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Regulation of interferon-g receptor (INF-gR) chains: a peculiar way to rule the life and death of human lymphocytes.

Abstract

Interferon-g (IFN-g) is a lymphokine produced by activated T lymphocytes and NK cells, that plays an important role in host defense mechanisms by exerting pleiotropic activities on a wide range of cell types. Cellular responses to IFN-g are mediated by its heterodimeric cell surface receptor (IFN-gR), which activates downstream signal transduction cascades, ultimately leading to the

regulation of gene expression. Several observations suggest that the signals resulting from the binding of IFN-g to its receptor depend on the number of surface receptors transducing the IFN-g signal. This review summarizes recent advances in the understanding of the fine regulation of the response of human lymphocytes to IFN-g through an interplay between surface expression of IFN-gR and a variety of environmental factors that combine to control their fate.

Full text

INTRODUCTION

By regulating proliferation [1], cytotoxic differentiation [2, 3] and apoptosis [4], interferon-gamma (IFN-gamma) plays a central role in deciding the life and death of human T lymphocytes. The first event in the induction of these responses is the specific binding of IFN-gamma to its heterodimeric cell surface receptor (IFN-gammaR), which is composed of two chains, IFN-gammaR1 or IFN-gammaRalpha binding chain (referred to hereafter as R1) [5] and IFN-gammaR2 or IFN-gammaRbeta transducing chain (referred to hereafter as R2) [6].

Recent investigation of IFN-gammaR chain regulation provided a clearer picture of the response of human lymphocytes to IFN-gamma. A change in the cell membrane expression of both chains greatly transforms the results of IFN-gamma's influence on T lymphocyte behavior. Flow cytometry indicates that R1 and R2 can be expressed at low (¾ 20% positive cells) or high (from 20 to 100% positive cells) levels. When it interacts with T cells expressing high R1 and low R2 membrane levels ($R1^{hi}R2^{lo}$), it promotes their proliferation [4, 7]. By contrast, when high levels of both chains are expressed ($R1^{hi}R2^{hi}$), it induces T cell apoptosis [7, 8].

Differential R2 chain expression critically alters the consequences engendered by the binding of the IFN-gamma to human T cells. The relative membrane expression of both chains is finely regulated during T cell activation and functional differentiation [7, 8]. The goal of this review is the elucidation of a few issues involved in these differences in regulation and their control of the destiny of lymphocytes.

THE IFN-gammaR COMPLEX

IFN-gammaR is a complex formed from two non-signal-transducing R1 chains [9] that bind to an IFN-gamma dimer. Two signal-transducing R2 chains then associate with the complex [10]. Formation of this entirely dimeric (R1-IFN-gamma-R2) complex is an essential prelude to the cascade of intracellular signals triggered by IFN-gamma binding [10]. The intracellular portions of the two R2 chains provide the Janus tyrosine kinases Jak1 and Jak2 docking sites [10, 11]. Phosphorylated Jak1 and Jak2 activate the signal transducer and activator of transcription-1 (STAT1) [10-13], whose phosphorylation and dimerization result in its passage to the nucleus, where it binds to specific DNA sequences called the IFN-gamma-activating sequences (GAS) and activates the transcription of numerous sets of genes [13].

The IFN-gamma signal transduction mechanisms are well known. The way in which the IFN-gamma-induced genes modulate all the pleiotropic activities elicited by IFN-gamma is less clear. A protein typically induced by transduction is the IFN regulatory factor-1 (IRF-1), a regulator of apoptosis involved in mature T cell apoptosis activated both by mitogens and growth factor deprivation [14]. Murine T cells lacking the gene for IRF-1 resist apoptosis induced by radiation or chemotherapeutic drugs, such as etoposide and adriamycin [15]. Moreover, inactivation of IRF-1 is associated with the development of human hematopoietic neoplasias [15, 16].

Furthermore, IRF-1 complexes with other transcription factors, such as the IFN-consensus sequence binding protein (ICSBP), the IFN-regulatory factor-2 (IRF-2) that promotes cell proliferation [17], and Pu-1 [18], with formation of protein complexes that differentially regulate target genes, including several linked with cell growth control and apoptosis, such as the cyclin-dependent-kinase inhibitor $p21^{/WAF1/CIP1}$ (p21), a protein that arrests cell proliferation [19], cas- pase-1 [20-22], Fas ligand (Fas-L) [23] and p53 [24]. An altered balance between these factors may be responsible for the inhibitory or proliferative effects of IFN-gamma.

The apoptotic pathway activated by IFN-gamma is also linked with that of the Fas- Fas-L, *i.e.* the molecular system primarily responsible for switching off the immune response [25]. In man, IFN-gamma up-regulation of the Fas-L leads to the negative regulation of both Th1 and Th2 cell activation [8].

Another interesting aspect of IFN-gamma signaling is the cross communication with IFN-alpha/beta receptor components. Although type I interferons transmit signals through distinct receptor components, namely IFNAR1 and IFNAR2 [26], it has been shown that IFNAR1 facilitates efficient assembly of the IFN-gamma-activated STAT1 [27]. This crosstalk is contingent on a constitutive, subthreshold IFN-alpha/beta signaling that is essential for maintaining IFNAR1 in a phosphorylated form and thereby providing a site on the IFN-gamma-activated STAT1 for efficient dimerization. This subthreshold signaling also strengthens an otherwise weak association of IFNAR1 with IFN-gammaR2 in a particular region of the cell membrane, namely the caveolar membrane domains [27].

HOW THE R2 CHAIN EXPRESSION IS MODULATED DURING THE ACTIVATION AND DIFFERENTIATION OF T LYMPHOCYTES

IFN-gammaR exerts its effects on cells by interacting with a specific receptor expressed at the cell surface. R1 is expressed on both lymphoid and nonlymphoid cells and is almost ubiquitous [9, 28]. Studies on distribution and regulation of R2 have been mainly focused on T lymphocytes in the mouse [29, 30] and humans [7, 8, 31, 32]. They have shown that the response of T cells to IFN-gamma is finely controlled through the regulation of R2 expression, particularly during their functional differentiation.

T helper (Th) cell differentiation is associated with development of opposing patterns of responsiveness to cytokines [33, 34]. Investigation of transduction of the IFN-gamma signal into mouse Th1 and Th2 clones by Pernis *et al.* has shown that IFN-gamma induces STAT1-inducible gene, IRF-1, in Th2 lymphocytes only, pointing to functional blockade of transduction in Th1 clones [29]. Both Th1 and Th2 clones express R1 mRNA in fact, whereas R2 mRNA is expressed by Th2 clones only. Transfection of the *R2* gene into Th1 clones restored their transduction [29].

Taken as a whole, these findings provide a model for regulation of the development of Th1 cells based on extinction of the IFN-gamma signal through negative regulation of the R2 chain. This model suggests that absence of this chain on Th1 cells shields them from the antiproliferative effect of the IFN-gamma that they themselves produce [35]. This escape route uses the R1 chain only, which may be supposed to act as a protective decoy receptor. The difference in R2 expression on mouse Th1 and Th2 cells aroused great interest,

since it suggested that a surface molecule could provide immunologists with an easy way of distinguishing them. Further studies, however, have shown that the absence of the R2 chain is not a phenotypic marker of Th1 cells, but the result of a singular mechanism they use to regulate expression of the receptor component responsible for signal transduction. Bach *et al.* have demonstrated that loss of the R2 chain is a specific $CD4^+$ cell response to exposure to IFN-gamma, rather than a specific gene expression event during Th1 differentiation [30]. Naive $CD4^+$ cells from a mouse transgenic for a specific T cell receptor (TCR) stimulated *in vitro* in the presence of IL-12, differentiated to Th1 cells and no longer displayed the R2 chain about 14 days later [30]. It was clear that this extinction was due to the negative regulation exerted by the IFN-gamma they were producing, since differentiated Th2 cells cultured for 7 days in the presence of IFN-gamma also failed to express the R2 chain [30]. The "desensitization" of a cytokine by a particular cell type indicated by these findings is an exception to the known forms of cytokine-interaction. In this case in fact, the negative regulation exerted by IFN-gamma is not directed against the receptor component that binds it, as usually occurs, but the subunit needed to transduce its signal. Reinstatement of the signal for IFN-gamma in Th2 clones switches off the response of chronically activated Th2 clones. However, results obtained from experimental mouse models cannot be completely extrapolated to the human scenario, since data from our laboratory indicate that IFN-gamma is needed for the induction and activation of human T and NK cells [1], and that during these events the T cell expresses $R1^{hi}$ [36]. The effects of IFN-gamma on T cells, however, are not so clear-cut. In addition to inhibiting the proliferation of Th2 clones [35], it acts as an activation or a death signal for Th1 clones. In the absence of accessory cells, Th1 activation induced by stimulation of the TCR leads to cell death. Neutralization of IFN-gamma with specific antibodies prevents cell death, whereas it is increased by the addition of IFN-gamma [37]. Further confirmation of the role of IFN-gamma in the regulation of T cell death is provided by the fact that mice lacking the IFN-gamma or the *R1* gene display increased T cell proliferation in response to mitogens [38], alloantigens [38] and mycobacterial antigens [39].

We have demonstrated that both resting and primary activated human T cells express $R2^{lo}$. Blockade of the R1 chain resulted in complete inhibition of the proliferative and cytotoxic response, whereas the subsequent re-stimulation of these activated cells led to a dramatic increase in cell death correlated with an $R1^{hi}R2^{hi}$ phenotype. This apoptosis in turn was totally inhibited by the presence

of anti-R1 mAb antibody [7]. Since, $R1^{hi}R2^{hi}$ phenotype seems to be correlated with IFN-gamma-induced cell death, but not proliferation, these data suggest that transduction of the apoptotic or proliferative signals depends on R1 and R2 chains expression. This would explain the double effect of IFN-gamma on human Th1 lymphocytes.

The general picture emerging from these results is that through its interaction with different IFN-gammaR expression phenotypes, IFN-gamma is a critical signal for both the triggering and the negative regulation of the proliferative response of human T cells. The $R1^{hi}R2^{hi}$ phenotype favors its antiproliferative/apoptotic effect, the $R1^{hi}R2^{lo}$ phenotype its promotion of proliferation, while $R1^{hi}R2^{null}$ favors the decoy receptor function whereby all effects of the bond between IFN-gamma and the R1 chain are annulled, although the chain itself is expressed. The complete absence of R2 ($R2^{null}$) has been observed in mouse Th2 cells only [29], not in humans [8].

These differing R2 thresholds are evident when its expression is studied during the differentiation of human Th1 and Th2 cells. As in the mouse, our and other results show that it is overexpressed, whether as mRNA or as protein, at the start of Th1 differentiation, which suggests that it plays a part in a resting lymphocyte's "decision" to become a Th1 or a Th2 [unpublished data and 31]. Resting $CD3^+$ cells are $R1^{lo}R2^{lo}$. When stimulated with PHA in the presence of IL-4 and anti-IL-12 antibodies (Th1 condition), they became $R1^{hi}R2^{lo}$ after 24 hours. When stimulated with IL-12 and anti-IL-4 antibodies (Th2 condition) they became $R1^{hi}R2^{hi}$. These observations suggest that IFN-gamma, by interacting with developing Th1 cells with a $R1^{hi}R2^{lo}$ phenotype, is an autocrine signal that favors their expansion (Figure 1), whereas by interacting with developing Th2 cells with a $R1^{hi}R2^{hi}$ phenotype, it is a paracrine signal that inhibits their expansion (Figure 1). If the culture is maintained for 1-2 week, however, functional polarization of cytokine production is apparent between cells differentiating to Th1 and Th2 respectively, but R2 chain expression is regulated negatively on both types. After two weeks, both populations display a $R1^{hi}R2^{lo}$ phenotype, although detectable R2 mRNA levels were still observed (unpublished results).Antigen-specific human Th1 and Th2 clones have also been investigated. Experiments with specific monoclonal antibodies have shown that they express both chains as mRNA and protein in the presence of IL-2. Th2 clones were $R1^{hi}R2^{lo}$, Th1 clones were $R1^{lo}R2^{lo}$. Following deprivation of IL-2 or stimulation with PHA, both clones became $R1^{hi}R2^{hi}$ (Figure 1) [8]. Suppression

by IFN-gamma of the activation of chronically stimulated Th1 and Th2 clones has been investigated with reference to the apoptosis it induces after stimulation of the TCR, which is the principal mechanism of homeostatic control of the immune response. TCR stimulation in the absence of antigen-presenting cells results in the apoptosis of human Th1 clones. This in turn is prevented by antibodies blocking the R1 or neutralizing IFN-gamma [8]. Th2 clones normally resist such apoptosis [40], whereas it is induced by exogenous IFN-gamma [8]. It is clear, therefore, that on chronically activated Th1 and Th2 clones with a $R1^{hi}R2^{hi}$ phenotype, IFN-gamma is an autocrine signal for Th1 and a paracrine signal for Th2, and essential for the suppression of their activation (Figure 1). It would thus seem that the kinetics of R2 chain expression governs the induction and differentiation of Th1 and Th2 cells, the suppression of their activation by apoptosis and also influences the extinction and reinstatement of the IFN-gamma signal.

HOW THE R2 CHAIN IS REGULATED IN T LYMPHOCYTES FROM PATIENTS WITH INHERITED DEFICIENCIES IN IFN-gamma SIGNALING

When naive T cells from both wild-type mice and mice lacking the *R1* gene are differentiated into Th2 cells by IL-4, they express equal surface levels of R2. Conversely, R2 is not expressed by wild-type cells when they are differentiated into Th1 by IL-12, but continues to be highly expressed in cells from R1-deficient mice [33]. This indicates that R2 down-regulation is induced by the interaction between IFN-gamma and its receptor. The mechanism of R2 down-regulation seems different in humans. Surface R2 expression was evaluated in T lymphoblasts from patients with a complete IFN-GR1 gene deficiency [41, 42, and manuscript in preparation], responsible for their severe and selective susceptibility to mycobacterial infections [43]. If autocrine utilization of IFN-gamma down-modulates R2 as in mice, activated T lymphocytes from these patients should express more surface R2 than those from normal individuals. We observed that T lymphoblasts from healthy donors, a patient carrying a mutation in the IFN-gamma binding site, impairing signal transduction without affecting the ability to express surface R1 [41], and another patient with a mutation abolishing the expression of detectable surface R1 [42], all displayed a $R1^{hi}R2^{lo}$ phenotype. The absence of an up-regulated R2 expression in *R1*-deficient patients indicated that endogenous IFN-gamma does not have a role in down-regulation of R2, and also suggests that surface expression of the two chains is independently regulated in humans. Collectively, these data point to a

difference in the regulation of R2 expression on human and mouse T cells. In particular, they suggest that in humans down-regulation of surface R2 is mainly involved in the prevention of IFN-gamma-mediated apoptosis rather than an event intrinsically linked to polarization of cells to the Th1 lineage.

HOW THE SURFACE EXPRESSION OF R2 IS KEPT LOW IN HUMAN T LYMPHOCYTES

While both resting T cells and proliferating human Th1 and Th2 clones express a $R2^{lo}$ phenotype, they express high levels of mRNA for R2 and the corresponding protein in their cytoplasm (Figure 2, left panel) [7, 8]. As already mentioned, binding to IFN-gamma of proliferating human Th1 and Th2 clones does not impair their viability, but stimulates their proliferation, induces their expression of IRF-1 and up-modulates their surface expression of class I MHC glycoproteins [8], which predisposes them to apoptosis if they interact again with IFN-gamma. Therefore, the mechanisms by which the surface expression of R2 is regulated, despite its continuous high cytoplasmic expression, control the destiny of T cells. The first issue is that $R1^{hi}R2^{lo}$ T cells respond to IFN-gamma. In addition, low surface R2 expression results from continuous, fast recycling of R2 between cytoplasmic stores and the cell surface. In effect, anti-R2 mAb are continuously taken up, but do not accumulate on the T cell surface [42]. Moreover, there is an obvious co-localization between R2 and CTLA-4, another cell surface receptor involved in negative regulation of T cell function whose trafficking involves clathrin-coated pits [44, 45]. Inhibition of internalization of these coated pits significantly reduced anti-R2 mAb uptake. CTLA-4 undergoes clathrin-mediated endocytosis and associates specifically with AP50, the medium subunit of the clathrin-associated protein complex AP-2 [46]. The sequence Tyr-*x*-*x*-*z* (where *x* stands for any amino acid and *z* for a large hydrophobic amino acid) is a frequent subtype of the consensus internalization motif observed in many receptors rapidly internalized and delivered to endosomes, including the transferrin receptor, EGF-receptor and CTLA-4 [47]. Interestingly, analysis of the amino acid sequence of the *R2* gene revealed the presence of the sequence 273-Tyr-Arg-Gly-Leu-276-COOH within its cytoplasmic domain. This further suggests that the two molecules might be associated with the same clathrin-associated protein complex controlling their internalization. Like CTLA-4, specific signals within the cytoplasmic domain of R2 may be required for selective internalization into coated vesicles with the involvement of cell-type-specific adaptors binding the domain [46]. Alternatively the same specific

adaptor could bind different R2 intracellular domain isoforms, resulting from a cell-specific mRNA splicing. Different cell-specific IL-12Rbeta1 isoforms, in fact, have been shown to transduce different pathways in response to IL-12 [48]. In addition, R2 internalization is independent of IFN-gamma signals, since it is observed equally in activated T cells from donors carrying inherited IFN-GR1 gene deficiencies [42], healthy donors and healthy and deficient donors, cultured in the presence of anti-IFN-gamma-neutralizing or anti-R1 blocking mAb.

This control mechanism whereby human T cells limit their surface expression of R2 is markedly inhibited following their first interaction with IFN-gamma. It is operative in T cells only and R2 surface expression is high on normal and malignant B and myeloid cells, which directly undergo apoptosis when first exposed to IFN-gamma [49]. Modulation of IFN-gamma secretion and R2 expression regulates the growth and apoptosis of hematopoietic cells.

HIGH R2 EXPRESSION: WHEN IFN-gamma INDUCES LYMPHOID CELL APOPTOSIS

The increasing evidence regarding the role of the differential expression of IFN-gammaR chains supports a novel view about their role in the final balance of the lymphoid cell-immune response.

Steady-state, normal, activated and neoplastic T lymphocytes express the $R1^{hi}R2^{lo}$ phenotype [4, 7, 8]. The binding of IFN-gamma to these T cells (Figure 2, left panel) results in a further down-regulation of surface R1, enhanced expression of class I MHC glycoproteins and cell proliferation [4].

The subsequent down-regulation of R1 causes an unbalanced expression of R2 which is further exaggerated by its progressive overexpression. At this point, further binding of $R1^{lo}R2^{hi}$ T cells with IFN-gamma puts T cells in the apoptotic pathway. The interplay between the repeated presence of IFN-gamma and the surface density of R2 are critical for a T cell's "decision" to undergo proliferation or apoptosis.

However, modulation of IFN-gammaR chains is not triggered by IFN-gamma alone, but also by a typical T cell answer to many stressing conditions. For instance, when T cells are kept in culture medium deprived of fetal bovine serum

or growth factors, there is a rapid and dramatic increase in the expression of both chains and a change in cell morphology accompanying their slow apoptosis. Apoptosis is strikingly accelerated by the addition of IFN-gamma [4, 7, 8].

A differential expression of IFN-gammaR is evident in the various leukocyte lineages and their state of maturation. The R1 chain is highly and uniformly expressed on the membrane of T, B and myeloid cells, whereas R2 is highly expressed on the surfaces of B and myeloid cells, but very limited on T cells (Figure 2) [50]. This pattern of expression is also observed in the normal counterpart of PBMC and suggests a homeostatic physiological function of cell type-specific internalization [49]. Moreover, hematopoietic precursor cells displayed an analogous differential R2 distribution, since $CD33^+$ cells express higher levels than $CD34^+$ cells (Figure 3). $R1^{hi}R2^{lo}CD34^+$ blasts (Figure 3, left panel) respond to IFN-gamma by increasing their proliferation, whereas $R1^{hi}R2^{hi}$ $CD33^+$ blasts (Figure 3, right panel) are susceptible to IFN-gamma-mediated apoptosis [49]. Unlike T cells that are constitutively $R1^{hi}R2^{lo}$ (Figure 2, left panel), B and myeloid cells are $R1^{hi}R2^{hi}$ (Figure 2, right panel). In B and myeloid cells, too, the correlation between $R2^{hi}$ expression, intensity of transduction events and IFN-gamma-induced apoptosis is evident. As IFN-gamma engages a higher number of functional receptors, these cells undergo apoptosis following their first binding to it [50].

HOW DOES R2 OVEREXPRESSION LEAD LYMPHOCYTES TO IFN-gamma-MEDIATED APOPTOSIS?

An explanation of the double effect of IFN-gamma on cell growth may emerge from the examination and characterization of the signal transduction mechanisms it mediates. Recent advances in understanding the role of IFN-gammaR chain expression reveal that the number of heterodimeric receptors IFN-gamma engages, influences the STAT1 activation kinetics and hence the activation or inactivation of genes involved or not in apoptosis.

The kinetics of IFN-gamma-mediated STAT1 activation showed that the density of R2 expressed on the cell surface is the limiting factor responsible for the number of receptor complexes that transduce the IFN-gamma signal [49]. Quantitative differences in this transduction pathway decide between lymphocyte proliferation and apoptosis. In the presence of IFN-gamma, $R2^{lo}$

membrane expression results in slow activation of STAT1 and the expression of low levels of the genes typically induced by IFN-gamma and involved in the promotion of apoptosis, such as IRF-1 [14] or caspases [49]. By contrast, $R2^{hi}$ surface expression results in a much faster activation of STAT1, a higher production of IRF-1 and activation of the endogenous caspases. These observations were from an experiment in which a forced R2 expression in T cells was obtained by either R2 transfection or serum deprivation [49 and manuscript in preparation].

These data indicate that a complex interplay between the density of R2 surface levels, the transcription levels of the genes typically induced by IFN-gamma and involved in the promotion of apoptosis and the cell death signal cascade regulates the response of human blood cells to IFN-gamma. The resulting balance is critical for their "decision" to proliferate or undergo apoptosis.

However, the apoptotic pathways activated are different in T and B and myeloid cells. The IFN-gamma-dependent up-regulation of both Fas and Fas-L leads to autocrine/paracrine apoptosis of $R1^{hi}R2^{hi}$ T cells [7]. This apoptosis is associated with the coordinated induction of both caspase-1 and caspase-3. As caspase-3 is mainly involved in Fas pathway activation, up-regulation of caspase-1 may be a later event that amplifies the initial caspase cascade [25, 51].

Conversely, the Fas/Fas-L system and caspase-3 seem inoperative in the IFN-gamma-mediated apoptosis of B and myeloid cells. Despite the presence of high Fas surface levels on these cells, IFN-gamma does not up-regulate Fas-L surface expression and caspase-3 activation, nor is anti-Fas blocking mAb effective. Caspase-1, instead, is up-regulated by IFN-gamma and thus seems to be a critical step in IFN-gamma-induced apoptosis. However, although there is strong evidence that caspase-1 plays an obligatory role in this apoptosis [52], other mediators may be involved in that of B and myeloid cells.

Therefore, IFN-gamma induces the apoptosis of T cells mainly by activating the Fas pathway, whereas it induces a Fas-independent apoptosis in B and myeloid cells [manuscript in preparation]. The evidence that IFN-gamma is still able to induce apoptosis in B cells from a patient with an inherited Fas deficiency further supports this conclusion.

THE ROLE OF GALECTINS IN THE REGULATION OF THE IFN-gammaR CHAIN EXPRESSION AND APOPTOSIS OF HUMAN T LYMPHOCYTES

The many studies that have investigated the interaction between IFN-gamma, IFN-gammaR chain expression and the response of lymphoid cells to IFN-gamma indicate its extreme complexity. Recent evidence shows that particular cytokine or growth factors and environmental signals [4, 7, 8, 53] are of great importance in IFN-gammaR chain expression and in the response of lymphoid cells to IFN-gamma.

One of these factors is the 15 kDa protein called beta-galactoside binding protein (betaGBP), a negative cell cycle regulator that blocks the transition from S to G_2 phase [54]. It is encoded by the LGALS1 gene [54, 55] and is physiologically released by fibroblasts [54]. Its structure places it in the galectins family, whose members are animal lectins characterized by their affinity for beta-galactoside residues [55]. betaGBP exists as a monomer [54] and a homodimer [56, 57]. Through its retention of associated cell-surface beta-galactoside residues, the homodimer displays a wide range of biological activities involving cell adhesion and immune regulation [55-61].

The monomer interacts with a high-affinity cell surface receptor expressed on target cells, since its biological activity is maintained even when the saccharide binding site is masked by a glycan complex [54]. Even in the presence of lactose, the monomer markedly inhibits the proliferation of T cells by arresting them in the S and G_2/M phases. In addition, by up-regulating the expression of both R1 and R2, it makes them sensitive to IFN-gamma-mediated apoptosis [53].

These findings show the important immunoregulatory role played by betaGBP by switching off T lymphocyte effector functions. Moreover, they provide evidence of the up-modulation by a negative cell growth regulator of IFN-gammaR expression, and particularly that of R2, on T lymphocytes.

In normal and neoplastic T lymphocytes, the $R1^{hi}R2^{hi}$ phenotype is induced by serum [4] and IL-2 deprivation [7, 8], TCR ligation [7], exposure to X rays [4] or chemotherapeutic drugs [62]. Since most of these treatments arrest T cells in S and G_2/M, and make them sensitive to IFN-gamma-mediated apoptosis [4, 7, 8], the findings for betaGBP effects suggest that up-regulation of IFN-gammaR is a general event related to T cell cycle arrest.

The betaGBP-dependent up-regulation of the two chains and the subsequent bias of T cells towards IFN-gamma-mediated apoptosis outlines a new, molecularly defined way in which the destiny of T cells encountering IFN-gamma is decided. Indeed, betaGBP can be seen as a factor equally involved in the IFN-gamma switch of the T cell program from proliferation to apoptosis. Control of this switch may be of importance to set up anti-cancer strategies.

The ability of betaGBP to convert IFN-gamma signals from proliferative into apoptotic could be a new way of switching off sustained proliferation of human malignant lymphocytes. In this regard, it is interesting to note that the outcome of betaGBP-induced cell cycle arrest is different for normal and neoplastic T cells.

Normal T cells arrested in S and G2/M express $R1^{hi}R2^{hi}$ phenotype and only undergo apoptosis in the presence of IFN-gamma. If this is not provided, they remain alive, although their ability to proliferate is inhibited. By contrast, malignant T cells exposed to betaGBP down-regulate the expression of Bcl-2 and slowly undergo apoptosis. This apoptosis, too, is accelerated by IFN-gamma. This difference is important, since betaGBP could be considered as anti-cancer-drug to selectively induce the apoptosis of malignant T lymphocytes only.

ROLE OF NO IN THE REGULATION OF IFN-gammaR CHAIN EXPRESSION AND THE APOPTOSIS OF NORMAL AND NEOPLASTIC LYMPHOCYTES

The outcome of the signal delivered by IFN-gamma on T lymphocytes depends on the density of R2 expression which can be regulated by environmental factors [4, 8] that can act as nonspecific tissue mediators. One of these mediators is nitric oxide (NO). NO produced by monocytes/macrophages following interaction with IFN-gamma or bacterial products [63, 64], or following a decrease of oxygen partial pressure [65], may interact with IFN-gamma producing T cells. There is evidence that the processes that induce NO production by macrophages also induce immune suppression. Anti-tumor therapy with IL-12 induces IFN-gamma-mediated NO production by macrophages, which suppress the T cell proliferative response [66]. Thus the interplay between NO and IFN-gamma may be critical in deciding both the proliferative and the apoptotic response of an activated T lymphocyte. NO influences the T lymphocyte response to IFN-gamma through its regulation of IFN-gammaR chain expression [67]. The role of NO on the apoptosis and IFN-

gammaR expression of malignant T cell lines corresponding to distinct stages of T lymphocyte differentiation has been investigated. Exposure to NO from a brief-delivery NO-donor transiently inhibited the proliferation of all these lines. This was due to NO triggering of an IFN-gamma-independent apoptosis, since these lines did not produce IFN-gamma constitutively, nor after the exposure. The surviving cells started to proliferate again, but being $R1^{hi}R2^{hi}$, were susceptible to IFN-gamma-mediated apoptosis. The addition of IFN-gamma completely abolished their growth and induced their apoptosis through expression of caspase-1 effector death [67].

These data indicate that NO induces an IFN-gamma-independent apoptosis of human T cells. They also identify NO as one of the environmental factors that, by inducing the recruitment of R1 and R2 chains from granule stores, increases their surface expression and converts the signal delivered by IFN-gamma from growth-promoting into apoptotic [67].

CONCLUSION

We have presented evidence that the interaction of IFN-gamma with high or low lymphocyte membrane expression of R2 chain is a new way by which the life and death of T lymphocytes is regulated. Modulation of surface expression of R2 is a physiological T lymphocyte response to a variety of environmental factors that, in this way, indirectly combine to control their fate.

Information concerning the mechanisms regulating R2 expression may an essential prelude to the building of new IFN-gamma based strategies to control the proliferation of neoplastic T lymphocytes. Differential R2 determines whether IFN-gamma will switch lymphocyte activation on or off. Following antigen stimulation, IFN-gamma promotes the activation and differentiation into effector cells of $R2^{lo}$ T lymphocytes, whereas it induces the rapid apoptosis of those that are $R2^{hi}$. Since T cells play a central role in the immunological control of tumor growth, information on signals down-regulating R2 expression may be used to promote the expansion and functional differentiation of T lymphocytes whose apoptosis or anergy is one cause of tumor overgrowth and immunodeficiencies [5-9, 15]. Alternatively, appropriate upregulation of R2 chain may convert IFN-gamma into an apoptotic signal for the control of autoreactive cells responsible for autoimmunity [14, 16] and in enhancing T cell functions in immunodeficiencies, where increased expression of R1 and R2 on T cells favors

their apoptotic death [5-9, 15]. Regulation of R2 expression can also lead to the identification of IFN-gamma-based protocols that inhibit the expansion of malignant lymphocytes [14, 16]. In our opinion, the convergence of these issues places research on lymphocyte modulation of the R1 and R2 chains at the cutting edge of immunological and cancer research.

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Figures

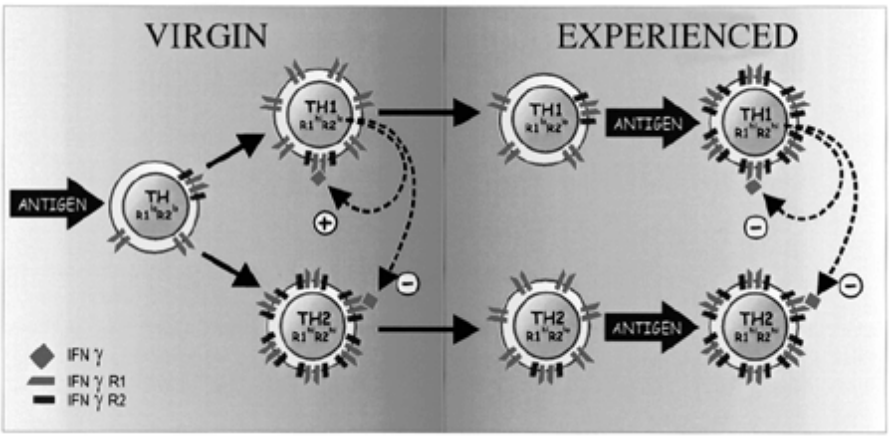


Figure 1

R1 and R2 expression during the differentiation of human Th1 and Th2.

Differing IFN-gammaR thresholds are evident during the differentiation of human Th1 and Th2 cells. Resting $CD3^+$ cells are $R1^{lo}R2^{lo}$. Following antigen stimulation, developing Th1 cells became $R1^{hi}R2^{lo}$ and developing Th2 cells became $R1^{hi}R2^{hi}$ (left panel). Th1-produced IFN-gamma, by interacting with developing Th1 cells with a $R1^{hi}R2^{lo}$ phenotype, is an autocrine signal that favors their expansion, whereas by interacting with developing Th2 cells with a $R1^{hi}R2^{hi}$ phenotype, it is a paracrine signal inhibiting their expansion. Chronically activated human Th1 and Th2 were $R1^{lo}R2^{lo}$ and $R1^{hi}R2^{lo}$ respectively (right panel). Following antigen restimulation, both subsets became $R1^{hi}R2^{hi}$. In Th1 and Th2 lymphocytes, which display a $R1^{hi}R2^{hi}$ phenotype, IFN-gamma is an autocrine signal for Th1 and a paracrine signal for Th2, and essential for the suppression of their activation (right panel).

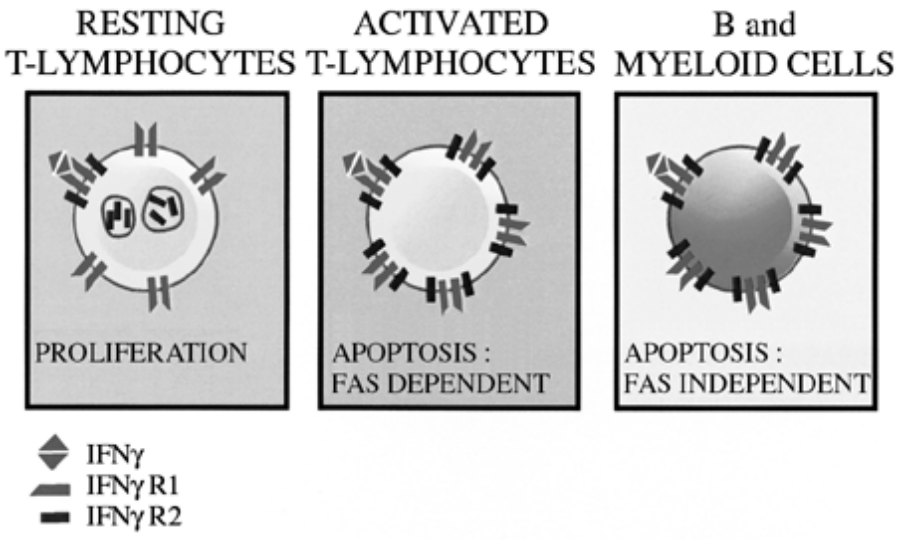


Figure 2

R1 and R2 expression in malignant T, B and myeloid cells.

T, B and myeloid cells reveal striking differences in R1 and R2 membrane expression. All cell types expressed high membrane levels of R1. In contrast, resting T lymphocytes (left panel) expressed barely detectable levels of R2 and highly expressed this protein in their cytoplasm, whereas its expression was significantly higher on activated T, B and myeloid cells (middle and right panels). Resting T lymphocytes expressing high membrane density of R1 only respond to IFN-gamma by increasing their proliferation, whereas activated T lymphocytes expressing high membrane density of both chains are susceptible to IFN-gamma-mediated apoptosis. Moreover, B and myeloid cells with high expression of both chains are sensitive to the antiproliferative effect of IFN-gamma.

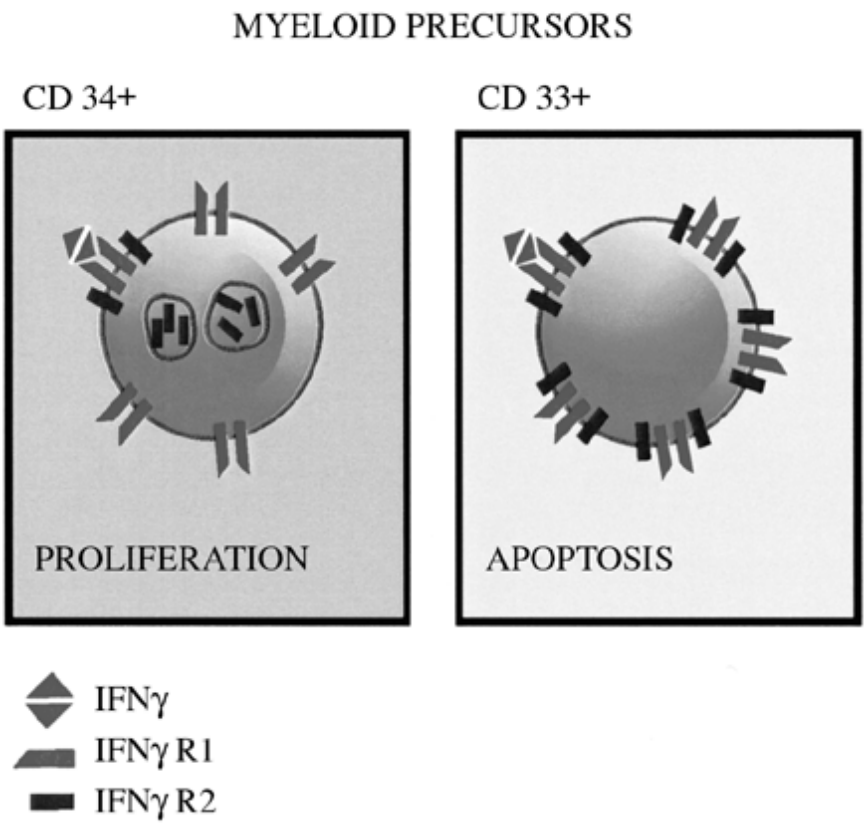


Figure 3

R1 and R2 expression in hematopoietic precursor cells.

Cell membrane R1 and R2 expression on myeloid precursors $CD33^+$ and $CD34^+$ is also different. $CD33^+$ (right panel) and $CD34^+$ (left panel) cells expressed significant levels of R1. By contrast, $CD34^+$ expressed barely detectable surface levels of R2 and high levels in their cytoplasm, and $CD33^+$ expressed high levels of surface R2. IFN-gamma can induce either apoptosis on $CD33^+$ or proliferation in $CD34^+$ cells, depending on their surface R2 chain expression.

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IL-10, recombinant, rat, cytokines.

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