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Role of Interleukin-18 in the Development and Pathogenesis of AIDS

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Abstract

Interleukin-18 is a proinflammatory, proapoptotic, and proatherogenic cytokine belonging to the interleukin-1 family of cytokines. The cytokine exerts many unique immunologic and biological effects. It is produced as a biologically inactive and leaderless precursor protein, which must be cleaved into its mature form by caspase-1. The caspase-1 also exists in an inactive precursor in the cytosol and needs proteolytic auto-cleavage, which is catalyzed by the assembly of a multi-protein complex called inflammasome.

Inside the circulation, interleukin-18 is bound to its naturally occurring antagonist called interleukin-18 binding protein. The antagonist is induced as a negative feedback to increased interleukin-18 production. It protects body cells and tissues from the potentially destructive and harmful proinflammatory effects of the cytokine.

Several researchers have reported that the concentrations and biological activities of the cytokine are increased in the circulation of HIV-infected patients. Unlike interleukin-18, the concentrations of its antagonist, interleukin-18 binding protein, are decreased in these persons. The cytokine may play a major role in the development and pathogenesis of AIDS in HIV-infected persons. Insufficient/lack of interleukin-12 and related cytokines may compromise the ability of interleukin-18 to induce interferon-gamma production from natural killer and T-cells. By inducing production of T-helper 2-type cytokines like interleukin-4, -5, -9, and -13 from basophils and mast cells, interleukin-18 promotes the development and differentiation of $CD4^+$ naive T-cells into T-helper 2-type effector cells, which blunt anti-HIV immunity. The effect may be more pronounced in HIV-infected persons with compromised production of interleukin-12. Interleukin-18 also directly enhances viral replication. Because of its proapoptotic effects, the cytokine decreases survivability and promotes the death of various immune and nonimmune cells. It has also been documented to play a role in the depletion and wasting of subcutaneous fat from the limbs and face. The wasting is a characteristic feature of HIV-associated lipodystrophy. The cytokine is also likely to be involved in the higher incidence of atherosclerotic plaques and systemic insulin resistance in these patients.

Finally, increased production of the cytokine in the brain may lead to motor and cognitive dysfunctions, leading to the development of HIV-associated dementia.

In conclusion, increased interleukin-18 concentrations in HIV-infected persons are likely to play an important role in the development and progression of the infection toward AIDS and associated clinical

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conditions. Therefore, its neutralization may represent an appropriate and useful immunotherapeutic strategy in these patients. It may delay AIDS progression and improve the immune status of infected persons. The best way to achieve this goal may be using exogenous interleukin-18 binding protein.
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Key words

AIDS. Cytokines. HIV-1. IL-18. IL-18BP. Lipodystrophy. HIV-associated dementia.

Introduction

Several studies have shown that interleukin-18 (IL-18) concentrations are increased in the circulation of HIV-infected persons as compared to HIV-seronegative healthy subjects. Here we provide an overview of our current state of knowledge on the biology of this cytokine and discuss, in the light of published literature, how these increased concentrations of the cytokine might contribute towards the pathogenesis of AIDS and its associated clinical conditions like lipodystrophy, systemic insulin resistance, and dementia.

A unique proinflammatory cytokine

Interleukin-18 represents the fourth member of the IL-1 family of cytokines. It is a multifunctional and pleiotropic, proinflammatory cytokine with many unique biological effects (Table 1). The cytokine is produced by a wide variety of cells including macrophages, dendritic cells, keratinocytes, adipocytes, Kupffer cells, intestinal and respiratory tract epithelial cells, microglial cells, ependymal cells, and certain neurons in the brain (reviewed[1-3]).

Interleukin-18 gene expression has been documented in several organs and tissues of the body, e.g. liver, lungs, thymus, heart, placenta, kidneys, pancreas, adipose tissue, brain, etc. Physical and emotional stress has been shown to induce IL-18 production from adrenal cortex[4,5]. Like IL-1β, the prototype member of the family, IL-18 secretion does not follow the classical secretory pathway via endoplasmic reticulum and Golgi apparatus. Instead, the cytokine is produced as a leaderless and biologically inactive 24 kDa precursor protein called Pro-IL-18, which is cleaved by IL-1β converting enzyme (ICE; more commonly known as caspase-1) to produce 18 kDa mature and biologically active cytokine[6,7].

It is noteworthy that caspase-1 itself exists in an inactive 45 kDa precursor form whose activation requires assembly of multi-unit complexes involving certain nucleotide-binding and oligomerization domain (NOD)-like proteins. These complexes, known as inflammasomes, recruit and activate caspase-1 precursor molecules (reviewed[8,9]). The process leads to IL-18 maturity and secretion.

As shown in figure 1, an increased production of biologically active IL-18 requires two distinct stimuli: one increases IL-18 gene expression at mRNA and protein levels and usually comes from recognition of pathogen products by a pattern-recognizing receptor (e.g. toll-like receptor); the second signal causes inflammasome assembly, caspase-1 activation, and secretion of mature IL-18.

Understanding the stimuli and the molecular mechanisms that lead to inflammasome assembly and the secretion of biologically active IL-18 is a burgeoning area of research. A variety of cellular products (e.g. extracellular adenosine triphosphate, amyloid β crystals,

Table 1. Some unique properties of interleukin-18

- Despite being a member of the IL-1 family, IL-18 has several unique properties:
- It does not induce fever; but does induce sleep and anorexia
- In synergy with IL-12, it induces IFNγ production from natural killer and T-cells
- It induces IL-4, IL-5, IL-9, IL-13 and histamine from mast cells and basophils
- Its effects are proapoptotic on target cells, while other members of the family exert pro-survival effects
- It is also produced in adrenal cortex in response to physical and emotional stress
- Its antitumor effects are uniquely mediated by enhanced FasL-mediated cytotoxicity of natural killer cells and T-cells
- Implicated in acute hepatic injury in endotoxemia and mouse models of viral hepatitis
- One of the rare cytokines that are kept inactive in the body by a naturally produced antagonist
- It promotes the development of atherosclerotic plaques
- It is involved in the maintenance of homeostasis of energy: its enhanced concentrations promote insulin resistance

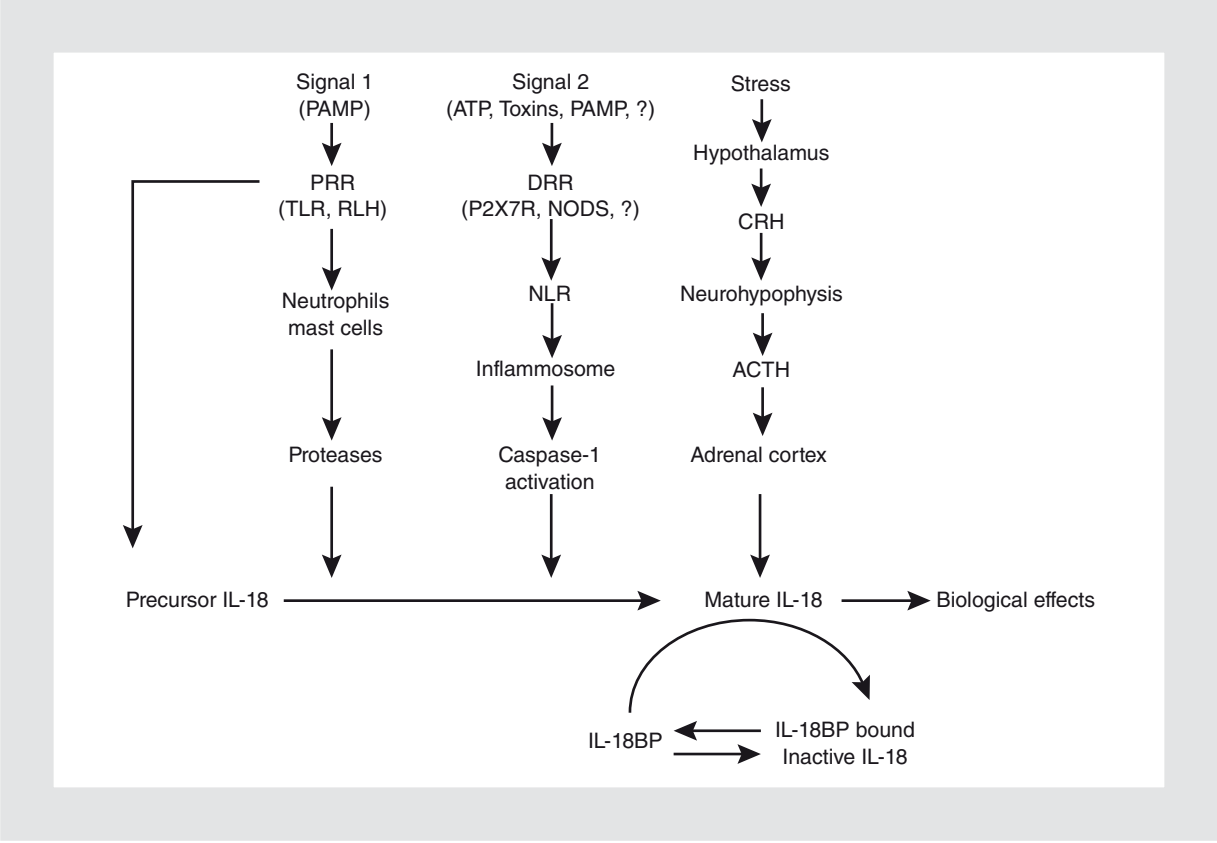

Figure 1. *Production, processing and control of interleukin-18. The figure depicts two signaling pathways needed to produce precursor IL-18. In addition to pathogens and their products, stress can also induce IL-18 production in adrenal gland and in certain brain cells (not shown). IL: interleukin; BP: binding protein; ACTH: adrenal corticotrophic hormone; CRH: corticotrophic releasing hormone; DRR: danger recognizing receptors; NOD: nucleotide oligomerization and dimerization domain-containing proteins; NLR: NOD-like receptors; PAMP: pathogen-associated molecular patterns; PRR: pattern recognizing receptors; RLH: RIG-like helicase. A question mark (?) indicates unknown receptors or stimuli.*

reactive oxygen, and nitrogen species), pathogen products (e.g. bacterial and viral nucleic acids, bacterial muramyl dipeptide, bacterial toxins) and environmental pollutants (e.g. silica particles, aluminum compounds) are known to cause inflammasome assembly[10-14]. Along with the mature form, the unprocessed precursor form is also released from IL-18-producing cells. Certain proteases e.g. matrix metalloprotease (MMP)-9, neutrophil-derived proteinase-3 and elastase, mast cell-derived chymase, etc. can process the extracellular IL-18 precursor into biologically active forms[1-3].

Once secreted, mature IL-18 is subjected to a further layer of control; a protein (named as IL-18 binding protein; IL-18BP) specifically binds and inactivates mature IL-18 in the circulation. The IL-18BP-bound cytokine is able to bind the "α" chain of IL-18 receptor (IL-18R; see below), but is unable to recruit its "β" chain. Consequently, it cannot transduce signals in target cells[15,16].

The human IL-18BP exists in four isoforms, which result from alternate splicing of the IL-18BP mRNA[15]. The isoforms have been named "a-d"; only "a" and "c" can bind and inactivate IL-18. It is noteworthy that the "a" isoform exhibits a tenfold higher affinity for IL-18 as compared with the "c" isoform. The former isoform accounts for practically all the IL-18 neutralizing activity in the human body. It binds IL-18 with high affinity and low dissociation rate in 1:1 stoichiometric complexes[17].

The IL-18BP is produced constitutively from several types of cells and tissues in the body. The protein is normally present in the circulation in 20-fold molar excess as compared to IL-18[17]. This ensures protection from tissue damage, which otherwise might occur from uncontrolled biological activities of the cytokine.

The production of IL-18BP is also enhanced as a negative feedback mechanism in response to enhanced IL-18 production. For example, increased levels of IL-18 are accompanied by increased levels of IL-18BP in the circulation of mice during sepsis[17]. *In vitro* studies have shown that interferon gamma (IFNγ) acts as a powerful stimulus for inducing expression of

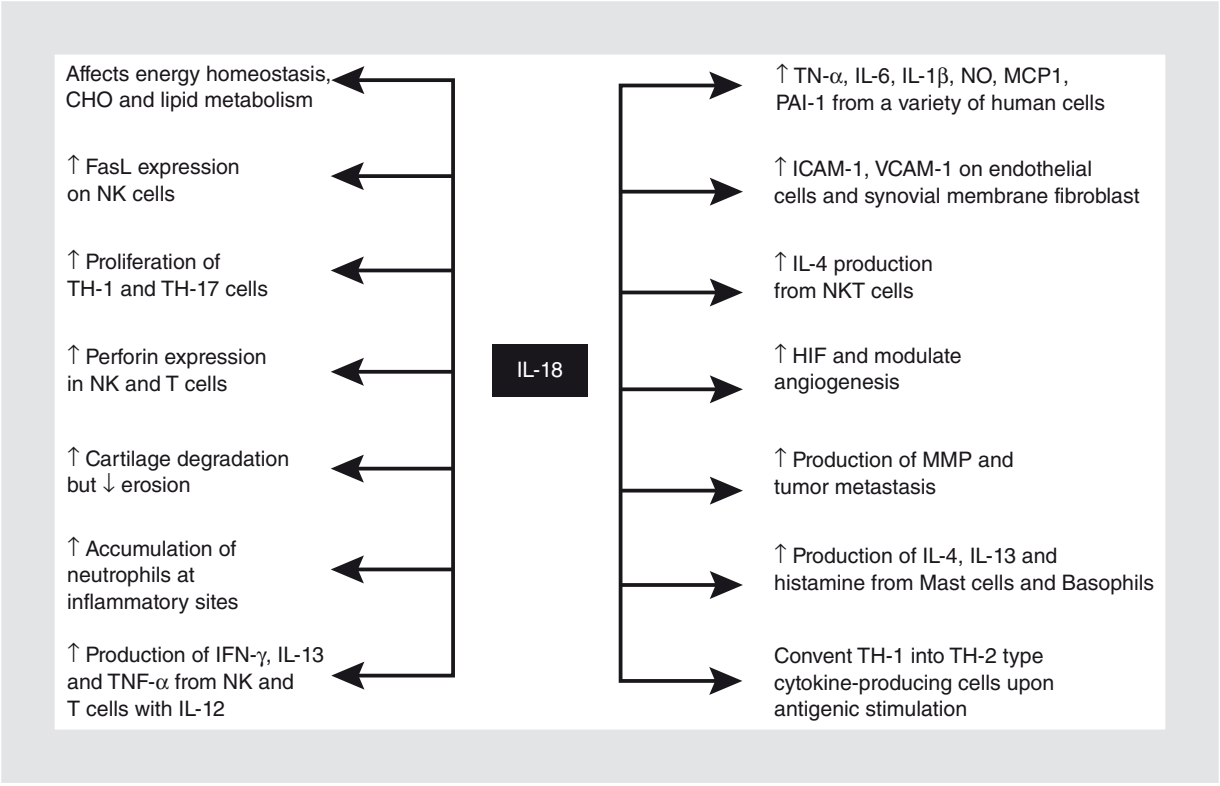

Figure 2. *Biological effects of interleukin-18. IL: interleukin; TH: T helper; NK: natural killer; AT: adipose tissue; CHO: carbohydrate; ICAM-1: intercellular cell adhesion molecule 1; MCP-1: macrophage chemotactic protein 1; MMP: matrix metalloproteinase; NO: nitrous oxide; PAI-1: plasminogen activator inhibitor 1; VCAM: vascular cell adhesion molecule; VEC: vascular endothelial cells.*

IL-18BP. Production of IL-18BP mediated by this interferon is an important factor in the operation of this negative feedback mechanism[18,19].

Interestingly, several poxviruses carry a homolog of the IL-18BP gene in their genomes. The viral IL-18BP acts as a virulence factor and antagonizes the virus-induced IL-18 responses of the infected host[20,21]. The IL-18BP acts as an anti-inflammatory and immunosuppressive mediator[2,3,22], and it represents an ideal therapeutic tool for neutralizing IL-18 in chronic inflammatory diseases.

Interleukin-18 exerts its biological effects on target cells and tissues via IL-18 receptors (IL-18R; Fig. 2). The IL-18R is heterodimeric and consists of two distinct polypeptide chains: α and β. Immunoglobulin (Ig)-like domains are present in the extracellular regions of the receptor chains and bind IL-18. Toll-IL-1 receptor (TIR) domains present in the cytoplasmic tails of the receptor chains transduce signals in the target cells[2,3].

The cytokine initiates inflammatory responses by inducing production of several proinflammatory cytokines and chemokines (e.g. TNFα, IL-8, IL-1β, MIP-1α, NO, MMP) from a variety of human cells. It induces accumulation of neutrophils in the lungs and liver during septicemia[23]. The cytokine chemo-attracts dendritic cells to the site of viral infection and causes their maturation[24]. It also plays an important role in enhancing adhesion of dendritic cells, macrophages, natural killer (NK) cells, and T-cells to vascular endothelial cells by enhancing expression of vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1)[25].

The most significant biological effect of IL-18 is induction of IFNγ production from NK, T-, and NK T-cells. However, it does so in concert with other cytokines, e.g. IL-12, IL-15, or IL-21. Interleukin-18 and IL-12 together represent the most powerful stimulus in inducing IFNγ from NK and T-cells[26] (reviewed[27]). In fact, the cytokine was originally discovered in 1989 as an "IFNγ-inducing factor" that was present in the serum of the Bacillus Calmette-Guerin-infected mice after challenge with lipopolysaccharide. The "factor" induced IFNγ production from IL-2-activated mouse splenocytes[23]. Several years later it was named as IL-18 upon cloning and expression of its gene[28,29]. Many of the cytokine's biological effects can be attributed to its ability to induce IFNγ. The interferon induces expression of IL-12Rβ1 chain on the surface of naive $CD4^+$ T-cells and renders them responsive to IL-12, which induces their differentiation into T-helper 1 (Th1) effector T-cells. The interferon also

inhibits differentiation of these naive cells into Th2- or Th17-type effector cells[30,31]. During the differentiation process, IL-12 induces IL-18Rβ chain on $CD4^+$ T-cells. Consequently, IL-18 can amplify the Th1-type $CD4^+$ T-cell responses. These responses have been shown to be more effective in controlling intracellular pathogens like HIV-1.

It is noteworthy that in the absence of collaborating cytokines (e.g. IL-12), IL-18 has little ability to induce IFNγ from NK and T-cells. However, it can also exert many biological effects that are independent of its IFNγ-inducing ability. The cytokine induces IL-4, IL-5, IL-9, and IL-13 from basophils, mast cells, and ligand-activated NK T-cells[32]. Furthermore, the presence of IL-18 can efficiently convert $CD4^+$ effector T-cells into Th2-type cytokine-producing cells upon their antigen-specific activation[33,34]. The Th2-type cytokines promote allergic inflammatory responses (mastocytosis, eosinophilia, and IgE production) needed to expel extracellular parasites. Thus, an excess of IL-18 production would blunt Th1-type responses and promote Th2-type responses in the body. Interleukin-18 augments the FasL-mediated cytotoxicity of NK and T-cells[35,36]. The cytokine exerts its antitumor effects mainly via the Fas/FasL pathway. Few antitumor effects of the cytokine were observed in Fas or FasL knockout (KO) mice. The IL-18-mediated enhanced FasL expression has been implicated in the cytokine-induced hepatotoxicity in septicemia and mouse models of hepatitis[37].

Imbalanced production of interleukin-18 and interleukin-18 binding protein in HIV infection

Several researchers have consistently reported increased concentrations of IL-18 in the circulation of HIV-infected persons[38,39] (reviewed[40]). The cytokine concentrations did not correlate with viral load or with $CD4^+$ T-cell counts in these patients[38,39]. More recent studies have shown that the cytokine increases in the circulation of infected persons early in the course of the infection, and its concentrations correlate with viral loads in untreated persons[41,42]. The cytokine levels decrease in HAART-treated patients, but they remain above physiological concentrations. The authors suggested using the levels of the cytokine as a measure of response to therapy[43]. Another study demonstrated that seroconversion in HIV-infected persons was accompanied by increased levels of the cytokine in the circulation, and the levels correlated with viral loads in these patients[44].

As stated above, IL-18 production is accompanied by a negative feedback mechanism, which induces production of its antagonist IL-18BP. We have found that, in sharp contrast to IL-18, the concentrations of IL-18BP are significantly decreased in the circulation of HIV-infected persons as compared to HIV-seronegative healthy subjects (Iannello A, et al. submitted). Thus, IL-18-induced negative-feedback mechanisms appear to have become defective in HIV-infected persons. This results in increased concentrations of "free" and biologically active IL-18 in the circulation of HIV-infected persons. Indeed, we have previously shown that IL-18 present in the sera of HIV-infected persons is biologically active[38]. As mentioned earlier, IFNγ plays an important role in inducing IL-18BP from human cells, and IL-18 needs to act in concert with other cytokines, like IL-12 or IL-15, for inducing production of this interferon from human cells. Given that the production of IL-12 and IL-15 decreases in HIV-infected persons[45-47] (reviewed[48]), this may result in a decreased ability of IL-18 to induce IFNγ from NK and T-cells. A decreased production of IFNγ may be at least in part responsible for a decreased production of IL-18BP in HIV-infected persons.

Implications of increased interleukin-18 levels for HIV infection

An increased production of IL-18 as well as an increase in its biological activities may contribute to the development of AIDS (Fig. 3) as described below.

Adverse effects on antiviral immunity

Because of its ability to induce IFNγ from NK and T-cells, IL-18 may play a role in protecting the host from intracellular pathogens. As mentioned earlier, IL-18 could promote type 1 or type 2 immune responses, depending upon the context. Induction of IFNγ and promotion of type 1 immune responses by IL-18 depends upon the presence of collaborating cytokines like IL-12, IL-15, or IL-21. In the absence/insufficiency of these cytokines, IL-18 has little ability to induce IFNγ from NK and T-cells. Under these conditions, IL-18 may in fact blunt these responses by inducing IL-4, IL-5, IL-9, IL-13, and histamine from basophils and mast cells. These cytokines promote the development and differentiation of Th2-type $CD4^+$ T-cells, which induce type 2 immune responses. A decreased production of IFNγ and a predominance of type 2 immune responses frequently occur in HIV-infected persons and have been implicated in the development of AIDS[49-51].

Increased concentrations of IL-18 have been documented in several chronic inflammatory conditions. Levels of IL-18 in these conditions were shown to correlate with reduced NK cell numbers[52,53]. We have found that

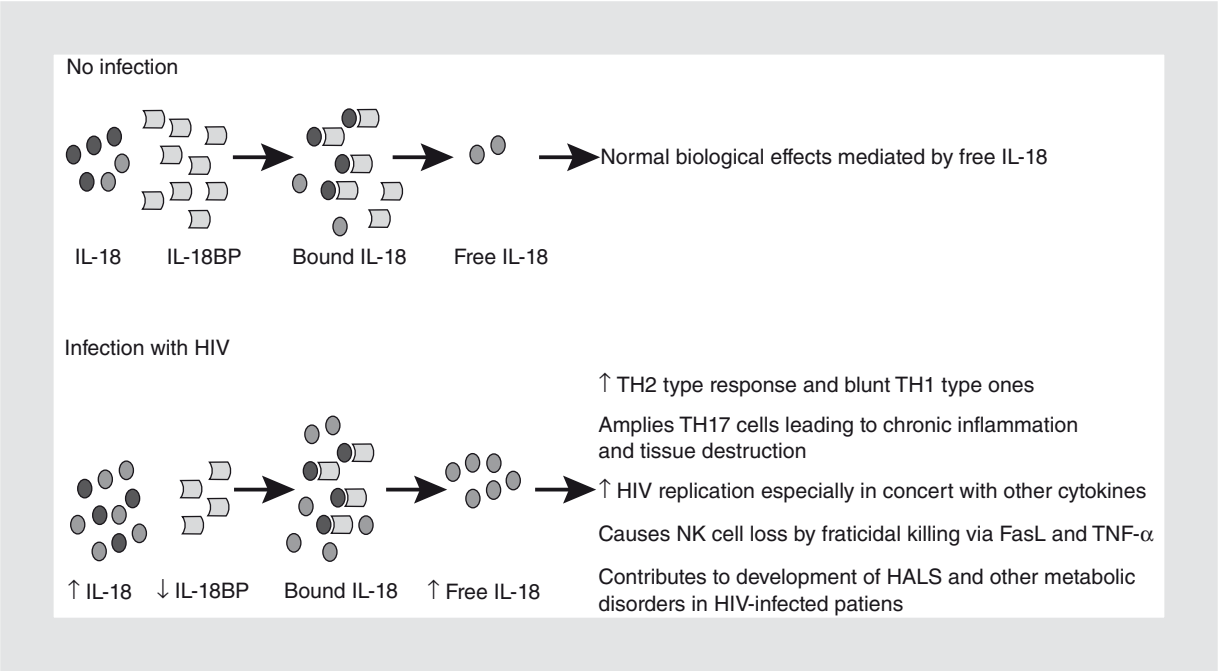

Figure 3. *Potential contributions of interleukin-18 to AIDS pathogenesis. The figure depicts various mechanisms by which IL-18 might contribute towards AIDS pathogenesis. Note increase in free IL-18 concentrations in the circulation of HIV-infected persons. IL: interleukin; TH: T helper; NK: natural killer; BP: binding protein; HALS: HIV-associated lipodystrophy syndrome.*

a similar situation exists in HIV-infected persons[54]. We further found that the cytokine induces FasL expression on primary human NK cells, and decreases their survivability by reducing the expression of an antiapoptotic protein, Bcl-XL. These changes result in fratricidal killing of NK cells in their *in vitro* cultures. It is conceivable that a chronic exposure of NK cells to high concentrations of IL-18 *in vivo* may cause their depletion and, hence, defective innate immunity. The cytokine has been shown to enhance FasL-mediated cytotoxicity of murine $CD4^+$ Th1 cells[35]. Although not formally shown, it is also likely to enhance expression of FasL in human $CD4^+$ Th1 cells. However, depletion of this type of cell in chronic inflammatory conditions has not been reported. It is likely that the cytokine exerts differential effects on the two types of target cells and does not decrease the survivability of $CD4^+$ Th1 cells. By inducing enhanced expression of FasL on NK and $CD4^+$ Th1 cells, the cytokine may promote the destruction of normal Fas-positive cells in the body and promote autoimmunity. It is noteworthy that increased Fas/FasL-mediated killing has been implicated in the immunopathogenesis of AIDS (reviewed[55]).

Effects on HIV replication

Proinflammatory, immune-enhancing cytokines often enhance HIV replication. Concerning the effects of IL-18 on HIV replication, controversial results have been reported. The cytokine has been shown to enhance the viral replication in acutely or chronically infected human monocytic and T-cell lines[56-58]. However, it was reported to inhibit HIV replication in human peripheral blood mononuclear cells (PBMC)[59]. The inhibition was ascribed, at least in part, to IL-18-mediated IFNγ production in the human cell cultures. However, it is important to note that production of this interferon from PBMC in response to IL-18 becomes compromised in HIV-infected persons[41]. This compromise could be due to increased circulating concentrations of immunosuppressive cytokines, like IL-10, IL-32, and transforming growth factor-beta (TGFβ), and/or due to decreased concentrations of immune-enhancing cytokines like IL-12, IL-15, and IL-21[45-47,60-62] (reviewed[48]). In this regard, we have found that IL-18 enhances HIV replication in *in vitro* infected purified human $CD4^+$ T-cells, but has no effect on viral replication in *in vitro* generated human monocyte-derived macrophages (Iannello A, et al. submitted). Much of the controversy concerning the effects of IL-18 on HIV replication probably could be ascribed to differences in the expression of IL-18R and/or concomitant induction of IL-18BP from human cells. In IL-18R-positive cells, the cytokine is more likely to induce HIV replication. An enhancing effect of IL-18 on HIV replication is supported by results from *in vivo* studies in animal models. In these

studies, pathogenic, but not nonpathogenic, chimeric SIV/HIV-1 (SHIV) viruses caused increased IL-18 levels. The infected animals with increased levels of the cytokine experienced a more rapid loss of $CD4^+$ T-cells and higher set points for viral load[63]. The cytokine seemed to promote disease progression in these studies, although it would have been more desirable to investigate the effects of *in vivo* neutralization and of administration of the cytokine on viral replication and disease progression. In NOD-SCID mice grafted with human cells, IL-18 also enhanced HIV replication[64]. Taken together, these studies strongly suggest that IL-18 promotes HIV replication in HIV-infected persons.

Biological effects of interleukin-18 beyond immune system

The IL-18Rs are expressed on the surface of adipocytes, vascular endothelial cells, and in certain brain cells. This allows IL-18 to exert biological effects in the body beyond immune system. Like other proinflammatory cytokines, it inhibits lipogenesis and promotes lipolysis (reviewed[65,66]). The transcripts for IL-18 and its receptor have been detected in adipose tissue including adipocytes[67]. Consequently, the cytokine may cause lipo-depletion and it is not surprising that the cytokine has been implicated in HIV-associated lipodystrophy syndrome. The syndrome, first described in 1998[68], is characterized by a redistribution of body fat. The patients usually lose subcutaneous fat on face ("empty cheek syndrome"), arms, legs, and trunk, and gain fat on the dorsocervical region ("buffalo hump condition"), breast, and viscera (reviewed[66]). HIV-associated lipodystrophy syndrome also occurred in HIV-infected persons before the advent of antiretroviral therapies; however, the use of HAART has significantly increased its incidence and severity. Both reverse transcriptase inhibitors and protease inhibitors have been implicated in hastening this syndrome[66]. About one-third of HIV-infected persons undergoing antiretroviral therapy experience it in one form or another.

Experimental studies have demonstrated that inhibition of lipogenesis (differentiation of pre-adipocytes into adipocytes) and increased lipolysis in adipocytes are responsible for loss of fat in HIV-infected persons[66,69]. Increased numbers of adipocytes undergoing apoptosis in the adipose tissues have been observed in these patients[70]. It is believed that one of the mechanisms that underlie the causation of this syndrome is induction of proinflammatory cytokines, which may result from direct effects of the virus, viral gene products, and/or antiviral drugs. Among these cytokines, the potential role of IL-18 in the etiopathogenesis of this syndrome is beginning to emerge. Although the levels of the cytokine increase in the circulation of HIV-infected persons, they are higher in the patients with HIV-associated lipodystrophy syndrome than in the patients without it[71]. The gene is also expressed at higher levels in the adipose tissues of these patients. In two separate studies involving subcutaneous fat of the limbs and femoral gluteal tissues, the level of IL-18 gene expression correlated with the degree of lipoatrophy[71,72]. Another hallmark of HIV-associated lipodystrophy syndrome is diminution in the circulating levels of adiponectin, an adipocyte-produced anti-inflammatory mediator, which increases insulin sensitivity. It has been demonstrated *in vitro* that IL-18 inhibits production of adiponectin in the adipose tissues[73]. Increased concentration of IL-18 in the circulation of HIV-infected persons may be at least partially responsible for declining adiponectin levels in HIV-associated lipodystrophy syndrome as well as in obesity and type 2 diabetes.

Interleukin-18 has been associated with obesity. The condition is accompanied by low-grade inflammation resulting from production of several proinflammatory cytokines including IL-18 from adipose tissues. Increased concentrations of the cytokine have been reported in obese persons[65,74-76]. The cytokine, like other proinflammatory cytokines such as tumor necrosis factor alpha (TNFα) and IL-15, inhibits lipogenesis and promotes lipolysis. This may explain phenotype of the IL-18 or IL-18R KO mice, which become hyperphagic, obese, and develop insulin resistance[77]. Intracerebroventricular, but not intraperitoneal, injections of exogenous IL-18 reverse these effects.

Interestingly, continuous feeding of the cytokine in mice also leads to insulin resistance and the development of type 2 diabetes[78]. The cytokine appears to have differential effects on food intake and lipid metabolism when administered peripherally (intraperitoneally or intravenous) or centrally (intracerebroventricularly).

It is noteworthy that several manifestations of disturbances in homeostasis of energy, lipid, and carbohydrate metabolism, e.g. hypercholesterolemia, dyslipidemia (decreased HDL, hypertriglyceridemia, increased LDL and VLDL), increased fasting levels of glucose and insulin in the blood, etc. had occurred in HIV-infected persons without receiving antiretroviral therapy. The situation would have been exacerbated with the advent of HAART had these patients not been treated with lipolytic agents[78-81]. It has been shown that serum concentrations of IL-18 are significantly higher in HIV-infected patients with hypertriglyceridemia as compared to patients having normal triglyceride levels[82]. In view of the effects of this

cytokine on lipid metabolism and energy homeostasis, it is much more likely to be causally involved in precipitating these manifestations in these patients.

It is noteworthy that systemic insulin resistance is a major complication occurring in HIV-infected patients, especially in those presenting HIV-associated lipodystrophy syndrome[66,83]. Several studies have shown that IL-18 may contribute towards insulin resistance in these patients as well as in type 2 diabetes patients[74,75,78,84,85]. As currently understood, the insulin resistance develops gradually as a result of obesity-associated, chronic low-grade inflammation (reviewed[75,84,86]). The levels of the cytokine correlate with those of glucose and triglycerides in obese and type 2 diabetes patients[76]. Furthermore, elevated levels of the cytokine, especially with IL-6 or C-reactive protein, predict impending type 2 diabetes in middle-aged men and women[85]. The concentrations of several proinflammatory cytokines, e.g. IL-6, TNFα, C-reactive protein, IL-18, etc. are often increased in the circulation of obese persons. Interestingly, increasing IL-18 concentrations in the circulation predict the onset of insulin resistance and type 2 diabetes in obese persons.

The exact mechanisms by which IL-18 promotes insulin resistance and type 2 diabetes are not fully understood. It may do so by its lipolytic actions that may cause lipidemia and an increase in free fatty acids in the circulation. The cytokine may also interfere with insulin-induced signaling directly as well as indirectly by inducing expression of the suppressors of cytokine signaling proteins.

Importantly, IL-18 and its receptor genes are expressed in human pancreas. The cytokine has also been implicated in causing acute pancreatitis and death of insulin-producing cells[87,88]. A direct role of IL-18 in causing destruction of insulin-producing cells comes from the streptozotocin-induced diabetes in mice. Neutralization of endogenous IL-18 by exogenous administration of IL-18BP-Fc fusion protein relieves hyperglycemia and diabetes[89]. Furthermore, the pancreas becomes larger in size in IL-18 KO mice[77]. Further studies are needed to determine whether the cytokine may cause tissue destruction in the pancreas via Fas/FasL interaction as it does in the liver in septicemia.

Apparently, it seems contradictory that if IL-18 is implicated in the development of insulin resistance, then why do IL-18 KO and IL-18R KO mice become obese and develop insulin resistance. While the exact answer is not known, it may relate to increased appetite, feed intake, lipogenesis, decreased lipolysis, and disturbed energy homeostasis. These observations suggest very strongly that IL-18 may play a contributing role in inducing systemic insulin resistance in HIV-infected patients.

Several observational studies have documented an increased incidence of atherosclerotic lesions as well as of cardiovascular events in HIV-infected patients without any apparent known risk factor[90-93]. It is noteworthy that IL-18 is highly atherogenic. Atherosclerotic lesions begin with infiltration of macrophages and T-cells in subendothelial spaces. Functional IL-18R occur on vascular endothelial and smooth muscle cells[94]. By inducing expression of VCAM-1 on vascular endothelial cells and ICAM-1 on macrophages and T-cells, the cytokine promotes adhesion of these cells to vascular endothelium and their subsequent migration to subendothelial spaces[94].

The cytokine also induces platelet-activating factor and plasminogen activator inhibitor-1 (PAI-1) from the endothelial and other target cells, and promotes activation of platelets and thromboembolic events (reviewed[95,96]). In fact we have previously reported a correlation between platelet activation and increased IL-18 concentrations in HIV-infected patients[97].

Interestingly, IL-18 induces IFNγ expression from vascular smooth muscle cells. The interferon-induced expression of CXCL-16/SR-PSOX on macrophages promotes uptake of oxidized LDL and converts them into lipid-laden "foam cells"[98]. The soluble form of CXCL-16 acts as a chemokine and attracts CXCR6-positive T-cells to the lesion. Administration of IL-18 increases atherosclerosis in aorta and aortic arch twofold in animal models of the disease[99]. Increased levels of the cytokine have been documented in the circulation of the patients suffering from this affliction, and these levels correlate with the severity of the disease[100,101]. Neutralization of this cytokine *in vivo* in animal models of the disease by using IL-18BP has been shown to slow progression of the disease[102]. In addition to increased levels of IL-18, increased concentrations of PAI-1 and enhanced platelet activation have been reported in the circulation of HIV-infected persons[97,103]. Furthermore, increased IL-18 concentrations are associated with plaque instability and myocardial infarction[104]. They are a strong predictor of diabetes-associated nephropathy as well as of death in cardiovascular diseases[105-107]. Increased IL-18 production represents a mechanistic link between psychological stress and increased occurrence of atherosclerosis and ischemic heart[108,109]. Increased concentrations of this cytokine in HIV-infected patients are likely to contribute towards increased incidence of atherosclerotic lesions and cardiovascular events.

HIV-associated dementia, a neurologic complication in HIV-infected persons, is characterized by the development of severe motor and cognitive dysfunctions. Proinflammatory cytokines like IL-18, which are produced in brain in response to HIV infection, play an important role

in the development of HIV-associated dementia in HIV-infected patients (reviewed[110]). They increase the permeability of the blood-brain barrier and promote infiltration of HIV-infected macrophages into the tissue.

Interleukin-18 is an important mediator of communication between nervous, endocrine, and immune systems. Biologically mature forms of the cytokine are produced in response to physical, emotional, and psychological stress or activation of the sympathetic system. Under these conditions, the hypothalamic-pituitary-adrenal axis is stimulated, leading to production of IL-18 from the adrenal cortex. Relaxation, on the other hand, activates the parasympathetic nervous system and inhibits production of this cytokine (reviewed[111]). It is noteworthy that stress-induced IL-18 does not result in enhanced production of IFNγ, as it does not cause increased production of collaborating cytokines like IL-12. The cytokine is also produced in response to these stimuli in the neurohypophysis and several different cell types in the brain, e.g. microglia, ependymal cells, and certain neurons in the medial habenula. Because of its expression in the brain, the cytokine is likely to contribute to neuroinflammation and neurodegeneration by activating microglia. The viral envelope glycoprotein Gp120 has been shown to induce activation of caspase-1 and secretion of IL-1β from a variety of brain cells[110,112]. These cells also express IL-18 and likely produce this cytokine in response to HIV infection. Increased levels of the cytokine have been reported to occur in the cerebrospinal fluid of HIV-infected persons suffering from opportunistic infections of the central nervous system[113]. A role for this cytokine in neurodegeneration is also supported by studies on the brains of Alzheimer patients (reviewed[111]). It may induce enhanced production of reactive oxygen and nitrogen species and cause death of neurons. It may also affect brain function by its direct effects on neurons. It impairs long-term potentiation and N-methyl-D-aspartate receptor-mediated transmission in rat hippocampus[114]. Increased concentrations of the cytokine present in the brain and cerebrospinal fluid of HIV-infected persons may be responsible, at least in part, for dementia and psychological disorders occurring in this infection.

Conclusions

By its proinflammatory and immune-enhancing properties, IL-18 protects the host from bacterial, fungal, and viral infections. Interleukin-18-induced IFNγ has the potential to inhibit viral replication by inducing an antiviral state in the host cells[115]. Indeed IL-18-induced IFNγ has been shown to protect mice *in vivo* from infections with HSV-1[116]. The interferon could also inhibit HIV replication by antagonizing the effect of Tat[117]. Furthermore, by providing an early source of this interferon, IL-18 may promote development of type 1 antiviral responses. The very fact that many poxviruses encode an IL-18BP-like protein for neutralizing the host IL-18 is strong evidence for an antiviral role of IL-18[20].

A similar antiviral role for IL-18 can be conceived in HIV infections, especially early in the course of the infection. However, the infection is accompanied by compromised production of several other cytokines like IL-12, IL-15, and IL-21[48]. With the decreased/insufficient production of these collaborating cytokines, IL-18 loses its ability to induce IFNγ. A decreased production of IL-18BP may exacerbate the condition. Under these conditions, the ability of IL-18 to promote type 2 responses may predominate. The cytokine may also blunt innate defense mechanisms and rather promote Fas/FasL-mediated tissue destruction. The cytokine may enhance viral replication, cause disturbances in lipid and carbohydrate metabolism and energy homeostasis precipitating HIV-associated lipodystrophy syndrome, insulin resistance, dyslipidemia, cardiovascular manifestations, and dementia in HIV-infected patients.

Clinical studies conducted in this connection in HIV-infected patients also suggest a pathogenic role of the cytokine in HIV-infected individuals. Higher levels of the cytokine were reported to occur in progressors than in nonprogressors. The patients in the latter category maintained these levels near physiological levels[43]. Thus, increased IL-18 concentration in these patients may be acting more as a bane than a boon. The situation may be ameliorated by the use of exogenous cytokines like IL-12, IL-15, or IL-21. This is rather impracticable as the cytokines are highly toxic. Alternately, IL-18 may be neutralized and its induction of Th2-type cytokines may be prevented. The neutralization of this cytokine may also ameliorate the adverse effects of the cytokine on energy and lipid metabolism.

Fortunately, for this purpose, an excellent tool exists in the form of IL-18BP; exogenous infusions of this IL-18 antagonist may be used to modulate IL-18 activity *in vivo* to desirable levels.

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