

● **Abstract**

Interleukin-6 (IL-6) is a typical pleiotropic cytokine that modulates a variety of physiological events in vertebrates, such as cell proliferation, differentiation, survival, and apoptosis, among others functions. IL-6 plays roles in the immune, the endocrine, the nervous, and the hematopoietic systems, in bone metabolism, regulation of blood pressure and inflammation. Furthermore, IL-6 has effects on other tissues and organ systems. Many cell types are reported to produce IL-6: T cells, B cells, polymorphonuclear cells, eosinophils, monocyte/macrophages, mast cells, dendritic cells, chondrocytes, osteoblasts, endothelial cells, skeletal and smooth muscle cells, islet cells, thyroid cells, fibroblasts, mesangial cells, keratinocytes, microglial cells, astrocytes, oligodendrocytes, adipose tissue and certain tumour cells. Here, we review the participation of the IL-6 protein in different diseases. The specific targeting of the IL-6 pathway can be a promising new approach for the treatment and prevention of neurodegenerative disorders, myocardial infarction, lupus, restenosis, arterosclerosis, reumathoid arthritis, and some infectious diseases in humans. Furthermore, blocking the effect of IL-6 may improve the autoinflammatory process both systemically and locally.

● **Introduction**

Interleukin (IL)-6 is a typical pleiotropic cytokine that modulates a variety of physiological events in

vertebrates, such as cell proliferation, differentiation, survival, and apoptosis. IL-6 plays roles in the immune system, the endocrine, the nervous, the hematopoietic system, and inflammation (1) (Figure 1).

dendritic cells, chondrocytes, osteoblasts, endothelial cells, skeletal and smooth muscle cells, islet cells, thyroid cells, fibroblasts, mesangial cells, keratinocytes, and certain tumour cells. In addition, adipose

Furthermore, IL-6 has effects on bone metabolism, and other tissues and organ systems (2) (Figure 1). Many cell types are reported to produce IL-6; these include T cells, B cells, polymorphonuclear cells, eosinophils, monocyte/macrophages, mast cells,

tissue is a source of IL-6. Microglial cells and astrocytes are also IL-6 producers (Figure 2).

The role of the pleiotropic cytokine interleukin- 6 (IL-6) during disease

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J. M-M finished his PhD in 1997 under Dr. Carlos Larralde (Emmeritus Professor) advisement, at the Department of Immunology in the Institute for Biomedical Research, UNAM, México in 1997. He spend 3 years of Posdoctoral training at the Department of Cellular Biology, at the University of Georgia, in Athens, USA, under Dr. Raymond T. Damian (Franklin and Emmeritus Professor) advisement, and currently holds a Tenure track position as Full time proffesor in the same Departament where he got his PhD. He has 32 research articles published, several prices and awards granted during his carrer, and has several grad and undergrad students under his advisement. His current research interests include the study of the neuroimmuno endocrinological network in health and in disease, focussing mainly in parasitic diseases. Also, the study of the role of molecules as IL-6 in the function of the neural and endocrine systems is of interest.

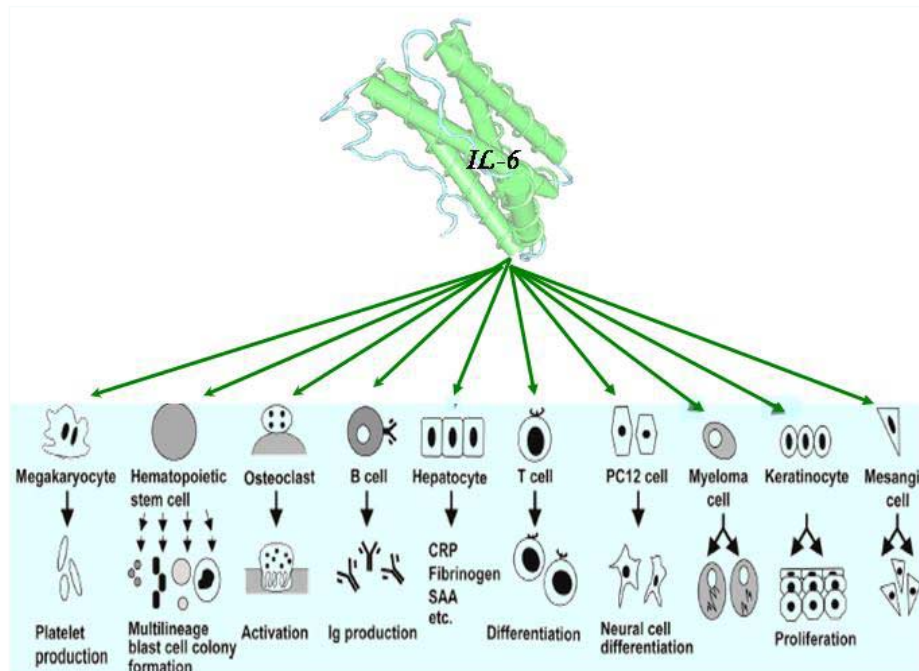


Figure 1: Schematic representation of the physiological effects of IL-6. IL-6 modulates a variety of physiological events in vertebrates by playing different roles in the function of the immune, the endocrine, the nervous, the hematopoietic systems, in bone metabolism, regulation of blood pressure and inflammation. A wide variety of cell types are reported to produce IL-6.

The mouse IL-6 protein is a refolded 185 amino acid polypeptide, 42% homologous to the human form and contains several potential O-linked glycosylation sites instead of the N-linked glycosylation site (5) (Figure 3).

● **Transcriptional control of IL-6**

The huIL-6 gene is located in the short arm of chromosome 7p21 and has a-174 G/C polymorphism in its promoter region (5,6). huIL-6 gene size is approximately 5 kb, consisting of five exons with four introns (7). The C allele at position-174 in the promoter of the IL-6 gene has been associated with reduced gene expression and reduced plasma levels of the protein (7). For the transcriptional control of IL-6, several potential promoter elements are found in the 5-flanking region of the IL-6 gene. These include the NF- κ B binding site, a multiple response element, the *c-fos* serum-responsive element homolog, a glucocorticoid-responsive element, the AP-1 binding site, cyclic AMP-responsive element, and the nuclear factor for IL-6 expression-binding site (CCAAT/enhancer binding protein) among others (8). The products of tumour-suppressor genes, p53 and retinoblastoma protein, are reported to repress the IL-6 promoter activity contained in the sequence from nucleotides -225 to +13 (8). IL-6 can undergo post-transcriptional modifications such as glycosylation (9) and serine phosphorylation (10). Because recombinant IL-6 protein produced by prokaryotes appears to be functional, its glycosylation seems not to be necessary for its biological activity (11) (Figure 3).

● **IL-6 receptor**

The receptor for IL-6 (IL-6R, also known as gp80 or CD126), contains an Ig-like domain and tandem fibronectin (FN) type-III domains including a four-cysteine motif and a tryptophan-serine-tryptophan-serine motif in the extracellular region. The four-cysteine and tryptophan-serine-tryptophan-serine motifs are responsible for the ligand binding, and thus are called the cytokine-binding module (CBM). Besides, the CBM, gp130 has three additional FN type-III domains in its extracellular region (12). The cytoplasmic domain

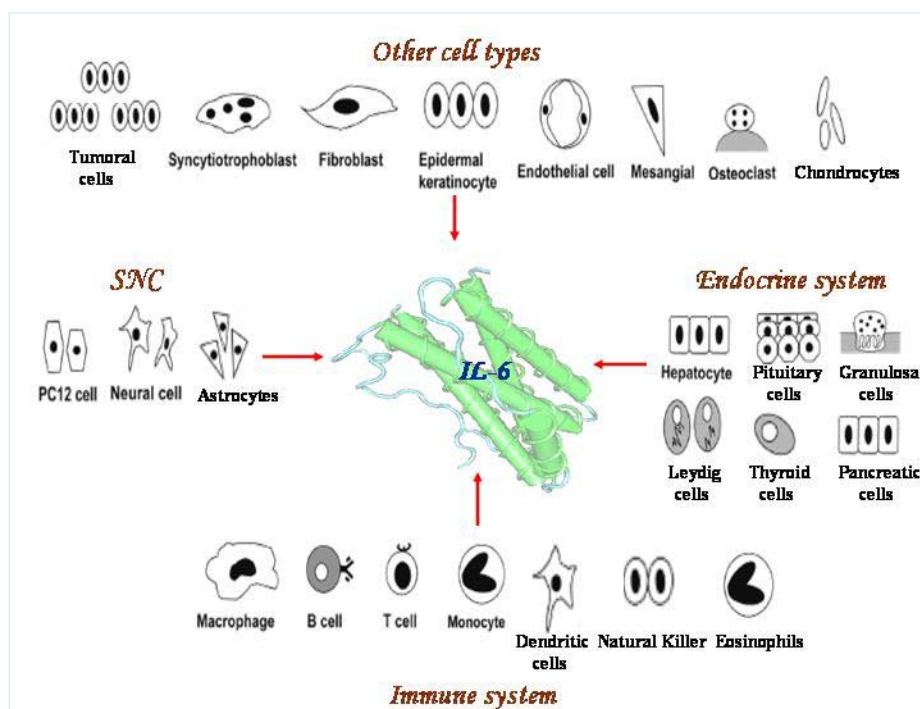


Figure 2: Diagram that shows the different types of cells that are reported to produce IL-6. Among others, T cells, B cells, polymorphonuclear cells, eosinophils, monocyte/macrophages, mast cells, dendritic cells, chondrocytes, osteoblasts, endothelial cells, skeletal and smooth muscle cells, islet cells, thyroid cells, fibroblasts, mesangial cells, keratinocytes, microglial cells, astrocytes, oligodendrocytes, adipose tissue and certain tumour cells reported IL-6.

of gp130 contains several potential motifs for intracellular signaling, recruitment motifs for STAT (signal transducer and activator of transcription) activation. Unlike many growth factor receptors, but common for cytokine receptors, gp130 does not have an intrinsic kinase domain (13). Instead, like other cytokine receptors, the cytoplasmic domain of gp130 contains regions required for its association with a non-receptor tyrosine kinase called Janus kinase (JAK), at which downstream signaling cascades are initiated (Figure 3). The expression of gp130 is ubiquitous (14), while that of IL-6R is more restricted. IL-6R is found on hepatocytes, intestinal epithelial cells (15), endocrine glands such as the pituitary and adrenal cortex (16), and leukocytes, but not on naïve B cells or certain cell lines. In addition, dexamethasone treatment upregulates IL-6R expression in osteoblasts (17).

IL-6R has at least two types of soluble forms (sIL-6R) that are generated by proteolytic cleavage of the membrane-bound form or by alternative splicing of its mRNA. Taking the widespread distribution of gp130 and the shedding of sIL-6R into consideration, it is easy to imagine how IL-6 can function in a wide variety of

systems in the body (Figure 3).

● **Immunological effects of IL-6**

IL-6 is normally involved in the regulation of the humoral immune response (Th2), acts on B cells to promote Ig production and is a growth factor for plasmacytoma *in vivo*, and it is an important *in vivo* SOS signal which coordinates activities of liver cells, macrophages and lymphocytes (18). IL-6 has the ability to stimulate B-cell differentiation, (19) activate thymocytes and T-cells for differentiation (20), activate macrophages (21), stimulate hepatocytes to produce acute-phase proteins (22) and activate natural killer (NK) cells (23). IL-6 also possesses anti-inflammatory properties (24,25). Mouse IL-6 also acts on B cells activated with anti-Ig or dextran sulfate (25).

The constitutive overexpression of IL-6 in mice leads to the development of mesangio-proliferative glomerulonephritis with IgG1 plasmacytosis in the C57BL/6 background (26), and the development of transferable plasmacytoma with chromosomal translocation (27) in the BALB/c background (28).

In T cells, IL-6 confers significant effects on proliferation,

survival, and type-1 helper T-cell (Th1)/Th2 responses. In addition, IL-6 prevents anti-CD3-induced apoptosis in T cells (29). IL-6 also affects the Th1/Th2 balance, by directing Th2 differentiation. When IL-6 is added to a culture under conditions that induce Th differentiation, T cells produce more Th2 cytokine (IL-4) and less Th1 cytokine (IFN- γ) than a culture lacking IL-6 (30). IL-6 upregulates the NFAT (nuclear factor of activated T cells) transcriptional activity by increasing the levels of NFATc2. In T cells from transgenic mice expressing a dominant-negative form of NFAT or in NFATc2 KO mice, the ability of IL-6 to promote Th2 differentiation is diminished (31). IL-6 also affects the differentiation of professional antigen-presenting cells such as macrophages and dendritic cells (DCs) (32). IL-6 also modulates leukocyte recruitment. The injection of carageenan into an artificially created subcutaneous dorsal air-pouch in mice induces local inflammation (33). The lung-specific or pancreatic islet cell-specific overexpression of IL-6 in mice results in the infiltration of mononuclear cells into the affected areas (34). These results further support the functional effect of IL-6 on leukocyte recruitment.

● IL-6 role on bacterial and viral infections

Several reports indicate that IL-6 plays an important role in the host response to bacterial and viral infection. IL-6 KO mice cannot efficiently control vaccinia virus and *Listeria monocytogenes* infections (35). IL-6 KO mice are also highly susceptible to infection by *Escherichia coli* (36) and *Candida albicans* (37). Conversely, the injection of recombinant IL-6 into mice, rendered them more resistant to *Listeria* infection (38) (Figure 4).

● IL-6 and its role in parasitic diseases

In considering the pathology associated with helminth infections, the most common host response to such infection is inflammation. The mechanism(s) whereby inflammation is initiated and the cell types involved will dictate the kinds of acute phase plasma changes that are associated with the infection. Parasites, appear

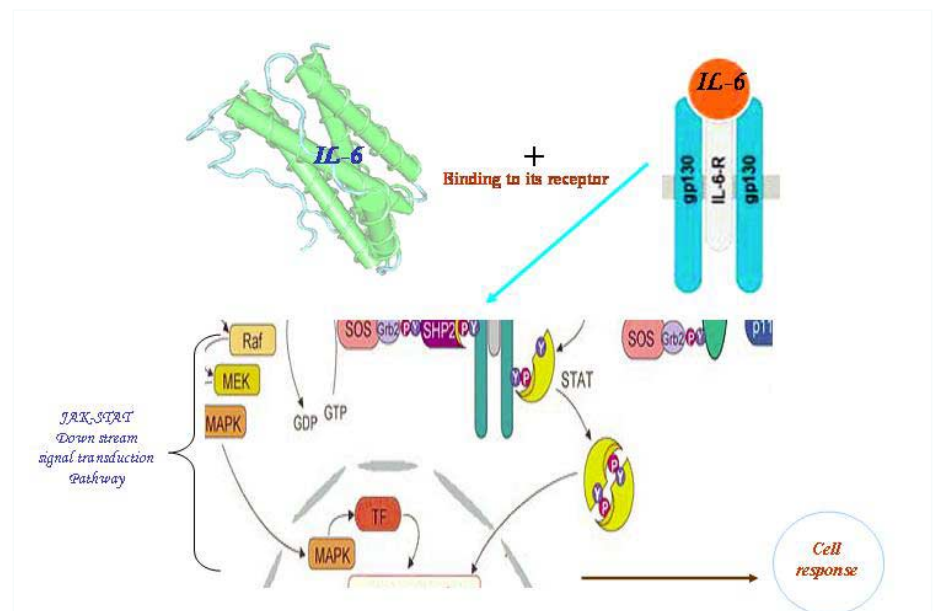


Figure 3: Structural model of the signalling of the IL-6-IL-6r complex. Upon binding, the IL-6-IL-6r complex activates the JAK/STAT pathway and the MAPK cascade, which induces specific gene expression, resulting in a specific cell function. In Fig. It is represented the structures for vIL-6/gp130, gp80, STAT3 and SHP2, as well as molecular models of a JAK2 kinase domain and SOCS1 are represented. In the extracellular part, IL-6 is shown in red, IL-6R alpha in green and the two gp130 molecules of the homodimer in cyan and blue. The domains D4–D6 of gp130, as well as the FERM, SH2 and kinase-like domains of the JAKs, are depicted as coloured ovals with the sizes corresponding to the tenascin FNIII, moesin FERM, SH2 and insulin receptor kinase domains. Arrangement of D4–D6 of gp130 as previously described. The cytoplasmic parts of gp130 and gp80, as well as the non-structured extracellular 'stalk' region of gp80, are represented as blue and green lines with lengths corresponding to non-structured polypeptides. The positions of the six tyrosine residues of gp130 are indicated and the box1 and box2 regions are drawn as black lines. Also, the cytoplasmically associated proteins are depicted in different colors.

to initiate the acute phase plasma response only when their migration leads to tissue destruction and local inflammation such as that caused by parasitemia with *Trypanosoma cruzi* (39) or with migration of *Nippostrongylus brasiliensis* (40), both in the mouse (Figure 4). The macrophage or monocyte, upon interaction with the infectious pathogen, becomes activated and secretes a number of factors, including IL-6, which have a marked effect on the total acute phase reaction. In addition to an effect on phagocytic and immune systems, IL-6 cause hepatocytes to markedly increase the secretion of plasma acute phase proteins. Some of these proteins return to the site of inflammation and interact with the infectious pathogen and/or cells and proteins of the host, thereby affecting the final outcome of inflammation (41).

The initial interaction of a parasite with the mammalian host involves early recognition by the macrophage, thereby initiating both the humoral and cellular acute phase reactions, and subsequently affects the

immune response against the parasite. Variations in the acute phase reaction may help to explain differences in susceptibility to infectious organisms and the presence or lack of host killing mechanisms for the parasite (42). One early reaction of the host to infection with protozoan parasites is the secretion of an array of potent cytokines including tumour necrosis factor (TNF), interleukin (IL-1) and IL-6. The combined action of these cytokines causes fever, leukocytosis and the production of acute phase proteins such as C-reactive protein (CRP). These early responses contribute significantly to the outcome of infection by influencing the course of infection directly and by regulating the specific immune response to the parasite (43) (Figure 4).

The infection of mice with *Plasmodium chabaudi* is characterized by a rapid and marked inflammatory response with rapid but regulated production of interleukin-12 (IL-12), tumor necrosis factor-alpha (TNF-alpha), and interferon-gamma (IFN-gamma). *P. chabaudi*-infected erythrocytes stimulate

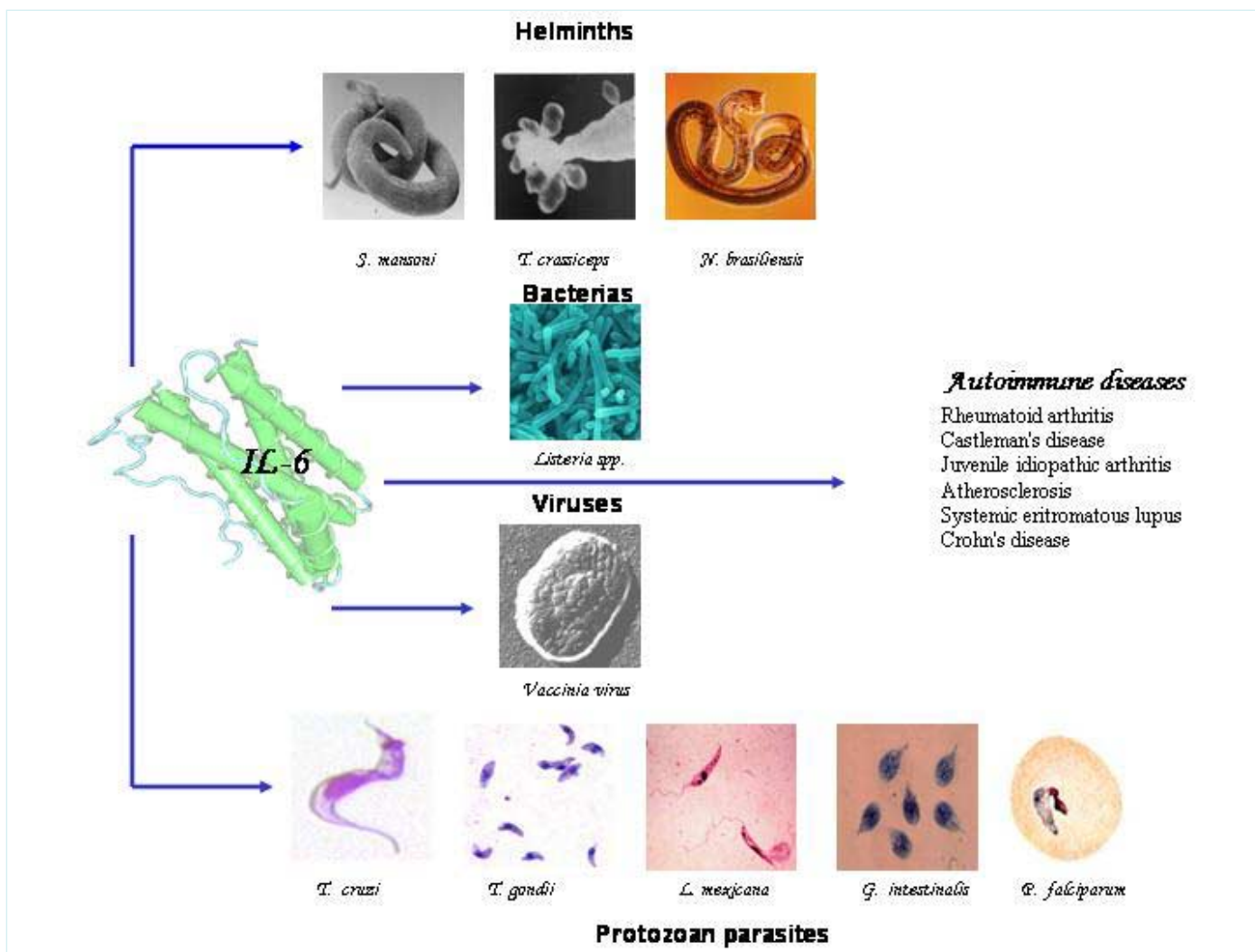


Figure 4: IL-6 has been show to play a protagonic role in the defense against parasitic (several worms and some protozoan), bacterial and viral infections, as well as being a key player during several autoimmune diseases. For instance, IL-6 determines the elimination of vaccinia virus and *Listeria monocytogenes* infections. With respect to parasitic diseases, the pathology associated with helminth infections is inflammation. The mechanism(s) whereby inflammation is initiated and the cell types involved will dictate the kinds of acute phase plasma changes that are associated with the infection. Parasites, appear to initiate the acute phase plasma response only when their migration leads to tissue destruction and local inflammation. The combined action of several cytokines, inclkuiding IL-6, causes fever, leukocytosis and the production of acute phase proteins such as C-reactive protein (CRP). These early responses contribute significantly to the outcome of infection directly and by regulating the specific immune response to the parasite.

an increase in the expression of co-stimulatory molecules and MHC class II on mouse bone marrow-derived DCs, and they are able to induce the production of IL-6, thus enhancing the Th1 response of naive T cells (44) (Figure 4).

Toxoplasma gondii is an intracellular protozoan parasite which invades various organs including the central nervous system. Immunity is crucial for preventing development of toxoplasmic encephalitis (TE) following infection. IFN-gamma-mediated immune response plays a central role in resistance (45). The activation of microglia and astrocytes by IFN-gamma or a combination of this cytokine with TNF-alpha appears to be an important effector mechanism in host immunity. IL-6 may participate in this activation. IL-6 plays a protective

role, at least in part, by up-regulating IFN-gamma production during the chronic stage of infection in mice. IL-6 also plays a role in regulating the infiltration of T cell subsets into the brain (46) (Figure 4).

A significant modulatory effects of IL-6 on the cell number per *in vitro* granuloma and on the morphology of the cells involved in the pathology produced by *Nippostrongylus brasiliensis* has been reported. Conceivably, elevated IL-6 levels may modulate granuloma formation with respect to the number of cells involved and in influencing distinct cell populations involved in granuloma formation (47). During *E. granulosus* infection, the coexistence of elevated quantities of IFN-gamma, IL-4, IL-5, IL-6

and IL-10 has been shown, which are observed in most of hydatid patients. These findings support Th1 and Th2 cell activation in human hydatidosis. In particular, Th1 cell activation seems to be related to protective immunity, and Th2 cell activation to susceptibility to disease (48) (Figure 4).

In early stages of experimental murine cysticercosis caused by *Taenia crassiceps*, there is a clear but transient Th1-type immune response (characterized by high levels of IIL-2, IFN-g, concanavalin A, and antigen specific response, and delayed-type hypersensitivity, that associates with a low rate of parasite reproduction. As time of infection progresses, an energetic and more permanent Th2-type response follows (characterized

by high levels of IL-4, IL-6, and IL-10) that in turn associates with an increment in the rate of parasite reproduction (49). Sequential activation of Th1-type and Th2-type responses in murine cysticercosis would appear to progressively favour parasite reproduction, explaining the long time residence and the massive parasite intensity reached in chronic infections (49) (Figure 4).

Also, during *Taenia crassiceps* cysticercosis, an impressive feminisation of male mice has been described during chronic infection, characterized by increased serum estradiol levels 100 times their normal values, while those of testosterone and dihydrotestosterone are decreased by 85 and 95% respectively. Concomitantly, the levels of follicle-stimulating hormone and IL-6 are increased 70 and 90 times their normal values in infected male mice. Interestingly, depletion of IL-6 using IL-6(-/-) knockout mice does not produce the feminisation process stated above, while restitution of the IL-6(-/-) knockout, irradiated, and thymectomized mice with murine recombinant IL-6 restores the feminisation process. Expression of the IL-6 gene was found only in the testes and spleen of infected animals (50). Moreover, IL-6 KO mice of both genders infected with *T. crassiceps* cysticercosis harbour similar numbers of parasites, with no change in sex-hormone levels. However, in wild-type strains, females have twice as many parasites as males. At the same time, there is a decrease of 80% in testosterone and dihydrotestosterone serum levels, and a 100-fold increase in the levels of estradiol in infected male mice. These results suggest a role for IL-6 in sex-associated susceptibility in murine *T. crassiceps* cysticercosis (51) (Figure 4).

In baboon schistosomiasis, temporal Northern blot analysis of cytokine messenger RNA (mRNA) expression in granulomatous baboon livers demonstrated tissue-specific expression of IL-6 at week 6 of infection and decayed thereafter. IL-6 may also regulate the function of the hypothalamic-pituitary-adrenal axis during schistosomiasis, since serum levels of corticotrophin-releasing hormone, adrenocorticotrophin,

cortisol and dehydroepiandrosterone were confirmed to be decreased in infected baboons as previously shown (52), with a concomitant expression of IL-6, in hypothalamic-pituitary-adrenal axis tissues. These results suggest that specific IL-6 expressed in hypothalamic-pituitary-adrenal axis tissues could regulate hormone secretion during schistosomiasis (52). Together, these data imply neuroendocrinological influences of IL-6 on disease progression in schistosomiasis (52).

Another report has shown that the levels of IL-6 in the sera of bladder cancer patients were correlated with the clinicopathological parameters, Bilharziasis and the occurrence of relapse of the carcinoma among Egyptian bladder cancer patients. IL-6 was strongly associated with malignant phenotype of Egyptian bladder tissues, so they may be used as additional markers for assessment of bladder cancer patients (53). In another study, using IL-6-deficient, 129 x C57BL/6 mice and normal littermate controls, the role of IL-6 in granulomas of mice infected with *Schistosomiasis mansoni* was studied. Granulomas from IL-6(+/-) mice produced large quantities of IL-6, derived from T, B, and myeloid cells. Yet, IL-6 mutant mice generated normal-appearing granulomas of appropriate size (53). Multiple-parameter flow cytometric analysis of dispersed granuloma cells revealed no substantial differences. Granuloma cells and splenocytes were cultured *in vitro* to measure cytokine and immunoglobulin production (53). Compared to control cells, IL-6(-/-) granuloma cells secreted more IL-4, IL-5, and IL-10. However, splenocytes secreted cytokines comparably. In the IL-6(-/-) state, the granuloma cells released less IgE and substantially more IgM, although IgG1, IgG2a, and IgA secretion remained normal. ELISPOT assay showed that dispersed granuloma cells from IL-6-deficient animals had substantially more IgM-secreting B cells. Thus, schistosome granulomas make IL-6 that is not essential for most aspects of granuloma development. However, IL-6 deficiency results in some disturbance of granuloma cytokine and immunoglobulin expression (54).

● IL-6 role in autoimmune diseases

Deregulated overproduction of IL-6 has been found to play pathological roles in chronic inflammatory diseases such as rheumatoid arthritis, Castleman's disease, juvenile idiopathic arthritis, atherosclerosis, systemic erythematous lupus and Crohn's disease. Humanized anti-IL-6 receptor antibody has been developed as a therapeutic agent for these diseases, and therapeutic benefits have been revealed in clinical studies (55).

Several reports, ranging from *in vitro* experiments, pathologic analysis and epidemiologic studies, show that atherosclerosis is intrinsically an inflammatory disease. The plasma concentrations of interleukin-6 (IL-6) appear to reflect the intensity of occult plaque inflammation and by inference may determine the vulnerability of plaque rupture (56). Indeed, circulating IL-6 levels are elevated in patients with acute myocardial infarction, and also in patients with unstable angina, but not in those with stable angina. The plasma IL-6 concentrations are also increased after percutaneous coronary intervention (PCI), and late restenosis is correlated with an increase in IL-6 concentrations after the procedure. This finding suggests that the expression of IL-6 may not only be related to the instability of atheromatous plaques, but also to the formation of restenotic lesions after PCI (55) (Figure 4).

Previously, an association between IL-6 and lupus was demonstrated in murine models of systemic erythematous lupus (SLE) and blocking IL-6 improved lupus in all models tested. Data from several studies suggest that IL-6 plays a critical role in B cell hyperactivity and immunopathology of human SLE, and may play a direct role in mediating tissue damage (56) (Figure 4).

● Other roles of IL-6

It has been recognized that high IL-6 levels after liver resection in humans correlate with low postoperative transaminase levels and beneficial outcome. Animal experiments confirmed this clinical observation as mice lacking IL-6

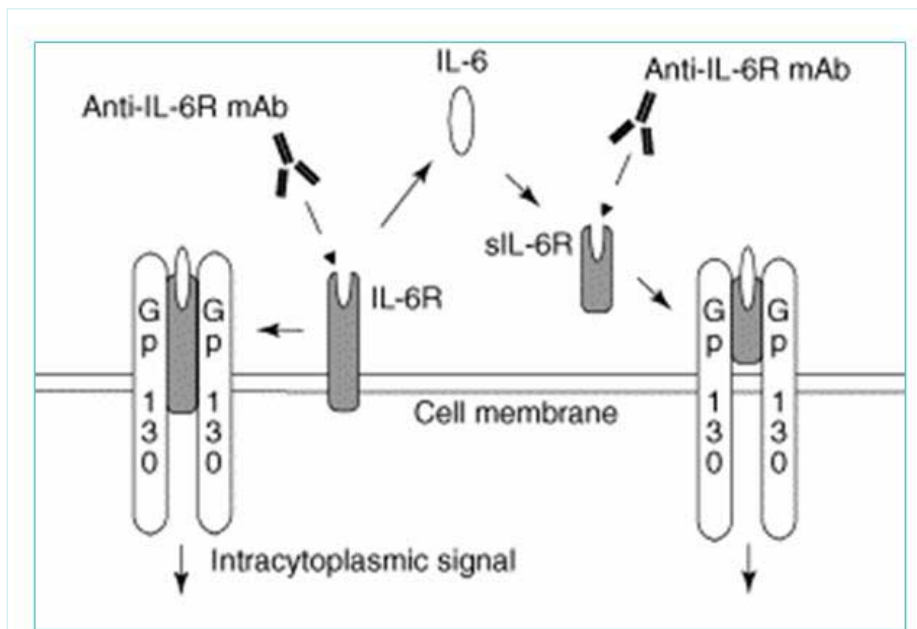


Figure 5: Scheme that shows the specific targeting of the IL-6/sIL-6R pathway. Therapies aimed at this complex can be a promising new approach for the treatment and prevention of neurodegenerative disorders, myocardial infarction, lupus, restenosis, arterosclerosis, rheumatoid arthritis, and some infectious diseases in humans. Then, blocking the effect of IL-6 may improve the autoinflammatory process both systemically and locally.

have impaired ability to regenerate and increase injury after liver resection, an effect that exogenous IL-6 before surgery corrected (57). Further studies showed that IL-6 is necessary for the induction of liver regeneration *in vivo*. IL-6-lacking mice exhibited impaired regeneration even in presence of TNF- α . IL-6 acts directly on hepatocytes inducing the translocation of STAT3 to the nucleus causing early gene activation and mitosis (58). In addition to this signaling effect on hepatocyte proliferation, IL-6 also protects the liver against various forms of liver injury, such as ischemia and reperfusion, toxins, and cell death mediated by Fas activation. IL-6-deficient mice have increased caspase 3 and 8 activities and reduced *Bcl-2* and *Bcl-x_L* levels (59). Administration of IL-6 results in the activation of the antiapoptotic mediators *Bcl-2* and *Bcl-x_L*, indicating that IL-6 might be an important regulatory cytokine of the apoptotic pathway in normal hepatocytes. These broad protective effects of IL-6 in lean livers suggest that this cytokine might become the ideal drug to apply in patients undergoing liver surgery involving ischemia and the need for regeneration (e.g., liver resection performed under inflow occlusion). Unfortunately, this use in patients

may not be appropriate because of potential side effects, such as fever, fatigue, arthralgias, hyperbilirubinemia, and thrombocytosis. In contrast, liver transplantation may offer a unique opportunity to use IL-6 because the cytokine can be given exclusively to the graft without directly exposing the recipient (60).

● Concluding remarks

The present literature search revealed an extremely complex NIE-network involving many molecules and IL-6 that foresees potent interactions in events generally attributed to the exclusive operation of single systems in response to simple precepts (reproduction, defence). So much plasticity and multifunctionality in a network are not without risk. Loss of control could lead to the loss of tolerance and autoimmunity, to be involved in the immune compromise of aging, and/or in the physiopathology of some infections in which inflammation is a prominent effector of pathology. The development of drugs specifically targeted against IL-6 may be useful in the prevention of plaque formation, myocardial infarction and restenosis. Based on the literature data, blocking the effect of IL-6 in humans may probably improve lupus by interacting with the autoinflammatory process both systemically and locally. The specific targeting of IL-6/sIL-6R

pathway will be a promising new approach for the treatment of autoimmune, parasitic and neurodegenerative diseases (Figure 5).

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