**RESUMEN**

Interleucina 4 (IL-4) es una citocina que regula múltiples funciones biológicas. IL-4 puede regular la proliferación, diferenciación y apoptosis en diversos tipos celulares de origen hematopoyético y no hematopoyético. Su papel en la diferenciación de los linfocitos Th0 es crítico durante la respuesta inmunaria normal. Las respuestas frente a infecciones parasitarias también están reguladas por linfocitos Th2 inducidos por la IL-4. Por el contrario, la IL-4 y su maquinaria intracelular han sido implicadas en el desarrollo de enfermedades inmunitarias incluida alergia, autoinmunidad y cáncer. Numerosas evidencias indican que la IL-4 y las células Th2 podrían promover el asma alérgica mientras que tendrían un efecto protector en artritis reumatoide. La respuesta celular a la IL-4 está mediada por un receptor que se expresa en la mayoría de los tipos celulares. Este receptor tipo I está formado por la cadena IL-4Rα y la cadena común gamma (γc). La cadena gamma puede ser sustituida por la cadena IL-13Rα1 formando el receptor tipo II. El tipo II receptor es también receptor para la IL-13, una citocina que comparte muchas funciones con la IL-4. La unión de la IL-4 a su receptor induce la activación de los tirosín cinasas JAK que median la fosforilación de proteínas intracelulares. Entre éstas, destaca el factor de transcripción STAT6. La importancia de STAT6 está demostrada por el hecho de que ratones que carecen de este factor de transcripción tienen un fenotipo similar a los que carecen del receptor de la IL-4. Además, el papel de la IL-4 en enfermedades está mediado a través de la activación de STAT6. Dada la importancia de estas proteínas en enfermedades alérgicas, autoinmunitarias y cáncer, los mecanismos moleculares implicados en la activación de STAT6 podrían servir como dianas para el desarrollo de futuros tratamientos para estas enfermedades.

**PALABRAS CLAVE:** Interleucina 4 / STAT6 / JAK / Asma / Artritis reumatoide.

---

**ABSTRACT**

*Interleukin-4 is a cytokine that regulates multiple biological functions. It can regulate proliferation, differentiation, and apoptosis in several cell types of hematopoietic and non-hematopoietic origin. It has a critical role in the regulation of Th0 cell differentiation during a normal immune response, and IL-4-driven Th2 cells direct host responses against parasitic infections. Conversely, IL-4 and its signaling machinery have been involved in the development of immune diseases including allergy, autoimmunity and cancer. Numerous evidences indicate that IL-4 and Th2 cells can promote allergic asthma while having a protective effect in rheumatoid arthritis. Cell responses to IL-4 are mediated by a cell surface receptor complex expressed in most cell types. This receptor consists of the IL-4Rα chain and the common gamma chain (γc). The γc chain can be substituted by the IL-13Rα1 chain forming the type II receptor. The type II receptor is also a receptor for IL-13, a cytokine that shares multiple biological effects with IL-4. The binding of IL-4 to its receptor provokes the activation of JAK tyrosine kinases that mediate the phosphorylation of several intracellular proteins. Among them, the transcription factor STAT6 plays a principal role in IL-4 signaling. The importance of STAT6 is reflected by the fact that mice lacking this transcription factor and the IL-4Rα exhibit similar phenotypes. Furthermore, the role of IL-4 in disease is greatly mediated through the activation of STAT6. Given the importance of these proteins in allergy, autoimmunity and cancer, the molecular mechanisms involved in the activation of STAT6 may be good targets to design novel treatments for these diseases.*

**KEY WORDS:** Interleukin-4 / STAT6 / JAK kinases / Asthma / Rheumatoid arthritis.
INTERLEUKIN-4

IL-4 is a cytokine that participates in the regulation of the immune system at multiple levels. It is a growth and survival factor for lymphocytes and eosinophils. Although it was discovered as a B cell differentiation and stimulatory factor, its role in regulating T cell differentiation is critical during the immune response. After antigen challenge, resting T cells differentiate towards Th1 or Th2 cells. The mechanisms involved in this process are dependent on cytokines. IL-4 plays an essential role by promoting Th2 cell differentiation while inhibiting Th1 cell differentiation. IL-4 is also able to protect lymphoid cells from apoptosis, but it is unable to promote proliferation of small resting lymphocytes without a co-stimulatory signal such as that provided through antigen receptor engagement. The effects of IL-4 are not restricted to lymphoid cells. Thus, IL-4 can regulate proliferation, differentiation, and apoptosis in multiple cell types of haematopoietic and non-haematopoietic origin including myeloid, mast, dendritic, endothelial, muscular, and neuronal cells. The pleiotropic effects of IL-4 reveal the important role that this cytokine plays during a normal immune response. For the same reason, an anomalous regulation of IL-4 may implicate immune disease. IL-4-driven Th2 cell differentiation is an essential step during immune responses against parasitic infections. This is demonstrated by the severity of haematomictic infections in mice lacking IL-4 receptor and STAT6 (Signal Transducer and Activator of Transcription 6). On the other side, IL-4 and its signalling machinery can participate in the development of allergic and autoimmune diseases. It has clearly been demonstrated in animal models that allergic asthma is a disease dependent on Th2 cells and the production of Th2 cytokines, mainly IL-4 and IL-13, a cytokine that shares receptors with IL-4. In contrast to allergic diseases, autoimmune diseases are believed to be dependent on Th1 and monocytic cytokines. IL-4 can therefore act as an anti-inflammatory cytokine in these diseases as evidenced by its protective effect in murine models of Rheumatoid Arthritis and Diabetes. Therefore, IL-4 could be considered a target for the treatment of allergic diseases but a potential tool for the treatment of autoimmune diseases. The effect of IL-4 in cancer is more complex. It has been found to be effective in the treatment of experimental glioblastoma tumours, but it can also sustain tumour progression. IL-4 signalling machinery can promote resistance to anti-tumour therapy, probably by its anti-apoptotic functions. These arguments clearly indicate the importance of IL-4 in the progression of several diseases. Therefore, to determine the molecular mechanisms involved in cell responses to IL-4 would be of considerable interest, since it may provide valuable information to design novel treatments for the diseases above mentioned.

IL-4 RECEPTOR

The production of IL-4 is tightly regulated and restricted to T cells, mainly Th2, mast cells, basophils and activated eosinophils. This fact reflects the importance of this cytokine during the response against parasitic infections and allergic diseases in which all of these cell types are involved. Conversely, IL-4 receptors are expressed in most cell types including haematopoietic, endothelial, muscular, and neuronal cells. However, its expression is usually very low ranging from 50-5000 receptors per cell. Two types of IL-4 receptor have been described so far (Fig. 1). The type I consists of the IL-4Rα chain and the common gamma chain (γc). The type II also contains the IL-4Rβ chain but the γc is substituted by the IL-13 low affinity receptor 1 (IL-13Rα1). The binding of IL-4 to the receptor provokes the heterodimerization of these chains and the activation of JAK tyrosine kinases. The activation of these kinases results in the phosphorylation of tyrosine residues within the cytoplasmic tail of the IL-4Rα. It is believed that JAK1 associates with the IL-4Rα chain and JAK3 with the γc chain. In the type II receptors, TYK2 can bind to the IL-13Rα1 chain.
receptors such as IL-2 and IL-7. This chain does not bind to IL-4, but it associates with the IL-4Rα chain after the binding of IL-4. The heterodimerisation of the γc with the IL-4Rα chain is required for the activation of kinases associated with the IL-4 receptor complex. The γc can be substituted by the low affinity chain of the IL-13 receptor (IL-13Rα1) that, along with the IL-4Rα chain, forms the type II receptor. The type II receptors expressed mainly in non-haematopoietic cells. The presence of type II receptors explains why cell lines derived from SCID patients, lacking JAK3 or γc, still respond to IL-4. The type II is also a receptor for IL-13.

To date, two chains have been demonstrated to bind IL-13 with low (IL-13Rα1) and high affinity (IL-13Rα2). The IL-4Rα is unable to bind IL-13 but it associates with the IL-13Rα1 chain and initiates the signalling machinery. The fact that cell responses to IL-4 and IL-13 are mediated through the IL-4Rα chain explains the multiple biological effects shared by these cytokines.

IL-4Rα is a transmembrane protein that lacks intrinsic enzymatic activity. However, the binding of IL-4 induces the activation of tyrosine kinases. It is well established that signalling through cytokine receptors provokes the activation of the Janus family of tyrosine kinases (JAK). Treatment of cells with IL-4 results in the activation of JAK1 and JAK3. JAK1 associates with the IL-4Rα chain through the box-1 motif while JAK3 associates with the γc. Binding of IL-4 to the receptor promotes the interaction of these kinases, which are believed to be activated by cross-phosphorylation. Once activated, these kinases would mediate the phosphorylation of specific tyrosine residues within the receptor. The phosphorylated IL-4Rα can thus recruit intracellular mediators to initiate signalling. The importance of JAK1 and JAK3 in cell responses to IL-4 was demonstrated by several studies performed in cell lines and mice lacking these kinases. In these studies, it was found that the activation of intracellular intermediaries including that of the IRS (Insulin Receptor Substrate) proteins and STAT6 was severely impaired. Additional studies have shown that IL-4 can also activate AKT2 and TYK2. AKT2 can associate with the IL-4Rα chain in the type II receptors expressed in human colon carcinoma cell lines. TYK2 associates with the IL-13Rα1 chain in the type II receptor and is activated in response to IL-4 and IL-13. In addition to JAKs, other tyrosine kinases have been found to be activated by IL-4. The intracellular domain of IL-4Rα contains a conserved acidic domain that in the context of the IL-2Rβ chain is required for the activation of Src tyrosine kinases. Moreover, this acidic domain is required for IL-4-induced proliferation and protection from apoptosis, suggesting that it might also mediate the activation of Src kinases by IL-4. In fact, IL-4 can also activate several members of this family of tyrosine kinases. The importance of Src in IL-4 signalling is still not well defined but a recent study indicates that its activation occurs during the earliest events that lead to the activation of STAT6. The kinase c-fes has also been found to be regulated by IL-4. This kinase may be involved in the regulation of cell proliferation by IL-4 through the phosphorylation of IRS proteins.

The cytoplasmic tail of IL-4Rα contains several sequences that are conserved among species. In addition to the box-1 and acidic domains mentioned above, there are five tyrosine residues that are highly conserved along with their surrounding sequences. Based on these tyrosine residues and the biological functions associated with them, the IL-4Rα chain can be divided in three different regions. The first region contains the Y497, which is very important since its mutation abrogates IL-4 signalling and biological effects. This tyrosine is able to recruit several intracellular messengers including IRS proteins, Shc, SHIP (SH2-containing inositol-5-phosphatase), FRIP (Interleukin-Four Receptor Interacting Protein), and it is necessary for full activation of STAT6. IRS proteins are very important in regulating cell proliferation and protection from apoptosis by IL-4. Studies performed in cell lines lacking IRS proteins indicate that cell proliferation induced by IL-4 is dependent on these proteins. The regulation of apoptosis by IL-4 seems to be more complex. It has been found that IL-4 signals protection from apoptosis by at least two different intracellular pathways. The first pathway is dependent on IRS activation while the additional pathways have not been fully characterized. The data presented so far suggest that in addition to Y497 and IRS, the phosphatase SHIP and the carboxyl-terminal domain of IL-4Rα may be involved in the regulation of apoptosis mediated by IL-4. The role for additional proteins activated through Y497 in IL-4 signalling is still under investigation. Shc has been clearly demonstrated to be activated by IL-4 in several cell types. Shc and FRIP are involved in the regulation of Ras. However, the data published so far indicate that IL-4 is not a universal regulator of the Ras pathway.

The second domain within the cytoplasmic tail of IL-4Rα is involved in gene regulation and contains three tyrosine residues (Y713, Y631, and Y633). These tyrosines are surrounded by a similar sequence and are able to recruit, upon phosphorylation, the transcription factor STAT6 through its SH2 domain. STAT6 will be discussed below given the importance of this transcription factor in the biological functions regulated by IL-4. Finally, there is Y713 that is included within an ITIM (Immunoreceptor Tyrosine-
based Inhibitory Motif). This tyrosine is believed to be involved in the activation of phosphatases and has been implicated in downregulating cell responses[50] but also in protection from apoptosis by IL-4[42]. However, further studies are necessary to delimit the proteins activated through Y713 and their role in signalling.

**STAT6**

IL-4 is able to activate several intracellular proteins, and the transcription factor STAT6 plays a critical role in cell responses to this cytokine[48]. Mice lacking STAT6 show a phenotype similar to those deficient for the IL-4R chain. In both cases, the production of IgE, CD23 expression, and Th2 cell formation is severely impaired[48-50]. Furthermore, the importance of IL-4 and IL-13 in disease is greatly mediated through the activation of STAT6. Thus, knockout mice for STAT6 or the IL-4R chain fail to respond to parasitic infections[48]. These animals are also prevented from allergic diseases[50], and in contrast, they experience more aggressive autoimmune diseases[48]. Therefore, the determination of the molecular mechanisms involved in the activation of STAT6 by IL-4 and IL-13 could be of crucial interest for these diseases.

Since their discovery, the activation of STAT transcription factors was associated with JAK kinases[48]. In fact, this metabolic pathway was named as the JAK/STAT pathway. The mechanisms of activation proposed for STAT6 are similar to those for other STATs[46]. Like other STATs, STAT6 is found in the cytoplasm in a monomeric non-phosphorylated form. The binding of IL-4 to its receptor provokes the activation of tyrosine kinases and phosphorylation of tyrosine residues within the cytoplasmic tail of the IL-4Rα chain. STAT6 binds through its SH2 domain to the phosphorylated residues Y573, Y603, and Y631[47]. In this complex, STAT6 is also phosphorylated at tyrosine residues Y576, Y603, and Y631[48]. Several IL-4-regulated genes are dependent on the promotion of inducible genes. STAT6 preferentially binds to the sequence TCCNCAAA although it can also recognize the most standard STAT sequence TCCNCAAA[51]. STAT6 leaves the receptor complex, dimerizes, and migrates to the nucleus where it binds to GAS consensus sequences in the promoter of genes. Consequently, tyrosine phosphorylation of STAT6 regulates DNA binding while serine phosphorylation regulates transcriptional activation. In both cases, the inhibition of phosphorylation abrogates the regulation of transcription by IL-4.

Several mechanisms have been proposed for the inhibition of STAT6 activity. They include dephosphorylation of tyrosine residues by phosphatases and proteolytic processing by specific proteases. The SHP-1 phosphatase has been demonstrated to participate in STAT6 down-regulation[49]. SHP-1 could be activated through Y575 within the gene
regulatory domain of the IL-4Rα(59) and Y713 within the ITIM motif in the carboxy terminal domain(59-61). In fact, the association of the Q576R mutation with atopy and asthma has been proposed to be due to a diminished activation of SHP-1 which would result in an enhancement of STAT6 activation(61). However, this proposal was not supported by other studies(60). The Y713F mutation has also been suggested to enhance IL-4-induced STAT6 activation by a SHP-1-dependent mechanism(60). A second way of inactivation of STAT6 is through proteolytic processing by proteases. The proteasome has been involved in the inactivation of STAT proteins through degradation of JAK kinases by a SOCS (Suppressor of cytokine signaling)-dependent mechanism(65). SOCS-1 and SOCS-3 down-regulate IL-4-induced STAT6 activation through degradation of JAK1. SOCS-5 is expressed in Th1 cells, and its constitutive association of the Q576R mutation with atopy and asthma was suggested to enhance IL-4-induced STAT6 activation by a SHP-1-dependent mechanism(60). A recent article describes that proteasome inhibitors increase the half-life of phosphorylated STAT6(60). However, it was not shown whether STAT6 was a direct target for proteasome. Two independent groups have found that additional nuclear proteases can proteolytically regulate target for proteasome(59). These inhibitors are normally induced through cytokine stimulation. They usually turn down signalling by inhibiting the kinase activity associated with the receptor. SOCS proteins can bind to phosphorylated cytokine receptors and JAK kinases through their SH2 domains. SOCS-1, SOCS-3, and SOCS-5 have been described to inhibit STAT6 activation(59, 65). SOCS-1 and SOCS-3 down-regulate IL-4-induced STAT6 activation by inhibiting JAK1 kinase activity since they target this kinase(59). SOCS-5 is unique in its ability to bind to unphosphorylated IL-4Rα(65). It binds to a fragment of the receptor next to the Box-1 motif, inhibiting the binding of JAK1. SOCS-5 is expressed in Th1 cells, and its constitutive expression inhibits IL-4-dependent STAT6 activation and Th2 cell production. For this reason, SOCS-5 has been proposed as a potential tool for the development of future treatments for allergic diseases in which Th2 cells and IL-4 are involved(60).

IL-4 AND DISEASE

Allergic Diseases: Asthma

Allergic diseases are a group of disorders originated by a Th2-dependent mechanism(65). They include several pathologies such as allergic asthma, atopic dermatitis, and systemic anaphylaxis. IL-4 and IL-13 are intimately involved in the origin of these diseases through STAT6-dependent mechanisms(16-18, 48-50). These cytokines are implicated in many cellular and biochemical events that account for asthma and allergy(25) (Fig. 3). They regulate Th2 cells, mast cells, eosinophils, neutrophils, globet cell hyperplasia, IgE production, adhesion molecules, chemokines, and airway hyperresponsiveness. This is reflected by the fact that administration of IL-4 or IL-13 to mice induces asthma symptoms including eosinophilia, mucus production, and airway hyperresponsiveness(67). However, the blockade of IL-4 during secondary antigen challenge had only reduced effects, suggesting that additional cytokines were involved during the secondary response to the allergen. Interestingly, IL-13 seems to be implicated in this process since selective neutralisation of this cytokine with a soluble IL-13 receptor ameliorates asthma symptoms induced by allergens(66). Moreover, mice lacking IL-4 or IL-13 experience mild asthma symptoms, indicating that both cytokines are necessary for the progression of allergic asthma(68). Based on these data, it has been proposed that IL-4 is important during allergen challenge, due to its role in regulating Th2 cell differentiation, while further processes are controlled by IL-13. The effect of these cytokines in asthma is dependent on STAT6 activation through the IL-4Rα chain. Thus, mice lacking this transcription factor are protected from allergen-
induced asthma(50). Furthermore, a soluble form of IL-4Rα that inhibits IL-4 and IL-13 signalling can prevent asthma in mice, suggesting that this can be a good approach for asthma treatment(18). Similar to mice, human allergic diseases seem to be also dependent on the production of cytokines by Th2 cells. Several evidences indicate that in humans, IL-4 and IL-13 also play a key role in allergic asthma. Atopy, the genetic predisposition to produce high levels of IgE is the principal predisposition to asthma(50). The production of this immunoglobulin is dependent on IL-4. The chromosome regions containing the genes encoding for IL-4, IL-13, IL-4Rα and STAT6 have been associated with atopy and bronchial asthma(46). Several studies have found that mutations within the gene encoding for the IL-4Rα chain can predispose to asthma. The mutations IVSIV(47) and Q57R(50) have been proposed to be associated with asthma, probably by enhancing STAT6 activation. However, additional studies did not confirm this hypothesis(50). A clinical trial is being performed to evaluate the therapeutic value of a soluble IL-4 antagonist form of the IL-4Rα(50). The results reported in this study are very promising. Subjects treated with this soluble receptor experience an improvement of asthma that can even allow the discontinuation of steroid treatments. Given the importance of STAT6 in the regulation of asthma symptoms by IL-4 and IL-13, it could be interesting to develop specific inhibitors of this transcription factor to investigate their efficacy in the treatment of this disease. Systemic anaphylaxis, another allergic condition, is also dependent on the activation of STAT6 through IL-4Rα(50). Therefore, these molecular pathways may also be good targets for developing therapeutic approaches.

Cellular and molecular mediators of allergic diseases are similar to those involved during the immune response against gastrointestinal parasites(50). They include IgE, mast cells, and eosinophils. The expulsion of gastrointestinal parasites is also dependent on Th2 cells and the production of IL-4 and IL-13(50). In fact, IL-13 seems to be more important than IL-4 during expulsion of nematodes such as N. brasiliensis(50). The effect of these cytokines is greatly mediated through the IL-4Rα chain and STAT6 activation(50). In addition to the effect of these cytokines in the immune system, the expression of IL-4Rα chain in non-haematopoietic cells is also required for the expulsion of parasites, indicating an important direct effect of these cytokines on gastrointestinal cells during this process(50). As mentioned above, inhibitors of IL-4 and IL-13 signalling are under investigation for the treatment of allergic diseases(50). These potential treatments may be considered in regions where nematode infections are endemic due to the critical role of these cytokines during the expulsion of parasites.

Autoimmune Diseases: Rheumatoid Arthritis

In contrast with allergic diseases, IL-4 can act as an anti-inflammatory cytokine in autoimmune diseases(75). These diseases are believed to be originated by an abnormal activity of the immune system(75). They are dependent on Th1 and monocyte cell activation. These cells produce pro-inflammatory cytokines such as IL-1, IL-6, IL-12, and TNFα that are at the origin of these diseases, as demonstrated for Rheumatoid Arthritis(75). As mentioned before, IL-4 can inhibit Th1 cell formation by driving Th0 cell differentiation towards the Th2 cell type(5). The ability of IL-4 to inhibit the production of pro-inflammatory cytokines by monocytes while inducing the production of anti-inflammatory factors such as IL-1R antagonist or soluble TNFα receptors is also well known(75). It is interesting to note that IL-4 production has not been detected in cells from the rheumatoid synovium, and the level of IL-4 in synovial fluid is very low or absent(75). These facts may explain the prevalence of Th1 cytokines and the high levels of inflammatory cytokines found in synovial fluids(75). Given the role of IL-4 in these processes, it has been proposed that IL-4 may be a potential therapeutic agent for the treatment of autoimmune diseases(75). Animal models evidence the importance of IL-4 in the progression of autoimmune diseases. Rheumatoid Arthritis is an inflammatory process that results in the destruction of tissues. The progression of this disease is more aggressive in animals lacking IL-4 than in the wild type counterparts(50). Gene therapy using adenoviral vectors and dendritic cells engineered to express IL-4 can reduce inflammation and ameliorate joint destruction in animal models of rheumatoid arthritis(50). This is very important since osteoclasts are required for joint destruction mediated by TNFα(50). For these reasons, it has been proposed that IL-4 could be a good complement for treatments based on anti-TNFα therapies(50). In humans, an IL-4 gene polymorphism has been associated with protection against joint destruction in chronic polyarthritis patients, suggesting that IL-4 can contribute to the regulation of joint destruction in rheumatoid arthritis as it happens in animal models(50). So far, mutations within the IL-4Rα that are associated with disease progression have not been described(50). The beneficial effects of IL-4 in rheumatoid arthritis seems to be mediated through STAT6 activation since mice lacking this transcription factor also experience a more aggressive disease(50). Autoimmune Diabetes type 1 is also dependent on Th1 cells(50). IL-4 could therefore be a protective cytokine in this disease since it promotes Th2 cell responses. Mice treated with recombinant IL-4 or constitutively expressing IL-4 were protected against the development of experimentally induced diabetes(50). Although these results are promising, it is not yet known whether IL-4 has similar effects on human autoimmune diseases.
from experimental autoimmune diabetes. Surprisingly, the lack of IL-4Rα protected mice against the induction of diabetes in a model of autoimmune insulin-dependent diabetes mellitus. The explanation for this unexpected finding has yet to be defined. Other autoimmune diseases driven by Th1 cells like psoriasis can also be improved by IL-4 treatment. It has recently been described that treatment with statins may improve experimental autoimmune encephalomyelitis (EAE) by a STAT6-dependent mechanism. EAE is a disease model of multiple sclerosis, a Th1-dependent autoimmune disease that affects the central nervous system. The authors found that treatment with statins induced the activation of STAT6. This effect promoted the differentiation of Th0 cells into Th2 cell type and the production of Th2 cytokines. As a result, the Th2 cell responses induced by statins protected mice from the induction of EAE. This could be an important example of the utility of IL-4 and STAT6 as potential tools for the treatment of autoimmune diseases.

**Other Diseases: Cancer**

The role of IL-4 in cancer has also been investigated. IL-4 is a potential anti-apoptotic cytokine. It is a survival factor for tumour cells, and it can protect tumour cells from apoptosis induced by multiple agents including those used in anti-tumour therapy. Therefore, it is possible that IL-4 participates in resistance to cancer treatments. This has been observed in mouse models. Mice lacking IL-4Rα and STAT6 were protected from tumour recurrence although by an IL-4-independent IL-13-dependent mechanism. In humans, the IL-4-inducible gene FIG1 is activated in primary B-cell lymphomas, suggesting that the IL-4 signalling pathways are constitutively stimulated in these cells. Conversely, IL-4 has been investigated as a therapeutic agent in cancer, perhaps by its toxic effects in some tumour cells. Thus, transfer of retrovirus expressing IL-4 and primary neural progenitor cells transfected with IL-4 was effective in the treatment of rat brain Glioblastomas. Moreover, several clinical trials have been undertaken to evaluate IL-4 as a potential agent for cancer treatment. IL-4 has been tested in patients with renal cell carcinoma, chronic lymphocytic leukemia, and non-Hodgkin’s lymphoma. In general, the results found have not covered the expectations and positive responses rarely occurred. In fact, treatment with IL-4 can enhance the number of CLL cells in blood, probably due to its antiapoptotic effects. In contrast, IL-4 collaborates with GM-CSF improving the number and functions of antigen presenting cells in cancer pathogenesis. The authors of this study suggest that these cytokines may be used as adjuvants for cancer treatments. IL-4 can also participate in HIV infection and disease progression. It induces the expression of HIV co-receptors CXCR4 and DC-SIGN, and activates HIV expression which can accelerate disease progression.

**REFERENCES**


**ACKNOWLEDGMENTS**

This work was supported by grants from Fondo de Investigación Sanitaria (01/0357), and Junta de Extremadura (2PR01C015). JZ is supported by Subdirección General de Investigación Sanitaria (Exp. 99/3192).

**REFERENCES**

Costimulation of resting B lymphocytes alters the IL-4-activated IKB/ubiquitin-signaling pathway in a STAT6-independent manner implicating for cell survival and proliferation. Cell Res. 2003. 11: 44-54.


55. Tinnell SB, Jacobs-Helber SM, Sterneck E, Sawyer ST, Conrad DH. 
53. Quelle, FW, Shimoda K, Thierfelder W, Fischer C, Kim A, Ruben 
52. Ihle JN. STATs: signal transducers and activators of transcription. 
49. Shimoda K, van Deursen J, Sangster MY, Sarawar SR, Carson RT, 
46. Ryan JJ, McReynolds LJ, Huang H, Nelms K, Paul WE. Characterization 
45. Wery S, Letourneur M, Bertoglio J, Pierre J. Interleukin-4 induces 
43. Nelms K, Snow AL, Hu-Li J, Paul WE. FRIP, a hematopoietic cell-
42. Zamorano J, Keegan AD. Regulation of apoptosis by tyrosine-
40. Deutsch HH, Koettniz K, Chung K, Kalthoff FS. Distinct sequence 
37. Deutsch HH, Koettniz K, Chung K, Kalthoff FS. Distinct sequence 
36. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
35. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
34. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
33. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
32. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
31. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
30. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
29. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
28. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
27. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
26. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
25. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
24. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
23. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
22. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
21. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
20. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
19. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
18. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
17. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
16. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
15. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
14. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
13. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
12. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
11. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
10. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
9. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
8. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
7. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
6. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
5. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
4. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
3. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
2. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 
1. Bennett BL, Cruz R, Liaoquin RG, Man-nung AM. Interleukin-4 

77. Miossec P, Naviliat M, D’Angelo AD, Saric J, Banchereau J. Low levels of Interleukin-4 and high levels of transforming growth factor b in rheumatoid synovitis. Arthritis Rheum 1990; 33: 1180-1187.