Chapter 17

ANTI-INFLAMMATORY CYTOKINES: ROLE IN REGULATION OF ACUTE LUNG INJURY

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"To every action, there exists an equal and opposite reaction" ... Sir Isaac Newton

INTRODUCTION

The concept of balance has been appreciated in the physical sciences for centuries. In the early study of inflammation, attention was focussed primarily on molecules categorized as proinflammatory (e.g. TNF) by virtue of the role they played in mediating leukocyte recruitment, endothelial damage, and tissue injury in critical illness. It was concluded that clinical states such as acute lung injury (ALI) and sepsis were a reflection of an overwhelming proinflammatory state of the host. Over the past decade, investigators have observed that at times the host is able to control or regulate the initial proinflammatory response resulting from activation of innate immune mechanisms. This response confers containment of the inflammation and is thought to afford protection from tissue injury and perhaps, hasten resolution. In the setting of the systemic inflammatory response syndrome (SIRS), this compensatory response was assigned the acronym CARS, or compensatory anti-inflammatory response syndrome (1). Perturbation of this response by exogenous factors, such as pathogens, or endogenous factors, such as genetic regulation of anti-inflammatory cytokine expression, can have important consequences on host survival. While a number of endogenous host factors participate in this necessary regulatory response, this chapter will focus on a series of cytokines that have been demonstrated to possess anti-inflammatory properties that serve to regulate the inflammation associated with ALI.

Cytokines with Anti-inflammatory Properties

While cytokines were initially thought of as strictly proinflammatory molecules on the basis of their biological properties outlined above, more recent data has documented the role of a number of cytokines as anti-

H. R. Wong et al. (eds.), *Molecular Biology of Acute Lung Injury*

inflammatory molecules (Table 1). Interleukin-10 (IL-10) may be the most well-studied member of this group that includes: IL-4, IL-13, TGF-ß and in some circumstances, the gp130 signaling proteins, IL-6 and IL-11. These molecules are linked by their common ability to inhibit the expression of proinflammatory molecules (e.g TNFα and IL-1β) in a variety of both *in vitro* and *in vivo* experimental models.

Table 1. Anti-inflammatory Cytokines

Cytokine	Sources	Actions
IL-10	Mononuclear cells, Th2 T-cells, B-cells	"Deactivation of monocytes", Inhibition of Th1 type response, Upregulation of regulatory molecules (e.g IL-1Ra)
IL-13	Th2 T-cells	Inhibition of monocyte cytokine production, NF-κB inhibition
IL-4	Th2 T-cells, B-cells, mast cells	Inhibition of monocyte cytokine production, Drives Th2 T-cell development, Increases VCAM-1
IL-6	Mononuclear cells, Neutrophils, B-cells	Inhibits TNF and IL-1, Drives acute phase response
IL-11	Fibroblasts,	Inhibits TNF and IL-1, Drives Th2 type response
TGF-ß	Mononuclear cells, most mammalian cell types	"Deactivation of monocytes"

Interleukin-10

Interleukin-10 (IL-10) is perhaps the best studied of the anti-inflammatory cytokines. IL-10 is an 18 kDa protein that was initially identified from activated Th2 helper T-cells on the basis of its ability to inhibit interferon production from Th1 T-cell clones (2). Subsequent cloning of the human cDNA has revealed its location on chromosome 1q (3). With the subsequent recombinant expression of the mature protein, IL-10 was demonstrated to be a potent inhibitor of TNFα production from stimulated monocytes (4). Over time, a number of anti-inflammatory properties have been ascribed to IL-10 (reviewed 5, 6). For example, *in vitro*, IL-10 has been shown to inhibit proinflammatory cytokines known to contribute to the development of ALI such as TNFα, IL-1β, IL-12 and chemokines, such as IL-8, MIP-1α and MIP-2. IL-10 down-regulates the expression of a number of cell surface receptors that are crucial to the host innate immune defense system such as MHC class II molecules, CD-14, and the co-stimulatory molecule, B7 (7). IL-10 can also upregulate additional anti-inflammatory molecules such as the IL-1 receptor antagonist protein (IL-1Ra) (8) and soluble TNF receptors (9). The mechanisms by which IL-10 is expressed and

subsequently mediates these various effects has been the target of much investigation over the past decade.

Gene expression of IL-10 appears to be regulated by both transcriptional and post-transcriptional mechanisms. Promoter analysis using the mouse gene has shown that expression of IL-10 is regulated by binding of the ubiquitous transcription factors, Sp1 and Sp3 (10). This unusual regulation may explain how IL-10 expression can occur when gene expression of other cytokines is low or non-detectable. An additional level of regulation occurs via a post-transcriptional mechanism in which the 3'-untranslated region of the IL-10 gene that contains multiple AUUUA motifs confers destabilization of the IL-10 mRNA which may be reversed following stimulation (11). Once expressed in its mature form, IL-10 circulates as an active homodimer binding to the IL-10 receptor complex that is ubiquitously expressed on a variety of cell types.

The IL-10 receptor complex is a structurally related member of the type II cytokine receptor family similar to the IFN-γ receptor. Two subunits have been identified, IL-10R1 that is principally responsible for IL-10 binding and IL-10R2 that is an accessory subunit, constitutively expressed in all cells and necessary for efficient IL-10 signaling (12). Members of the IFN receptor family are known to utilize the Jak-stat family of proteins for signal transduction. The Jak-stat family of proteins are tyrosine phosphorylated and translocate from the cytoplasm to the nucleus where they bind to enhancer elements such as the IFN-γ response region to activate the transcriptional machinery (13). Binding of IL-10 to its receptor on both monocytes and T-cells activates jak1 and tyk2 tyrosine kinases with which the IL-10 receptor is complexed, and results in phosphorylation and activation of stat-1α and stat3 (14, 15). Further insight into the mechanism of the recruitment and activation of stat proteins by IL-10 was provided by structural analyses showing that the ligand binding subunit of the IL-10 receptor contained tyrosine residues that were required for activation of stat3 (16). Despite this molecular insight, however, the linkage between these signal transduction pathways and the regulation of inflammatory gene expression remains incomplete.

Because of the recruitment of the Jak-stat pathway following IL-10 stimulation, investigators have focussed on these molecules, particularly stat3. Work performed in macrophages in which stat3 expression was eliminated showed that stat3 was necessary for IL-10 signaling, but not sufficient for cytokine inhibition (17). Other investigations have linked the inhibition of IFN-driven gene expression to IL-10-induced inhibition of stat1 tyrosine phosphorylation and activation (18). Finally, IL-10 can induce the suppressor of cytokine synthesis (SOCS)-3 protein, which may negatively regulate the transcription machinery driving proinflammatory cytokine expression (19). Other work has focussed on the effect of IL-10 on the MAP kinase signal transduction pathway (see Chapter 1). In these studies, IL-10 inhibited LPS-induced tyrosine phosphorylation of the Ras signaling

pathway with subsequent inhibition of downstream MAP kinase activation (20).

Because the mechanism by which IL-10 regulates proinflammation appears to be multifactorial, the effects of IL-10 on additional signal transduction pathways have been examined *in vitro*. In light of the multiple inflammatory gene products under transcriptional regulation by NF-κB, inhibition of this pathway by IL-10 has been studied. Several investigations have shown that pretreatment with IL-10 abrogates NF-κB activation with a variety of mechanisms described. It has been shown that phosphorylation and subsequent degradation of the inhibitory protein, IκBα, was impaired by IL-10 in a manner associated with inhibition of monocyte IκB kinase (IKK) activity (21). An additional study suggested that IL-10 negatively regulated this pathway by stabilizing the mRNA for IκBα, thereby sequestering NF-κB in the cytoplasm on the basis of increased IκBα (22). Interestingly, additional studies have supported a contrasting mechanism by which IL-10 decreases chemokine expression via destabilization of chemokine mRNA (23, 24). The AUUUA-rich sequences of the 3'-untranslated regions of many cytokine/chemokine transcripts provide a target for this mechanism (25). Together, these multiple inhibitory mechanisms mediated by IL-10 would be anticipated to substantially impair the expression of a number of pro-inflammatory genes.

Armed with this substantial body of *in vitro* data, investigators began to examine the ability of IL-10 to regulate proinflammation associated with ALI and sepsis *in vivo*. Exogenous administration of IL-10 in a number of experimental models was associated with decreased inflammatory makers and diminished organ injury. For example, in the setting of immune complex-mediated ALI in rats, IL-10 given intratracheally resulted in decreased inflammation and lung permeability that was associated with reduced bronchoalveolar lavage (BAL) fluid levels of TNF and IL-1ß (26). In other models of silica- and bleomycin-induced lung inflammation, bacterial pneumonia, and hypersensitivity pneumonitis, IL-10 administration abrogated the degree of lung injury (27-30). However, perhaps the most elucidating data concerning the role of IL-10 in modulating inflammation has been derived from studies using the IL-10 null mutant mouse (IL-10 -/-). Notably, IL-10 -/- mice bred and developed normally. However, over time these animals developed spontaneous colitis mimicking inflammatory bowel disease (31). If IL-10 -/- mice are kept in sterile, isolated conditions and fed sterile chow, the onset of this condition can be substantially abrogated, supporting the hypothesis that IL-10 is required to regulate the intestinal flora-induced, sub-clinical inflammation of the intestine. Further immunologic characterization of IL-10 -/- mice revealed that sub-lethal doses of endotoxin resulted in 100% mortality and was associated with substantially increased levels of proinflammatory cytokines (32). These data

suggested that IL-10 was a key endogenous anti-inflammatory molecule serving to regulate production of pro-inflammatory mediators.

That this regulation extended to the lung was supported by several studies using models of ALI. For example, in the immune complex-induced model of ALI, antibody neutralization of IL-10, resulted in increased inflammation that was associated with increased BAL fluid levels of TNFα and IL-1ß (33). Further work employing IL-10 -/- mice demonstrated that IL-10 regulated chemokine expression (MIP-1α and MIP-2) as both these mediators were significantly increased after intratracheal LPS in the IL-10 -/- mice, a finding that was reversed by the co-administration of IL-10 at the time of LPS challenge (23). A correlative finding in humans was demonstrated by Donnelly et al who showed that patients with higher mortality rates from ARDS had lower levels of IL-10 in their BAL fluid (34). Furthermore, the inability to sufficiently increase IL-10 expression in response to meningococcal infection was associated with increased mortality (35). Genetic mutations in the promoter region of the IL-10 gene were associated with a decreased level of IL-10 expression and support the concept that genetic regulation of the anti-inflammatory response may be a key modifier of disease outcome (36, 37).

In summary, IL-10 has been pursued as a potential therapeutic option in ALI as it possesses a number of anti-inflammatory properties. First, it inhibits cytokine synthesis in a negative, auto-regulatory manner to dampen the autocrine effect of proinflammatory cytokines. Second, it inhibits the adhesion of leukocytes to activated endothelial cells, thereby disrupting the leukocyte-endothelial cell adhesion cascade. Third, it inhibits many of the key signal transduction pathways associated with activation of the proinflammatory response. Fourth, IL-10 upregulates the expression of naturally occurring cytokine antagonists including IL-1Ra and soluble TNF receptors. Finally, IL-10 may serve to destabilize the mRNAs of cytokines possessing the AU-rich element. Thus, in light of the multiple mechanisms by which IL-10 regulates inflammation, exogenous administration of IL-10 appears promising and is currently being studied in clinical trials. Enthusiasm for this therapeutic approach is tempered by the evidence that IL-10 limits the hosts immune response directed at pathogen eradication in several *in vivo* models of infection, as well as human observations (6). Thus, titrating IL-10 to strike a balance between protection against dysregulated proinflammation and pathogen clearance remains a substantial clinical challenge.

Interleukin-4 and Interleukin-13

In a series of pioneering studies performed on T helper lymphocytes in the mouse, cDNA clones were discovered to be exclusively expressed by the Th2 subset (38). These cytokines have been broadly classified as Th2, or

type 2, cytokines and include most notably, IL-4 and IL-13. These type 2 cytokines are linked by their location on the long arm of chromosome 5, by modest sequence homology at receptor ligand binding sites (39), and by the receptor complexes they employ to initiate signal transduction (40). They have also been shown to be important modifiers of the lung immune response (see Chapter 4). Together, these cytokines display a number of anti-inflammatory properties.

Although, expressed exclusively in mouse Th2 cells, studies using human cells have shown that both Th1 and Th2 cells, as well as mast cells, basophils and eosinophils are important sources of IL-4 and IL-13 expression. The cloning and eventual recombinant expression of the human homologues of IL-4 and IL-13 have shown them to exert potent immunomodulatory properties on monocytes (41). For example, IL-13 was demonstrated to inhibit inflammatory cytokine (TNFα) and chemokine (MIP-1α) expression from macrophages, while also increasing the anti-inflammatory molecule, IL-1Ra (42, 43). Further *in vivo* work examined the regulatory role of IL-4 and IL-13 in lung inflammatory models. In the immune complex model of lung injury described above, the intratracheal instillation of recombinant IL-4 and IL-13 at the initiation of injury resulted in decreased pulmonary vascular permeability, and diminished neutrophil numbers that was thought to reflect decreased lung production of TNFα; though in these studies, the effect of IL-13 was substantially more than IL-4 (44). Other models of lung inflammation described similar results for IL-13. In guinea pigs, airway instillation of IL-13 inhibited the leukocyte accumulation following TNFα- and antigen-induced inflammation (45). Furthermore, in models of endotoxemia, transgenic over-expression of IL-4 and IL-13 were shown to reduce TNFα production and improve outcome (46, 47). Interestingly, in a cecal-ligation and puncture model of sepsis, increased local organ (e.g. lung, liver), but not systemic, expression of IL-13 was observed and neutralization of endogenous IL-13 resulted in increased mortality. These data suggested that IL-13 was key to the regulation of organ-specific inflammatory responses (48).

The mechanisms by which these cytokines exert their anti-inflammatory effects remains to be fully elucidated, though a great deal is understood with regards to the signal transduction pathways initiated by them. IL-4 and IL-13 share a common receptor, the IL-4Rα. In the case of IL-4, this receptor conjugates with the common γ–chain (a component of the IL-2 receptor) to form the high affinity IL-4R complex, whereas the IL-13Rα or IL-13Rα′ receptor appears to complex with the IL-4Rα subunit to form a high affinity IL-13R complex (reviewed 49, 50). Of note, in non-hematopoietic cells IL-13Rα′ may serve as the accessory chain comprising the IL-4 responsive receptor (49). On the basis of these shared common receptor subunits, it is no surprise that several overlapping biologic effects have been described. Subsequent signaling proceeds through activation of

the Jak kinases, Jak1 and Jak3, resulting in the phosphorylation of the IL-4Rα receptor with consequent recruitment and activation of Stat6 (51-53). Support for this pathway has been substantiated by studies employing the Stat6 null mutant mouse in which IL-4 and IL-13 signaling are substantially impaired (49, 54). However, the role of this pathway in mediating the observed anti-inflammatory effects is unclear. Further work in the immune complex-mediated model of lung injury not only identified IL-13 to be endogenously expressed in the lung, but also showed that exogenous IL-13 inhibited NF-κB activation in association with the preservation of the NF-κB inhibitory protein, IκB-α, suggesting an alternative mechanism of cytokine inhibition (55). Additionally, IL-4 has been demonstrated to increase the expression of the cytokine-induced SH2-containing (CIS) protein as well as SOCS1, 2 and 3 proteins that serve as negative regulators of the Jak-stat signaling pathway (56). Whether these proteins are necessary for the observed anti-inflammatory effects remains to be determined. Finally, the role of IL-4-mediated induction of phosphatases, which can deactivate kinase activities via dephosphorylation in the observed anti-inflammatory effects is also unknown (57).

The consideration of a therapeutic use for IL-4 and IL-13 in ALI is assuaged by the important observations regarding the role these cytokines play in mediating allergic lung inflammation. Although beyond the scope of this chapter, the reader is referred to recent reviews that summarize the mechanisms by which these Th2 cytokines, IL-4 and IL-13, contribute to the pathophysiology of airway hyperreactivity (58, 59). As an example, Elias and colleagues using a model of lung-specific, transgenic over-expression of IL-13 demonstrated increased inflammation, mucus production, subepithelial fibrosis, increased eotaxin production, and airway hyperreactivity all characteristic of the pathophysiology associated with asthma (60). More recently, analysis of the genetic regulation of both IL-4 and IL-13 has shown that there likely exists genotypic variances of these molecules. These variants influence the degree of IL-4 and IL-13 expression with consequent effects on both the development of a Th2 immune response as well as an atopic or allergic phenotype (61-63). Thus, until further insight is gained into how the interplay between the kinetics of expression, the presence of modifying factors, the diverse use of receptor subtypes, the nature of the inflammatory stimulus and the cell population involved influence the response to IL-4 and IL-13, therapeutic use in ALI remains a distant consideration.

gp130 Receptor Ligands: IL-6 and IL-11

IL-6 is a pleiotropic cytokine with a diverse set of functions. IL-6 can drive the acute phase response in hepatocytes, stimulate hematopoiesis, induce maturation of megakaryocytes, differentiate myeloid cells and induce neuronal differentiation (reviewed 64, 65). On the basis of further structural

characterization and the signal transduction pathway it utilized, IL-6 was identified as a representative member of a family of proteins that served as receptor gp130 ligands. This family now includes: interleukin-11 (IL-11), leukemia inhibitory factor, ciliary neurotropic factor, oncostatin M and cardiotrophin-1 (66). IL-6 has been viewed historically as a proinflammatory cytokine based on the frequent observation that it is increased in a number of inflammatory disease states such as sepsis and ALI (67-69); however, while IL-6 may be a valid marker for the degree of inflammation associated with sepsis and ALI, it has remained unclear as to whether it is a mediator of that inflammation.

In studies aimed at determining the role of IL-6 in regulating lung inflammation, a consistent finding of anti-inflammatory properties was observed. Initially, IL-6 was shown to inhibit LPS-induced TNFα expression from human monocytes (70) as well as rat alveolar macrophages (71). In a variety of lung injury models it was demonstrated that exogenous administration of IL-6 abrogated the amount of lung histopathology in association with decreased cytokine production and neutrophil accumulation (70, 72-74). It was subsequently shown that endogenous IL-6 was produced in the context of lung inflammation triggered by immune complex deposition, and that antibody neutralization of IL-6 resulted in a heightened inflammatory response characterized by increased BAL fluid levels of TNFα (71). Recently, investigators have employed the IL-6 null mutant (IL-6 -/-) mouse to further define the role of IL-6 in regulating acute inflammatory responses. In the IL-6 -/- mice the levels of TNFα and MIP-2 as well as the degree of neutrophilia were all significantly increased following aerosol exposure to endotoxin (75). These data supported the hypothesis that IL-6 was a key endogenous regulator of inflammation, however, the mechanism by which inflammatory cell signaling was impaired remained undefined. Because IL-6 induces acute phase response proteins, which have in turn demonstrated anti-inflammatory effects (76), it had been speculated that this is the mechanism by which IL-6 might exert its effects. Of note, following endotoxin challenge in the IL-6 -/- mice, the acute phase response was only moderately impaired in comparison to the degree of the anti-inflammatory effect, suggesting the regulatory mechanism in this model may be independent of the acute phase response (75). Additionally, no differences in IL-10 or TGF-ß levels were observed, suggesting the effect of IL-6 was unrelated to modulation of the expression of other anti-inflammatory cytokines. Of note, induction of the acute phase response in the IL-6 -/- mouse by stimuli other than endotoxin was significantly impaired (77).

A related cytokine, interleukin-11 (IL-11) employs the same gp130 receptor and has been examined for similar anti-inflammatory properties. Induction of IL-11 expression can be observed with a number of stimuli including proinflammatory cytokines (e.g. IL-1), TGF-ß, prostaglandins, and in particular viruses (e.g. respiratory syncytial virus) (78). Gene expression

of IL-11 appears to be mediated by both transcriptional and post-transcriptional mechanisms. The promoter of the IL-11 gene contains AP-1, Sp-1, and NF-κB cis-elements and mRNA expression induced by an AP-1 transcriptional complex containing junD has been observed (79). Additionally, the 3'-untranslated region contains multiple copies of an AUUUA sequence conferring constitutive instability to the transcript which can be stabilized following activation in a manner dependent on tyrosine kinase activity (79).

Because of its potent effect on megakaryocytopoiesis (80), IL-11 has entered clinical use as an inducer of platelet production in the setting of chemotherapy-induced thrombocytopenia (81). However, its role as an immunomodulating agent remains incompletely defined. Similar to IL-6, IL-11 has been shown to inhibit the inflammation observed in various models of ALI. For example, following immune-complex-induced lung injury, intrapulmonary administration of IL-11 abrogated the increases in lung vascular permeability, lung neutrophils, as well as BAL fluid TNF and C5a content (82). IL-11 has also been shown to attenuate lung inflammation resulting from endotoxin challenge (83), hyperoxia (84) and radiation-induced thoracic injury (85). As a result of these findings, investigators have attempted to elucidate the mechanisms by which both IL-6 and IL-11 exert their anti-inflammatory effects.

As mentioned previously, all members of this family share gp130 as at least one of the subunits of the receptor complex to which they bind. For IL-6 and IL-11, the signal transduction pathways are activated by engagement of the protein with homodimerization of the gp130 receptor. Following ligand engagement, multiple signaling pathways are activate including: Jak-stat tyrosine kinases (86, 87), MAP kinases (79), Src family kinases (88), and phosphatidylinositol 3-kinase (PI3K) (89). Homodimerization of gp130 activates the Jak family tyrosine kinases, Jak1, Jak2, and Tyk2, which in turn phosphorylate the cytoplasmic portion of gp130. This portion can then serve as a docking site for the Stat3 transcription factor, which becomes phosphorylated, dimerized, and translocated to the nucleus to drive gene transcription (90). In the context of Jak-stat coupled signaling, the novel SOCS family of proteins that serve as negative regulators of cytokine expression has recently been described to inhibit signaling by interfering with Jak kinase catalytic activity (91, 92). IL-6 has been shown to increase SOCS1 protein and may explain one mechanism by which cytokine production is disrupted by the gp130 family of proteins. Furthermore, the effect of IL-6 on inhibition of the Th1 type response (characterized by increased IFN-γ expression) is mediated via the SOCS1 expression (93). Alternatively, both IL-6 and IL-11 have been shown to impair NF-κB signaling both *in vitro* and *in vivo*. The mechanism by which this occurs appears to involve increased production of the inhibitors of NF-κB, IκBα and IκBβ (94). Whether additional regulatory pathways are activated by

these gp130 ligands remains to be determined; however, these agents may provide a therapeutic potential in both acute and chronic inflammatory states.

Enthusiasm for the use of IL-6 and IL-11 in ALI is tempered by the elucidation of the role these proteins appear to play in lung remodeling. In an elegant series of experiments employing lung-specific over-expressing transgenic mice, Elias and colleagues have provided novel insight into the role that IL-6 and IL-11 play in the development of subepithelial fibrosis, collagen deposition, and accumulation of α-smooth muscle actin-containing structural cells, thus contributing to the development of lung fibrosis (reviewed 95). Of note, targeted over-expression of IL-6 or IL-11 in a lung specific manner was not associated with eosinophilia or excessive mucus production that is characteristic of allergic inflammation driven by type 2 cytokines. In fact, both cytokines decrease allergen-induced eosinophilia and the production of Th2 cytokines that contribute to eosinophil recruitment (96, 97). Together, these data support the concept that IL-11 is a key endogenous mediator of airway healing following the development of airway inflammation. Further understanding of the pleiotropic effects of this family of cytokines and the modifying factors such as the timing, etiology, and immune nature of insult will be required prior to their therapeutic consideration in ALI.

Summary

The proinflammatory cytokines and the biologic effects they orchestrate are a necessary component of the immune responses directed against host invasion. It is naive to conclude that all critically ill patients with ALI require inhibition of the proinflammatory response, which may lead to undesired immunosuppression. Traditionally, because of the proximal role cytokines play in the inflammatory cascade, clinical investigators have attempted to directly block their activity. Though these strategies have proved promising in preclinical trials, their ultimate clinical efficacy in human trials has been disappointing (98, 99). In fact, over-expression of anti-inflammatory cytokines such as IL-10 and IL-13 may contribute to host immunosuppression and impair pathogen eradication, creating a need for boosting the proinflammatory cytokine armamentarium in selected patients. Thus, it is necessary that the host strike a homeostatic cytokine balance in its attempt to accomplish pathogen eradication, but not at the expense of organ injury (Figure 1). Further understanding of the mechanisms of anti-inflammatory activity in the context of improved identification of both the current immunophenotype (i.e. a predominant proinflammatory versus anti-inflammatory state) of the patient with ALI as well as pathologic challenge (i.e. infectious versus non-infectious) being faced is likely to lead to more prudent and selected use of anti-inflammatory cytokines in this challenging disease state.

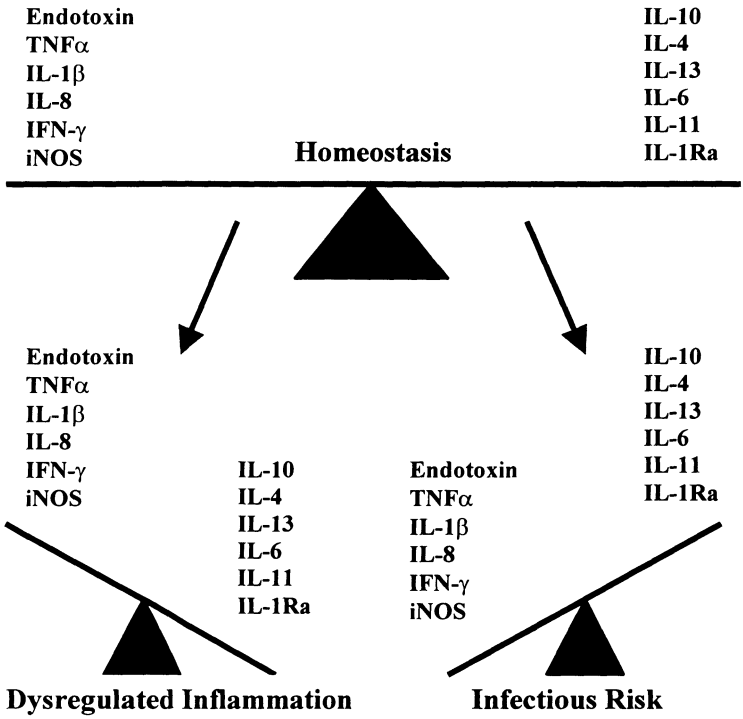

Figure 1. Balance between pro- and antiinflammatory cytokines aimed at preserving homeostasis in the context of inflammatory diseases states.

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