The role of interferon-γ on immune and allergic responses

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Allergic diseases have been closely related to Th2 immune responses, which are characterized by high levels of interleukin (IL) IL-4, IL-5, IL-9 and IL-13. These cytokines orchestrate the recruitment and activation of different effector cells, such as eosinophils and mast cells. These cells along with Th2 cytokines are key players on the development of chronic allergic inflammatory disorders, usually characterized by airway hyperresponsiveness, reversible airway obstruction, and airway inflammation. Accumulating evidences have shown that altering cytokine-producing profile of Th2 cells by inducing Th1 responses may be protective against Th2-related diseases such as asthma and allergy. Interferon-γ (IFN-γ), the principal Th1 effector cytokine, has shown to be crucial for the resolution of allergic-related immunopathologies. In fact, reduced production of this cytokine has been correlated with severe asthma. In this review, we will discuss the role of IFN-γ during the generation of immune responses and its influence on allergic inflammation models, emphasizing its biologic properties during the different aspects of allergic responses.

Key words: interferon-γ - lymphocytes - immune system - allergy - allergic inflammation

Airway allergic diseases are common disorders, which affect approximately 5% of the Western world population, and show reportedly increasing incidence in developing countries during the last decades. Asthma, rhinitis, and allergy represent the most common allergic diseases, which arise as a result of interaction between multiple genetic and environmental factors. Most patients exhibit an acute immediate hypersensitivity to inhaled antigens, known as allergens, as a consequence of a genetic predisposition for the development of deregulated immune responses (atopy). The inflammatory process may be divided into early- and late-phase reactions. The early (immediate) response is usually mediated by mast cell degranulation, whereas late phase is followed by neutrophil, eosinophil, and lymphocyte migration to the inflammatory site. This chronic inflammatory disorder of the lung is usually characterized by (i) airway hyperresponsiveness (AHR), (ii) reversible airway obstruction and mucus hypersecretion, and (iii) airway inflammation (Wills-Karp 1999). Although allergic diseases have been linked to an enhanced Th2 immune response associated with high levels of interleukin (IL) IL-4, IL-5 and IL-13, accumulating evidences demonstrate that a decreased Th1 immune response is also important in the pathogenesis of theses diseases, and that interferon-γ (IFN-γ) could act as a central regulator in this phenomenon. Therefore, in this review we have decided to focus on some of the major functions of IFN-γ that may be implicated in the pathogenic process of allergic inflammation.

The IFN-γ cytokine

The molecule - The cytokine IFN-γ belongs to the family of interferons, which are closely related by their ability to protect cells from viral infections. Based on several criteria, the IFN molecules have been divided into two distinct classes. The first class is named type I IFN and includes the IFN-α and IFN-β molecules, which are the classical interferons induced in response to viral infections. The second class is solely composed by IFN-γ (also termed type II or immune IFN), which is not related to the type I IFN at both the genetic and the protein levels. Although IFN-γ displays most of the biologic activities that have been described to the other IFN, it has a lower specific antiviral activity, but presents more immunomodulatory properties than the type I interferons (Farrar & Schreiber 1993).

Both human and mouse IFN-γ genes generate a unique 1.2 kb mRNA that encodes an amino acid polypeptide of 166 and 134 residues, respectively (Boehm et al. 1997). Two polypeptide chains self-associate in an antiparallel fashion, producing a molecule that exhibits a twofold axis of symmetry with an apparent molecular weight of 34 kDa (Farrar & Schreiber 1993, Bach et al. 1997). Only the dimer displays biologic activity, possibly because it is the only conformation of the molecule that can induce IFN-γ receptor (IFN-γR) dimerization (Farrar & Schreiber 1993). For a long time, the production of IFN-γ has been considered to be restricted to activated natural killer (NK) cells, CD4^{+} T helper-1 (Th1) cells, and CD8^{+} T cytotoxic cells (Farrar & Schreiber 1993, Boehm et al. 1997). However, we now know that these cells are the most potent, but not the only sources of IFN-γ. Several studies have identified additional IFN-γ-secreting cell types, including γδ T cells, NKT cells, macrophages, dendritic cells, naive CD4^{+} T cells, and even B cells (Frucht et al. 2001, Szabo et al. 2003).

Molecular mechanisms of gene expression - Much of the knowledge regarding the molecular mechanisms for IFN-γ expression has been described in T lymphocytes,

since these cells are excellent producers of this cytokine. Its gene expression is dictated by several transcription factors, which bind to DNA elements located within specific regulatory regions of the IFN-γ locus (Murphy et al. 2000, Szabo et al. 2003). DNase I-hypersensitive experiments have shown that the IFN-γ regulatory region encompasses more than 8.0 Kb of genomic DNA, and consists of promoter cis elements, intronic regions and distal enhancers. The promoter region contains binding sites for a sort of IFN-γ-inducers, such as NF-kB, NFAT, STAT-4, and T-bet (Murphy et al. 2000, Szabo et al. 2003).

The expression of the IFN-γ gene has showed to be repressed by the immunosuppressive drug cyclosporin. In fact, three binding sites for the cyclosporin-sensitive NFAT family of transcription factors have been identified through the proximal region of the IFN-γ promoter. These sites are required for maximal IFN-γ expression in T cell lines and primary T lymphocytes (Sweetser et al. 1998). The NFAT and NF-kB transcription factors are thought to bind to similar DNA sequences, and may thus coordinately cooperate for the regulation of IFN-γ gene expression. Hence, NF-kB induction within T cells is crucial for substantial IFN-γ production and Th1 response (Sica et al. 1997). It has also been shown that both IL-12 and IL-18 augments IFN-γ production through the activation of NF-kB pathway. However, the influence of the IL-12/IL-18 pathway on IFN-γ production in Th1 effector cells depends mainly on STAT4, which is able to directly bind to the promoter region of the IFN-γ gene. Even so, STAT4 does not seem to be essential for the initial production of IFN-γ, but to amplify the amount of IFN-γ produced by individual cells since STAT4-/- T lymphocytes are still able to produce this cytokine (Murphy et al. 2000, Szabo et al. 2003).

While some nuclear factors are ubiquitous regulators of gene expression, others are required for selective gene expression in specific cellular subsets. In CD4^{+} T lymphocytes, T-bet (T-box expressed in T cells) was recently identified as the master switch of Th1 differentiation and to be the key regulator of IFN-γ expression in these cells (Szabo et al. 2000). T-bet is largely expressed in the lymphoid system, and also has shown to transactivate the IFN-γ gene and induce chromatin remodeling of the IFN-γ locus (Szabo et al. 2003). Three putative T-box binding sites were identified in the IFN-γ gene locus, two sites located 2 Kb from the start site and one in the third intron. Recently, Reiner and collaborators have identified two transcription factors also related to IFN-γ production: Hlx, a potential interacting partner for T-bet that has presented synergistic effects on IFN-γ production (Mullen et al. 2002); and Eomesodermin, a T-bet paralogue that controls effector functions of CD8^{+} T cells, including IFN-γ production (Pearce et al. 2003). Although some transcription factors are conserved regulators of IFN-γ gene expression among different cell types, it remains to be determined the key effectors of each cell lineage. Furthermore, the regions responsible for tissue-specific expression of the IFN-γ gene remain to be elucidated.

The signaling pathway - IFN-γ exerts its pleiotropic effects through a specific interaction with the cell surface IFN-γR. The receptor complex consists of two chains: IFN-γR1 (also known as IFN-γ receptor α), which is the major ligand-binding subunit, and IFN-γR2 (also known as IFN-γ receptor β), which is obligatory for IFN-γ signal transduction, and also increases the affinity of IFN-γR1 for its ligand, presumably by enhancing the stability of the complex (Boehm et al. 1997, Tau & Rothman 1999).

Signal transduction starts with an interaction of the IFN-γ homodimer with two α-chain receptors, thereby inducing α-chain dimerization and the subsequent recruitment of two β-chains to the complex. Each chain is constitutively associated with a specific Janus kinase (JAK) (the α-chain with JAK1 and the β-chain with JAK2) (Igarashi et al. 1994). The aggregation of the receptor components brings inactive JAKs into close proximity with one another. Once clustered, JAKs are reciprocally activated through sequential auto and transphosphorylation events. After activation, JAKs then phosphorylate a specific tyrosine residue near the C-terminus of the IFN-γR1, which serve as a docking site to the binding of STAT1 (Heim et al. 1995). The recruitment of STAT1 is followed by its phosphorylation on tyrosine residue 701 by the receptor-associated JAKs. This phosphorylation leads to a rapid dissociation of the receptor and to the formation of STAT1 homodimers (also called GAF, for gamma-activated factor) (Greenlund et al. 1995). At some point during the early phase of activation, STAT1 is also phosphorylated on serine 727 by a process involving phosphatidylinositol 3-kinase (PI3-K) and Akt that is required for maximal transcriptional activity (Nguyen et al. 2001). The STAT1 homodimer then translocates into the nucleus, where it is able to bind to defined DNA sequences (known as GAS, for gamma-activated site) and initiate or suppress transcription of IFN-γ-regulated genes (Darnell et al. 1994) (Fig. 1). In addition to the well known Jak-STAT pathway, IFN-γ activates several additional signal-transduction proteins (Ramana et al. 2002). In fact, targeted disruption of the STAT1 gene in mice has revealed STAT1-independent pathways in IFN-γ-dependent signaling (Gil et al. 2001). The role of these pathways in the variety of physiological and pathological conditions remains to be elucidated.

In summary, by activating the latent cytosolic transcription factor STAT1, IFN-γ initiates the transcription of a number of genes containing STAT1-binding sites in their promoter regions. Many of these induced genes are transcription factors (for example, IRF-1) that are able to further drive the regulation of the next wave of transcription. The total number of IFN-γ-regulated genes is estimated to be ~500 (Boehm et al. 1997). It has been demonstrated that IFN-γ upregulates the transcription of genes related to antigen presentation (MHC class I and II, β2-microglobulin, TAP), Th1 phenotype development (STAT1, T-bet), chemokine-based recruitment of monocytes, T cells, eosinophils and basophils (MCP-1, MCP-2, MCP-3, RANTES), cellular adhesion (VLA-4, ICAM-1, VCAM-1 molecules), immunoglobulin heavy chain class switch (IFN-γ upregulates IgG and downregulates IgE), cytokines network (IL-12, IFN-γ, CD40), apoptosis (CD95, caspases), lymphocyte activation (B7-1 and B7-2 molecules), and others (Boehm et al. 1997). As we shall dis-
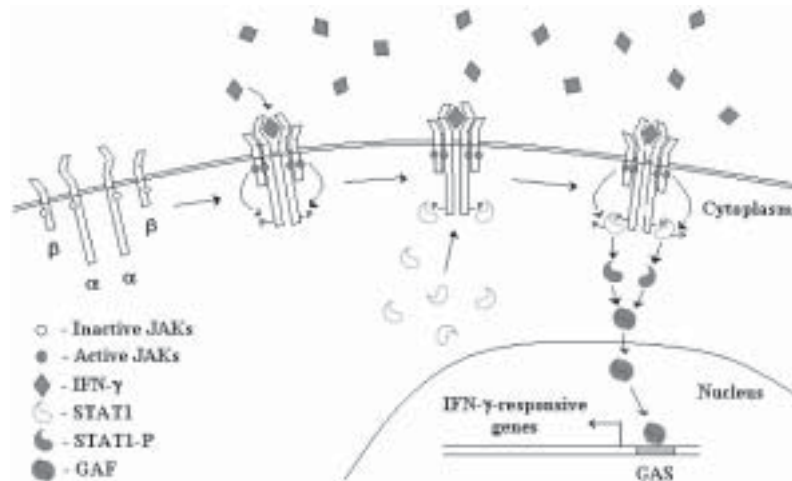
Fig. 1: interferon-γ (IFN-γ) signaling pathway. IFN-γ binds to its receptor (IFN-γR) and leads to the aggregation of α and β-chains, which are constitutively associated with Janus Kinases (JAKs). Once actived, JAKs phosphorylate the IFN-γRα chain, creating a docking site for STAT1, which is then phosphorylated and associated in homodimers (named GAF, for gamma-activated factor). The STAT1 homodimer translocates to the nucleus where it is able to bind to specific DNA sequences (named GAS, for gamma-activated site) and regulate the expression of IFN-γ-responsive genes.

cuss here, these IFN-γ-regulated genes take part in the generation of immune responses related to several stages of some allergic processes.

Immunologic basis of allergic diseases

Allergic inflammation has been closely associated with CD4^{+} Th lymphocytes, since a classical Th2 pattern of cytokine production has shown to contribute to the pathogenesis of this disease (Renauld 2001). Elevated numbers of Th2 cells have been identified in the bronchoalveolar lavage (BAL) fluids and airway biopsies from asthmatic patients. These lymphocytes produce high levels of IL-4, IL-5, IL-9, and IL-13, which orchestrate the recruitment and activation of effector cells related to allergic responses, such as eosinophils and mast cells. The cytokine IL-4 was originally identified as a B cell growth factor, and further showed to promote IgE isotype switch in B cells. In addition, IL-4 is required for optimal Th2 and mast cell differentiation, whereas IL-5 is a selective factor for eosinophil activation and development. IL-4 and IL-5 also increase eosinophil adhesion to vascular endothelial cells, and promotes its infiltration to inflammatory sites by regulating surface markers on eosinophils (such as VLA-4) and endothelium (such as VCAM-1). These cytokines may be produced not only by CD4^{+} T cells, but also by mast cells and eosinophils themselves. Still considering Th2 cytokines, IL-13 is responsible for the mucus hyper-secretion of submucosal glands and/or epithelial cells, and IL-9 has been recently related to mast cell and eosinophil proliferation/differentiation (Wills-Karp 1999, Renauld 2001).

In line with all these features, allergic inflammation is correlated with pronounced levels of serum IgE, eosinophil migration to the site of inflammation, and activation of specific cellular compartments. Together with allergen recognition, IgE antibodies bind to Fc receptors (FcR) present on the surface of mast cells and basophils, and

thus trigger the release of inflammatory mediators (such as histamine, prostaglandin and leukotrienes), as well as chemotactic factors (such as eotaxin/CCL11, MCP-1/CCL2 and RANTES/CCL5) and cytokines that in a fine-tuned way are responsible for several allergic reactions. In the mucosa, these mediators of hypersensitivity reactions rapidly induce vascular changes, edema, mucus production, and smooth muscle constriction. Furthermore, it seems that eosinophils are also involved in the pathogenesis of allergic diseases because they usually infiltrate to the target tissues, where they release several inflammatory mediators and cytokines that contribute to airway wall epithelium damage. Finally, chemokines, or chemoattractants, are also relevant in allergy not only for their role in regulating leukocyte recruitment (mainly basophils, eosinophils, and mast cells), but also because they can regulate cellular activation and inflammatory mediators release, IgE synthesis, and Th2 cell recruitment to the site of allergic inflammation. Taken all together, these findings indicate that Th2 cells and their cytokines can account for some of the initial hallmarks of airway inflammation, and are crucial for the pathogenesis of allergic diseases (Wills-Karp 1999, Renauld 2001). During the next sections, we will focus on how IFN-γ regulates Th immune responses, and may thus control allergic diseases.

IFN-γ and Th immune response

A critical aspect of the immune response to allergens is mediated by the helper function of CD4^{+} T cells. After engagement of the T cell receptor (TCR) by the appropriate peptide-MHC complex, naive CD4^{+} T cells rapidly undergo a differentiation process that leads to the development of two functionally distinct cell subsets. These subsets are characterized by a mutually exclusive pattern of cytokine secretion. Th1 cells secrete IFN-γ and TNF-β and are efficient in eliminating intracellular pathogens. Th2 cells produce IL-4, IL-5, IL-10 and IL-13, which affect

humoral immunity to helmintic parasites and are responsible for immune responses to persistent allergens (Abbas et al. 1996). Several factors can influence the differentiation pathway of CD4+ Th cells, specially the cytokines prevailing within the microenvironment where these cells encounter antigens (Constant & Bottomly 1997). IL-12 and IL-4 are known to be the major Th1- and Th2-inducing cytokines, respectively (Abbas et al. 1996). The Th1/Th2 balance is extremely important and may determine whether the immune response is appropriate or leads to severe immunopathologies. Overproduction of Th1 cytokines has been implicated in delayed-type hypersensitivity reactions and autoimmune diseases. On the other hand, it is notorious that the basis for allergic disorders remains on the dysregulation of the Th2 phenotype as previously stated here (Abbas et al. 1996).

Accumulating evidences have shown that altering cytokine-producing profile of Th2 cells by inducing Th1 responses is protective against Th2-related disorders such as asthma and allergy. It has been demonstrated that Th1 lymphocytes and cytokines such as IFN-γ and IL-12 may counteract and suppress Th2 responses of allergic diseases (Iwamoto et al. 1993, Cohn et al. 1999, Dow et al. 1999). In fact, defective IFN-γ production predisposes toward the development of allergic diseases, and patients with severe asthma present significantly reduced IFN-γ production in response to allergen when compared to control individuals (Leonard et al. 1997, Renzi et al. 1999). Moreover, resolution of allergy seems not to be related with a reduction in Th2-cytokine production, but with normalization of IFN-γ levels (Smart et al. 2002). Interestingly, it has also been reported an inverse association between dominant IFN-γ immune responses to intracellular pathogens in childhood and the incidence of asthma (Shirakawa et al. 1997). These results emphasize the inhibitory character of IFN-γ on the response against allergens.

IFN-γ is the principal Th1 effector cytokine, and it has a crucial role in Th1 differentiation. IFN-γ has the ability to act in a great number of cell types that are involved in Th differentiation. It induces IL-12 production by antigen presenting cells (APC), such as dendritic cells and macrophages (Snijders et al. 1998, Szabo et al. 2003). These APCs provide the first contact of naive CD4+ T cells with the antigen, therefore this IL-12 production is of great importance on the differentiation pathway towards a Th1 phenotype. In addition to its role on APC, IFN-γ exerts effects on the CD4+ T cells themselves. This cytokine is capable of enhancing the development of Th1 effector cells from BALB/c mice by increasing naive CD4+ T cells responses to IL-12 (Wenner et al. 1996). Actually, IFN-γ is responsible for inducing/maintaining the expression of the β chain of the IL-12 receptor (IL-12Rβ2) through T-bet activation, stating an important role of IFN-γ on the Th1 effects mediated by IL-12 (Mullen et al. 2001, Afkarian et al. 2002). Studies on CD4+ T cells from C57BL/6 mice have also revealed a direct role for IFN-γ as an inducer of Th1 polarization via an autocrine mechanism, independent of IL-12 (Bradley et al. 1996) (Fig. 2).

IFN-γ also exerts direct inhibitory effects on Th2 cytokines, reducing the levels of IL-4 and IL-5 production. The IFN-γ signaling pathway activates T-bet protein, the Th1-specific and Th2-suppresing transcription factor (Lighvani et al. 2001, Afkarian et al. 2002). In fact, ectopically expression of T-bet was able to repress IL-4 and IL-5 in Th2 cells (Szabo et al. 2000). In a model of atopic dermatitis, Th2 cells retrovirally transfected with a vector expressing T-bet conferred Th1-like cytokine production and migratory capacities to those cells (Lametschwandtner et al. 2004). Consistently, T-bet-deficient mice have impaired IFN-γ production and also develop spontaneous AHR similar to allergic patients (Finotto et al. 2002). Also, T-bet expression in CD4+ T cells is diminished in the lungs of asthmatic patients, who present sig-
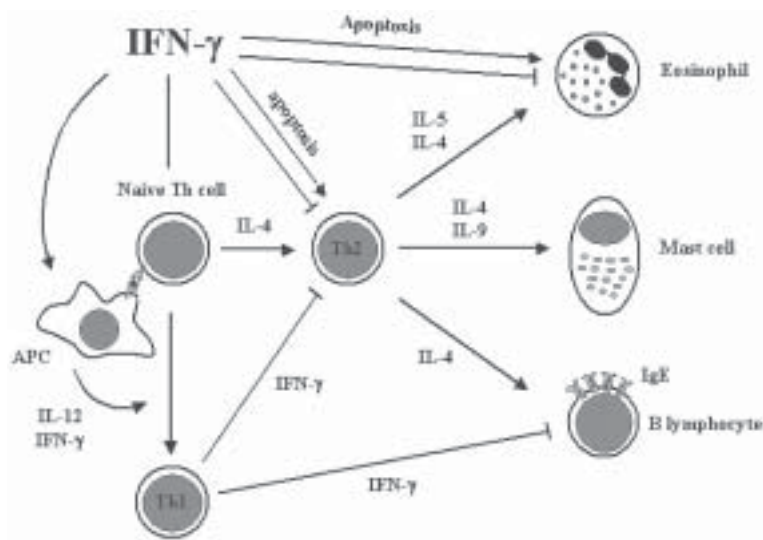

Fig. 2: interferon-γ (IFN-γ) controls Th immune and allergic responses. IFN-γ is produced by different cell sources. It may counteract Th2 immune responses (by suppressing the development of Th2 lymphocytes), induce Th1 differentiation (by enhancing IL-12 production by APC or skewing naive Th lymphocytes toward the Th1 phenotype), and control several steps of allergic responses (by inducing eosinophil apoptosis and blocking IgE isotype switch in B cells).

nificantly lower IFN-γ secretion by peripheral blood mononuclear cells when compared with healthy individuals (Nurse et al. 1997, Finotto et al. 2002). On the other hand, the Th2-induced transcription factor GATA-3 specifically controls the expression of Th2 cytokines, which are essential to induce allergic inflammation in vivo (Zheng & Flavell 1997). In fact, increased levels of GATA-3 mRNA expression have been reported in asthmatic airways when compared to those of control subjects and correlated with increased IL-5 expression (Nakamura et al. 1999). The expression of a dominant-negative mutant of GATA-3 led to a reduction in the levels of all Th2 cytokines and attenuated mucus production, IgE synthesis, and airway eosinophilia in the transgenic mice (Zhang et al. 1999).

IFN-γ has indeed a crucial role on inhibiting Th2 responses but not only through T-bet expression. Loss of IL-4 receptor responsiveness may be another mechanism that suppresses Th2 development in polarizing Th1 cells (Huang & Paul 1998). Other studies have shown that IFN-γ directly suppresses IL-4 gene expression through IRF-1 and 2, which bind to three distinct IL-4 promoter sites and act as transcriptional repressors (Elser et al. 2002). In vivo, IFN-γ-mediated Th2 repression can be shown by experiments based on models of pulmonary inflammation orchestrated by Th2 cytokines. In IFN-γR-/- mice previously sensitized with OVA and rechallenged intranasally with the same antigen, the inflammatory lung disease persisted long after it was resolved by wild type mice (Coyle et al. 1996). As discussed before, IFN-γ acts not only as a potent activator of the Th1 phenotype, but also as a suppressor of Th2 development.

Besides the counteracting roles of IFN-γ in the Th2 differentiation process, IFN-γ has a role in inhibiting the proliferation of Th2 cells. In fact, over a decade ago Gajewski and Fitch (1988) have observed that IFN-γ was responsible for the inhibition of proliferation and IL-1-induced responses of some Th2 clones. Further experiments have shown that Th1 cells decreased their expression of the β chain of the IFN-γR while Th2 cells did not, suggesting a mechanism by which IFN-γ could inhibit selectively the proliferation of Th2 clones (Pernis et al. 1995). The role of IFN-γ in promoting Th1- and inhibiting Th2-type responses has also been subject of some controversy. Recently, Bocek and colleagues (2004) have shown a quite unexpected function for IFN-γ as an IL-4-production inducer. The authors suggest that the precise amount of cytokines may be the key to whether the dominant effect of IFN-γ is to enhance or suppress Th2 priming (Bocek et al. 2004).

IFN-γ and allergic inflammation

The suppressive effects of IFN-γ on allergic diseases have been shown to be mediated by various mechanisms, such as the (1) regulation of allergen presentation to T lymphocytes, (2) differentiation of naive T cells toward Th1 phenotype and/or inhibition of Th2 cell recruitment/differentiation, (3) suppression of Th2 cytokine release from activated T cells, (4) inhibition of effector cell recruitment to the site of inflammation, (5) induction of apoptosis in T cells and eosinophils, (6) blockage of IgE isotype switch in B cells, and (7) induction of nitric oxide (NO) production. Actually, IFN-γ is known to be a pleio-

tropic cytokine that induces and modulates an array of immune responses. Therefore, in this section we have decided to focus on some of the major functions of this cytokine not discussed until here that may be implicated in allergic diseases in a certain manner.

One of the important physiologic roles of IFN-γ during the generation of immune responses is its ability to upregulate the expression of MHC class I and II proteins in several cell types. While this upregulation enhances antigen presentation in macrophages, it has been shown that IFN-γ almost completely abrogates the capacity to present antigens by mast cells, central mediators of allergic reactions (Farrar & Schreiber 1993, Frandji et al. 1995). Since Th cells can be activated in the airway mucosa, mast cells could act as APCs in the absence of IFN-γ, inducing Th2-type responses through their ability to produce substantial amounts of IL-4 (Hamid et al. 1991, Frandji et al. 1995, Constant & Bottomly 1997).

It has been demonstrated that IFN-γ is responsible for regulating the activation, differentiation and recruitment of eosinophils. In fact, IFN-γ induces a decrease in the expression of the eotaxin receptor (CCR3), which was recently showed to be an important inducer of eosinophil differentiation from hematopoietic progenitor cells (Lamkhioued et al. 2003). Lung eosinophil recruitment is one of the hallmarks of atopic asthma and IFN-γ seems to play an important inhibitory role on these cells. Through the induction of the chemokine Mig (CXCL9), IFN-γ inhibits the eotaxin-dependent recruitment of eosinophils to the lung (Fulkerson et al. 2004). In vivo models of allergic inflammation have also proved the properties of IFN-γ to regulate allergen-induced eosinophilic infiltration. Recombinant IFN-γ treatment before inhalation of aerosolized antigen prevented eosinophil infiltration into the trachea of sensitized mice (Iwamoto et al. 1993). Targeted disruption of the IFN-γ receptor gene has resulted in a prolonged airway eosinophilia in response to allergen, suggesting that IFN-γ signaling pathway is crucial to control eosinophil recruitment in vivo (Coyle et al. 1996). In human studies, nebulized IFN-γ has also reduced the number of eosinophils in the BAL of asthmatic patients (Boguniewicz et al. 1995). However, it is unlikely that this cytokine directly acts on the eosinophils during its infiltration to inflammatory tissues. In agreement, several reports have concluded that IFN-γ directly prevents allergen-induced CD4^{+} T cell infiltration into the tissue and thereby inhibits the following IL-5-dependent eosinophil recruitment.

IFN-γ also plays a role in the nitric oxide pathway, inducing iNOS, an NO synthase (Boehm et al. 1997). Through the induction of NO production, IFN-γ inhibits IgE-mediated degranulation of mast cells (Eastmond et al. 1997). Moreover, NO itself is a bronchodilator, and inhalation of high concentrations of NO has resulted in a small bronchodilatory response in asthmatic patients (Högman et al. 1993). NO has also shown a role in inhibiting proliferation and DNA synthesis in airway smooth muscle cells (Patel et al. 1999). Since hyperplasia and hypertrophy of airway smooth muscle are thought to contribute to airway dysfunctions such as asthma, NO induction could be an important inhibitor of these diseases (Patel et al. 1999).

Another critical role of IFN-γ in allergic reactions is its ability to inhibit immunoglobulin class switching to IgE, which is an important mediator of allergic pathologies induced by Th2 cytokines as discussed before (Boehm et al. 1997). Besides inhibiting IgE class switch, IFN-γ induces IgG production instead. IgG may neutralize inhaled allergens, and through interactions with Fcγ receptors (FcγR), may promote activation of accessory cells and enable FcγR-mediated endocytosis of allergen-IgG complexes, thereby promoting allergen capture and presentation by APC, such as alveolar macrophages (Sehra et al. 2003). This results on the activation of specific Th subsets, specially cells from the Th1 lineage, since several studies have shown that the APC activity of macrophages is associated with Th1 cell priming (Desmedt et al. 1998). In fact, treatment with anti-allergen IgG in the airways of sensitized mice was followed by an increment of secreted IFN-γ along with a shift from a Th2-skewed response to a more balanced Th1/Th2 response. In addition, a resulting reduction in eosinophils in the bronchoalveolar lavage (BAL) fluid of these mice has also been observed after treatment (Sehra et al. 2003). For these reasons, it has been suggested that the induction of IFN-γ may be beneficial in regulating IgE-mediated inflammation. Thus, the decreased production of IFN-γ in asthmatic patients may enable an increase in IgE levels by either permitting IgE isotype switch of B cells or by permitting more CD4+ T cell progenitors to differentiate into Th2 cells.

It has also been reported the involvement of IFN-γ in apoptotic events. Inflammatory responses induced by allergen exposure cause mucus cell metaplasia by differentiation of existing and proliferating epithelial cells into mucus-storing cells. IFN-γ has a role in inducing apoptosis of these cells through the induction of caspases and Bax, two proapoptotic proteins, thereby recovering the original proportions of cell types in the airway epithelium (Shi et al. 2002, Tesfaigzi et al. 2002). Accordingly, IFN-γ has shown to induce apoptosis in T cells and eosinophils through caspase and CD95/Fas-mediated mechanisms, respectively (Luttman et al. 2000, Refaeli et al. 2002). Also, it has been indicated a correlation between increased IFN-γ production and enhanced apoptosis of eosinophils and CD4+ T cells in allergic airway infiltrates (Kodama et al. 2003). Thus, IFN-γ-mediated apoptosis induction of CD4+ T cells and eosinophils may be an alternative explanation for the suppressive effects of IFN-γ directly on the local recruitment of these cells in allergic situations.

The adoptive transfer of IFN-γ-producing cells into allergen-sensitized recipients has also protected from airway eosinophilia after antigen challenge. Indeed, when transferred into recipient mice, CD4+ Th1 cells have inhibited Th2-induced eosinophilia and mucus secretion through the production of IFN-γ, since IFN-γR-/- mice had prolonged eosinophilia (Cohn et al. 1999). However, other studies have suggested that adoptively transferred Th1 cells might induce an inflammatory response encountered in asthma due to the proinflammatory properties of IFN-γ. It really seems that an inflammatory response is necessary to activate lung macrophages to produce reactive oxygen species, which are important to airway remodeling. Lung macrophages are also able to selectively promote Th1 responses during secondary exposure to inhaled allergen, thereby suppressing Th2-mediated allergic airway inflammation (Tang et al. 2001). Finally, IFN-γ secretion by transferred CD8+ T cells has also controlled airway eosinophilia in a model of allergen-challenged rats (Suzuki et al. 2002). Although increasing evidences suggest a protective role for IFN-γ against allergic diseases, conflicting results still regard its involvement in these responses (Hansen et al. 1999). Therefore, strengthening Th1 responses of allergic patients either by the adoptive transfer of activated antigen-specific T cells or by the administration of recombinant IFN-γ may only be considered as a potential immunotherapy intervention after further intensive investigations.

Concluding remarks

Several experimental findings have strongly supported the idea that the pathogenesis of allergic diseases is related to a misbalance between Th1/Th2 immune responses. For the past few years, it has been demonstrated that allergic inflammation is associated to an enhanced Th2 immune response. However, we now know that the absence of competent Th1 immune responses, specially the downregulation of IFN-γ, accounts for the establishment of these diseases. We reviewed here the recent data that demonstrate the importance of this cytokine in the modulation of allergic diseases. The development of novel therapeutic strategies has been designed to inhibit the development of Th2 cells (or the effect of their cytokines) and shift the immune response into a Th1 phenotype. In fact, the potent inhibitory property of IFN-γ on Th2 responses and allergic inflammation has suggested that it might be a possible treatment approach for such diseases. However, initial studies have shown unexpectedly high toxicity and several side effects related to IFN-γ administration to allergic patients. Even so, based on all findings related to IFN-γ modulation of Th immune response and allergy, any new possible immunotherapy approach developed for allergic inflammation will need to take into account the potent immunoregulatory properties of this cytokine.

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