in the pathogenesis of AIDS in a rather unexpected way, such that anti-IFN-γ intervention may be more desirable than the administration of IFN-γ itself.

Conclusion and perspective

IFN-γ, being a master key in the immune system and in inflammation, holds many perspectives for the design of novel therapeutic strategies. A salient point is the fact that there may turn out to be as many applications for antagonists of IFN-γ as for IFN-γ itself. A severe problem is that the effects of therapy, one way or the other, are almost unpredictable; only experiment can tell. This makes clinical evaluation rather difficult, especially in diseases with a protracted and capricious course.

Perhaps the most immediate results for IFN-γ therapy are to be expected as a confirmation of observations in infections that resist conventional therapy (e.g. leishmaniasis) or in chronic granulomatous disease. Application in chronic autoimmune disease (rheumatoid arthritis, multiple sclerosis, lupus) will probably have to be held in abeyance until more information is available from animal model systems. It is quite possible that in some of these diseases antagonization of IFN-γ may be more desirable than its activation.

Antagonization of IFN-γ, e.g. by the administration of humanized monoclonal antibodies to the cytokine, holds great promise as a possible procedure for treatment or prevention of septic shock. The incidence of this condition is increasing, as the number of patients in intensive care units increases. Antibiotic treatment, while quite effective in arresting bacterial proliferation, has proven to be inefficient to prevent shock. In fact, by killing bacteria already present, antibiotic treatment may precipitate LPS release and septic shock. In these conditions, antagonization of IFN-γ may add a valuable tool to our therapeutic arsenal. In fact, it may bridge the gap between antibacterial intervention and palliative measures directed only at the terminal stages of the condition.

REFERENCES

1. Celada A, The interferon-γ receptor. *Lymphokine Res* **7**: 61–73, 1988.
2. Langer JA and Pestka S, Interferon receptors. *Immunol Today* **9**: 393–400, 1988.
3. Celada A and Schreiber RD, Internalization and degradation of receptor-bound interferon-γ by murine macrophages. Demonstration of receptor recycling. *J Immunol* **139**: 147–153, 1987.
4. Aguet M, Dembic Z and Merlin G, Molecular cloning and expression of the human interferon-γ receptor. *Cell* **55**: 273–280, 1988.
5. Murray HW, Interferon-gamma, the activated macrophage, and host defense against microbial challenge. *Ann Intern Med* **108**: 595–608, 1988.
6. Wilkinson M and Morris G, Interferon and the immune system 1: Induction of interferon by stimulation of the immune system. In: *Interferons: From Molecular Biology to Clinical Application, Proceedings of the Thirty-Fifth Symposium of the Society for General Microbiology, Leeds, UK, September 1983* (Eds. Burke DC and Morris AG), pp. 149–179. Cambridge University Press, Cambridge, 1983.
7. Bancroft GJ, Schreiber RD, Bosma GC, Bosma MJ and Unanue ER, A T cell-independent mechanism of macrophage activation by interferon-γ. *J Immunol* **139**: 1104–1107, 1987.
8. Le J and Vilcek J, Accessory function of human fibroblasts in mitogen-stimulated interferon-γ production by T lymphocytes: Inhibition by interleukin 1 and tumor necrosis factor. *J Immunol* **139**: 3330–3337, 1987.
9. Matsumura H and Nakano M, Endotoxin-induced interferon-γ production in culture cells derived from BCG-infected C3H/HeJ mice. *J Immunol* **140**: 494–500, 1988.
10. Bernton EW, Meltzer MS and Holaday JW, Suppression of macrophage activation and T-lymphocyte function in hypoprolactinemic mice. *Science* **239**: 401–404, 1988.
11. Reem GH and Yeh N-H, Interleukin 2 regulates expression of its receptor and synthesis of gamma interferon by human T lymphocytes. *Science* **225**: 429–430, 1984.
12. Dinarello CA, Biology of interleukin 1. *FASEB J* **2**: 108–115, 1988.
13. Wong GG and Clark SC, Multiple actions of interleukin 6 within a cytokine network. *Immunol Today* **9**: 137–139, 1988.
14. Billiau A, Interleukin-6: Structure, production and actions. In: *Monokines and Other Non-lymphocytic Cytokines* (Eds. Powanda CM, Oppenheim JJ, Kluger MJ and Dinarello CA), pp. 3–13. Alan R Liss, New York, 1988.
15. Van Damme J, Van Beeumen J, Decock B, Van Snick J, De Ley M and Billiau A, Separation and comparison of two monokines with lymphocyte-activating factor activity: IL-1β and hybridoma growth factor (HGF). Identification of leukocyte-derived HGF as IL-6. *J Immunol* **140**: 1534–1541, 1988.
16. Basham TY and Merigan TC, Recombinant interferon-γ increases HLA-DR synthesis and expression. *J Immunol* **130**: 1492–1494, 1983.
17. Adams DO and Hamilton TA, Phagocytic cells: Cytotoxic activities of macrophages. In: *Inflammation: Basic Principles and Clinical Correlates* (Eds. Gallin JI, Goldstein IM and Snyderman R), pp. 471–492. Raven Press, New York, 1988.
18. Rappolee DA and Werb Z, Secretory products of phagocytes. *Curr Opinion Immunol* **1**: 47–55, 1988.
19. Gallin JI, Goldstein IM and Snyderman R, Overview. In: *Inflammation: Basic Principles and Clinical Correlates* (Eds. Gallin JI, Goldstein IM and Snyderman R), pp. 1–3. Raven Press, New York, 1988.
20. Snapper CM and Paul WE, Interferon-γ and B cell stimulatory factor-1 reciprocally regulate Ig isotype production. *Science* **236**: 944–947, 1987.
21. Finkelman FD, Katona IM, Mosmann TR and Coffmann RL, IFN-γ regulates the isotypes of Ig secreted during *in vivo* humoral immune responses. *J Immunol* **140**: 1022–1027, 1988.
22. Landolfo S, Cofano F, Giovarelli M, Prat M, Cavallo G and Forni G, Inhibition of interferon-gamma may suppress allograft reactivity by T lymphocytes *in vitro* and *in vivo*. *Science* **229**: 176–178, 1985.
23. Wall DA, Hamberg SD, Reynolds DS, Burakoff SJ, Abbas AK and Ferrara JLM, Immunodeficiency in graft-versus-host disease. I. Mechanism of immune suppression. *J Immunol* **140**: 2970–2979, 1988.
24. Gajewski TF and Fitch FW, Anti-proliferative effect of IFN-γ in immune regulation. IFN-γ inhibits proliferation of Th2 but not Th1 murine helper T lymphocyte clones. *J Immunol* **140**: 4245–4252, 1988.
25. Ransom J, Fischer M, Mosmann T, Yokota T, DeLuca D, Schumacher J and Zlotnik A, Interferon-γ is produced by activated immature mouse thymocytes and inhibits the interleukin-4-induced proliferation of immature thymocytes. *J Immunol* **139**: 4102–4108, 1987.
26. Landolfo S, Gariglio M, Gribaudo G, Jemma C, Giovarelli M and Cavallo G, Interferon-γ is not an antiviral, but a growth-promoting factor for T lymphocytes. *Eur J Immunol* **18**: 503–509, 1988.
27. Van Dissel JT, Stikkelbroeck JJM, Van de Barselaar MT, Michel BC, Leijh PCJ and Van Furth R, Inability of recombinant interferon-γ to activate the antibacterial activity of mouse peritoneal macrophages against *Listeria monocytogenes* and *Salmonella typhimurium*. *J Immunol* **139**: 1673–1678, 1987.
28. Bermudez LEM and Young LS, Tumor necrosis factor, alone or in combination with IL-2, but not IFN-γ, is associated with macrophage killing of *Mycobacterium avium* complex. *J Immunol* **140**: 3006–3013, 1988.
29. Dijkmans R, Decock R, Heremans H, Van Damme J and Billiau A, Interferon-γ is cytotoxic for normal mouse fibroblasts: Enhancement by tumor necrosis factor and interleukin 1. *Lymphokine Res* **8**: 25–34, 1989.
30. Endres S, Van der Meer JWM and Dinarello CA, Interleukin-1 in the pathogenesis of fever. *Eur J Clin Invest* **17**: 469–474, 1987.
31. Bernton EW, Beach JE, Holaday JW, Smallridge RC and Fein HG, Release of multiple hormones by a direct action of interleukin-1 on pituitary cells. *Science* **238**: 519–521, 1987.
32. Heremans H, Dijkmans R, Sobis H, Vandekerckhove F and Billiau A, Regulation by interferons of the local inflammatory response to bacterial lipopolysaccharide. *J Immunol* **138**: 4175–4179, 1987.
33. Ho M, Kono Y and Breinig MK, Tolerance of the induction of interferons by endotoxin and virus: Role of a humoral factor. *Proc Natl Acad Sci USA* **119**: 1227–1232, 1965.
34. Stewart WE II, *The Interferon System*, pp. 125–129. Springer, New York, 1979.
35. Stringfellow DA, Hyporeactivity to interferon induction: Characterization of a hyporeactive factor in the serum of encephalomyocarditis virus-infected mice. *Infect Immun* **11**: 294–302, 1975.
36. Vervliet G, Claeys H, Van Haver H, Carton H, Vermylen C, Meulepas E and Billiau A, Interferon production and natural killer (NK) activity in leukocyte cultures from multiple sclerosis patients. *J Neurol Sci* **60**: 137–150, 1983.
37. Billiau A, Monocyte and T-cell activating cytokines in

the acquired immune deficiency syndrome (AIDS): Pathogenesis-promoting or -limiting factors? In: *Cytokines* (Ed. Sorg C), Vol. 1, pp. 193–203, Karger, Basel, 1989.

38. Anderson KP, Fennie EH and Yilma T, Enhancement of a secondary antibody response to vesicular stomatitis virus "G" protein by IFN-γ treatment at primary immunization. *J Immunol* **140**: 3599–3604, 1988.
39. Paul NL and Ruddle NH, Lymphotoxin. *Annu Rev Immunol* **6**: 407–438, 1988.
40. Fiers W, Beyaert P, Everaerts B, Suffys P, Tavernier J, Van Haesebroeck B and Van Roy F, Tumor necrosis factor: A potential antitumor agent? *J Interferon Res* **7**: 627–634, 1987.
41. Kettelhut IS, Fiers W and Goldberg AL, The toxic effects of tumor necrosis factor *in vivo* and their prevention by cyclooxygenase inhibitors. *Proc Natl Acad Sci USA* **84**: 4273–4277, 1987.
42. Torti FM, Dieckmann B, Beutler B, Cerami A and Ringold GM, A macrophage factor inhibits adipocyte gene expression: An *in vitro* model of cachexia. *Science* **229**: 867–869, 1985.
43. Patton JS, Shepard HM, Wilking H, Lewis G, Aggarwal BB, Eessalu TE, Gavin LA and Grunfeld C, Interferons and tumor necrosis factors have similar catabolic effects on 3T3 L1 cells. *Proc Natl Acad Sci USA* **83**: 8313–8317, 1986.
44. Brostoff S and Mason D, Experimental allergic encephalomyelitis: Successful treatment *in vivo* with a monoclonal antibody that recognizes T helper cells. *J Immunol* **133**: 1938–1942, 1984.
45. Waldor MK, Sciram S, Hardy R, Herzenberg LA, Lanier L, Linn M and Steinman L, Reversal of experimental allergic encephalomyelitis with monoclonal antibody to a T cell subset marker. *Science* **227**: 415–417, 1985.
46. Billiau A, Heremans H, Vandekerckhove F, Dijkmans R, Sobis H, Meulepas E and Carton H, Enhancement of experimental allergic encephalomyelitis in mice by antibodies against IFN-γ. *J Immunol* **140**: 1506–1510, 1988.
47. Jacob CO, van der Meide PH and McDevitt HO, *In vivo* treatment of (NZB × NZW)F_1 lupus-like nephritis with monoclonal antibody to γ interferon. *J Exp Med* **166**: 798–803, 1987.
48. Campbell PA, Canono BP and Cook JL, Mouse macrophages stimulated by recombinant gamma interferon to kill tumor cells are not bactericidal for the facultative intracellular bacterium *Listeria monocytogenes*. *Infect Immun* **56**: 1371–1375, 1988.
49. Badaro R, Falcoff E, Badaro FS, Carvalho EM, Pedral-Sampaio D, Barral A, Carvalho JS, Barral-Netto M, Brandely M, Silva L, Bina JC, Teixeira R, Falcoff R, Rocha H, Ho JL and Johnson WD Jr, Treatment of visceral leishmaniasis with pentavalent antimony and interferon gamma. *N Engl J Med* **322**: 16–21, 1990.
50. Ezekowitz RAB, Dinauer MC, Jaffe HS, Orkin SH and Newburger PE, Partial correction of the phagocyte defect in patients with X-linked chronic granulomatous disease by subcutaneous interferon gamma. *N Engl J Med* **319**: 146–151, 1988.
51. Grau GE, Heremans H, Piguet P-F, Pointaire P, Lambert P-H, Billiau A and Vassalli P, Monoclonal antibody against interferon γ can prevent experimental cerebral malaria and its associated overproduction of tumor necrosis factor. *Proc Natl Acad Sci USA* **86**: 5572–5574, 1989.
52. Beutler B, Milsark IW and Cerami AC, Passive immunization against cachectin/tumor necrosis factor protects mice from lethal effect of endotoxin. *Science* **229**: 869–871, 1985.
53. Tracey KJ, Beutler B, Lowry SF, Merryweather J, Wolpe S, Milsark IW, Hariri RJ, Fahey TJ III, Zentella A, Alber JD, Shires GT and Cerami A, Shock and tissue injury induced by recombinant human cachectin. *Science* **234**: 470–474, 1987.
54. Tracey KJ, Fong Y, Hesse DG, Manouge KR, Lee AT, Kuo GC, Lowry SF and Cerami A, Anti-cachectin/TNF monoclonal antibodies prevent septic shock during lethal bacteraemia. *Nature* **330**: 662–664, 1987.
55. Billiau A, Heremans H, Vandekerckhove F and Dillen C, Anti-interferon-γ antibody protects mice against the generalized Shwartzman reaction. *Eur J Immunol* **17**: 1851–1854, 1987.
56. Ho DD, Rota TR and Hirsch M, Infection of monocytes/macrophages by human T lymphotropic virus. *J Clin Invest* **77**: 1712–1715, 1986.
57. Gartner S, Markovits P, Markovitz DM, Kaplan MH, Gallo R and Popovic M, The role of mononuclear phagocytes in HTLV-III/LAV infection. *Science* **233**: 215–219, 1986.
58. Fuchs D, Hausen A, Hengster P, Reibnegger G, Schulz T, Werner ER, Dierich MP and Wachter H, *In vivo* activation of $CD4^+$ cells in AIDS. *Science* **235**: 356, 1987.
59. Pitha PM, Biegel D, Yetter RA and Morse HC III, Abnormal regulation of IFN-α, -β and -γ expression in MAIDS, a murine retrovirus-induced immunodeficiency syndrome. *J Immunol* **141**: 3611–3616, 1988.
60. Asher MS and Shepard HW, AIDS as immune system activation: A model for pathogenesis. *Clin Exp Immunol* **73**: 165–167, 1988.