Balancing susceptibility to infection and autoimmunity: a role for leptin?

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The immune responses to many infections have long been known to share features with autoimmune responses. In particular, both types of response are typified by the enhanced reactivity of T helper 1 cells – with high levels of interleukin-2, interferon γ and tumor necrosis factor α – and are accompanied often by organ-specific and/or systemic damage and the production of IgG. Paradoxically, the geographical distributions of incidence of infectious diseases and autoimmunity are complementary, rather than coincident. In less-developed societies, an epidemiological association between susceptibility to infection and malnutrition has been observed, whereas in affluent countries, an increased incidence of autoimmune diseases has been described. We suggest that these observations can be explained partly by taking into consideration the immune effects of the adipocyte-derived hormone leptin, which has been shown recently to act as a link between nutritional status and the immune response.

During the past century, improved economic, hygienic and nutritional conditions have reduced significantly the incidence of infectious diseases, at least in the most-developed countries [1,2]. In parallel with the improvement in nutritional status, an increase in susceptibility to autoimmune disease has emerged [3–5]. However, an epidemiological association linking these apparently independent findings is missing at present. Recently, it has been proposed that the lifestyle in developed countries, with reduced exposure to environmental pathogens (e.g. mycobacteria), could be relevant to the increase in the prevalence of autoimmune and allergic diseases [4]. Conversely, in less-affluent societies, exposure to microorganisms (e.g. helminths) and other environmental influences might promote the development of T regulatory responses that protect against both autoimmune and allergic responses [4,6].

Leptin, an adipocyte-derived hormone of the long-chain helical cytokine family, has been proposed recently to act as a link between nutritional status and immune function [7,8]. Leptin has multiple biological effects on nutritional status, metabolism and the neuroimmunoendocrine axis. The circulating concentration of leptin is proportional to fat mass [8], and reduced body fat or nutritional deprivation [8] – associated typically with hypoleptinaemia – is a direct cause of secondary immunodeficiency and increased susceptibility to infection [2,7,9,10]. The reason for this association was not apparent until recently. Now, it can be hypothesized that a low concentration of serum leptin increases susceptibility to infectious diseases by reducing T helper (Th)-cell priming and direct effects on thymic function [10,11]. Furthermore, a genetic deficiency of leptin has been found to be associated with increased frequency of infection and related mortality [11–13]. By contrast, the Th1-promoting effects of leptin have been linked recently to enhanced susceptibility to experimentally induced autoimmune diseases, such as experimental autoimmune encephalomyelitis (EAE) [14,15] and insulin-dependent diabetes mellitus (IDDM) [16]. These latter observations suggested a novel role for leptin in determining the gender bias of susceptibility to autoimmunity, because female mice and humans, which are relatively hyperleptinaemic, have an increased frequency of autoimmune diseases compared with males, which are relatively hypoleptinaemic [7,8].

'…immune–endocrine crosstalk can play a key role in both adipocyte and lymphocyte homeostasis.'

In view of these findings, we suggest the use of leptin as a novel therapy for pathological conditions characterized by low body weight, impaired cell-mediated immune responses and low serum concentrations of leptin. Conversely, we propose an anti-leptin-based approach, aimed at reducing serum levels of leptin, for the treatment of inflammatory and cell-mediated autoimmune diseases [14–19].

Leptin, adipose tissue and the immune system

Leptin, the product of the *obese* gene, is structurally similar to interleukin-2 (IL-2), IL-6 and IL-15 [7,8]. Leptin was described originally as a 'fat-o-stat' cytokine-like hormone, secreted by the adipose tissue to regulate food intake and promote basal metabolism and the β-oxidation of fatty acids [7]. Fat deposits are distributed widely in the body and surround organs such as the heart, kidney and gut, playing a structural and heat-insulation role [7,8].

The structural similarities between the leptin receptor and hematopoietic cytokine receptors suggested new functions for adipose tissue in influencing hematopoiesis and immune function [7,8]. Indeed, bone-marrow stromal cells with a preadipocyte phenotype support lymphopoiesis and myelopoiesis *in vitro* by cell–cell interactions and the

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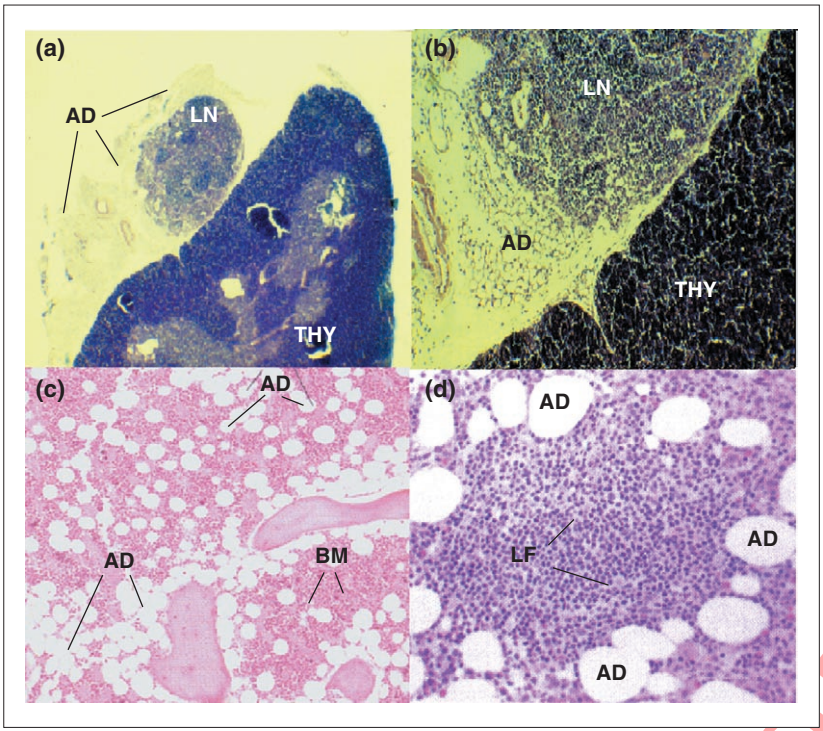

Fig. 1. Adipose tissue and lymphoid organs are in strict anatomical and functional contact. Section of (a) thymus (THY) and (b) mediastinic lymph node (LN) of a C57BL6/J mouse. Note that adipose tissue (AD) surrounds both organs. (c) Anatomical contiguity suggests that the adipose tissue within the bone marrow (BM) is important for the homeostasis of both lymphoid and myeloid precursors. (d) A lymphoid follicle (LF) in the context of bone marrow surrounded by adipocytes. Magnification: (a) × 200; (b) × 400; (c) × 200; and (d) × 600.

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release of macrophage colony-stimulating factor, granulocyte colony-stimulating factor and IL-6 [20]. Also, leptin was found to affect thymic function, and the growth and survival of bone-marrow CD34$^+$ precursors and CD4$^+$ T cells [7,8,10,11]. In this context, it is noteworthy that organs such as the bone marrow, lymph nodes and thymus are all connected with and surrounded by adipose tissue, such that the *in situ* production of leptin can support T-cell homeostasis and proinflammatory immune responses (Fig. 1). Interestingly, both naturally leptin-deficient (*ob*/*ob*) [12] and leptin-receptor-deficient (*db*/*db*) mice [21], despite their great body-fat mass, have thymic and lymph-node atrophy, reduced numbers of bone-marrow precursors and impaired cell-mediated immune responses (Table 1). These observations suggest the presence of a functional axis linking lymphoid cells and adipocytes through leptin and its receptor. Furthermore, leptin is able to exert differential effects on naive versus memory CD4$^+$ T cells [10] (Fig. 2), as well as on the monocyte–macrophage lineage [22]. In particular, during the antigen-specific stimulation of CD4$^+$ T cells, the addition of leptin increases the proliferation of and IL-2 secretion by naive T cells, but augments the production of interferon γ (IFN-γ) by memory T cells, with little effect on proliferation (Fig. 2). Also, leptin stimulates the secretion of IL-6, IL-18 and tumor necrosis factor α (TNF-α) *in vitro* and *in vivo* [23]. In *ob*/*ob* mice, the delayed-type hypersensitivity (DTH) response is impaired and the antibody response is polarized towards secretion of IgG1 and suppressed production of IgG2a, and in normal mice, starvation or malnutrition (which decreases leptin levels) results in the suppression of Th1-mediated inflammatory responses [10,14]. Importantly, leptin replacement can reverse this condition, indicating that leptin plays a major role in the immunosuppression that is secondary to nutritional deficiency (Fig. 2).

Although the immune system can be influenced by adipocytes, the reverse holds true also; namely that lymphocytes and monocytes can influence fat deposition. In this regard, it is of interest that intercellular adhesion molecule 1 (ICAM-1)-deficient mice develop obesity late in life, associated with the impaired migration of leukocytes to peripheral tissues, increased susceptibility to infections, impaired T-cell function and peripheral leptin resistance [24–26] (Table 1). These observations suggest further that immune–endocrine crosstalk can play a key role in both adipocyte and lymphocyte homeostasis. This is true also for cytokines involved in this crosstalk, such as TNF-α and IL-6 [27,28].

Nutritional status and immunity: how to keep infections at bay

Epidemiological observations indicate an association between susceptibility to infection and malnutrition [1–3]. It is well established that nutritional deficiency impairs cell-mediated immunity, phagocyte function, and cytokine and antibody production [2,9]. Indeed, malnutrition is the most common cause of secondary immunodeficiency worldwide [2]. More specifically, protein-energy malnutrition (PEM) [29,30], a nutritional deficiency in which individuals suffer from protein but not calorific malnutrition, is one of the highest priority public-health concerns, affecting approximately one billion undernourished or malnourished people in the developing world [1,9]. PEM results when the supply of energy from protein and micronutrients in the diet is insufficient to meet bodily needs. In experimental animal models, PEM selectively compromises components of the cellular immune response, such as the secretion of IFN-γ, TNF-α and nitric oxide (NO), which are all important for the control of infection with *Mycobacterium tuberculosis* [9]. Strikingly, PEM causes a dramatic reduction of body-fat mass and decrease in the circulating concentration of leptin, which, in turn, impairs the production of IFN-γ, TNF-α and NO [9,31].

The recently named nutritionally acquired immune deficiency syndrome (NAIDS) refers to childhood malnutrition, which is a leading cause of mortality in developing countries [32]. Usually, NAIDS can be corrected by appropriate nutritional intervention. NAIDS might compound the problems of AIDS; HIV infection often causes malnutrition and can lead to the secondary development of NAIDS,

Table 1. Characteristics of different animal models of obesity associated with leptin deficiency or leptin resistance and their susceptibility to infections and autoimmunity[a]

Mouse strain	Deficiency	Immune phenotype	T-cell response	Obesity	Serum leptin	Infections	Autoimmunity	Refs
ob/ob	Leptin	$CD4^+$ T cells increased; $CD8^+$ T cells and B cells unchanged or increased	Th1 decreased; Th2 increased; DTH decreased	Early in life	Undetectable	Increased susceptibility	Resistant to EAE, hepatitis, AIA and colitis	[10–12,14, 17,18,23]
db/db	Leptin receptor	$CD4^+$ T cells decreased; $CD8^+$ T cells and B cells unchanged or increased	Th1 decreased; Th2 increased; DTH decreased	Early in life	Very high, leading to leptin resistance	Increased susceptibility	ND	[7,21]
ICAM-1$^{-/-}$	ICAM-1	$CD4^+$ and $CD8^+$ T cells unchanged; neutrophils in periphery increased	DTH decreased; neutrophil migration decreased	Late in life	High, leading to leptin resistance	Increased susceptibility	Resistant to IDDM	[24–26]

[a]Abbreviations: AIA, antigen-induced arthritis; *db*, leptin receptor gene; DTH, delayed-type hypersensitivity; EAE, experimental autoimmune encephalomyelitis; ICAM-1, intercellular adhesion molecule 1; IDDM, insulin-dependent diabetes mellitus; ND, not determined; *ob*, leptin gene; Th, T helper.

resulting in additional immunological dysfunction. Proper nutritional support during HIV infection can delay the development of NAIDS and improve the survival rate of infected individuals [32]. In addition, nutrients such as zinc, selenium, vitamins A, C and E, polyunsaturated fatty acids and arginine, which have been shown to influence immunological responses, might enhance immunity in critically ill and/or surgical patients [7,33–35]. Whether these micronutrients operate directly or indirectly through the action of leptin needs to be investigated.

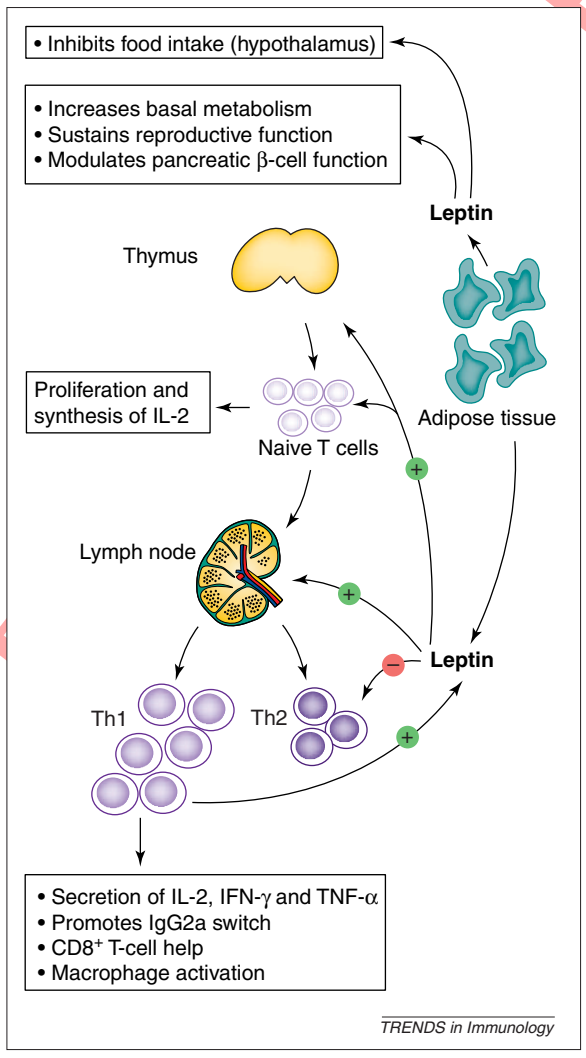

Fig. 2. Model summarizing the central and peripheral effects of leptin. After secretion by adipocytes, leptin exerts central effects on the hypothalamus by inhibiting food intake. In the periphery, leptin increases basal metabolism, inhibits insulin secretion from pancreatic β-cells and sustains reproductive function. Also, leptin promotes the generation of naive T cells by the thymus, stimulates T-cell proliferation and IL-2 secretion after antigen-specific stimulation, and favors Th1 responses while inhibiting the secretion of Th2 cytokines. Abbreviations: IFN-γ, interferon γ; IL-2, interleukin-2; Th, T helper; TNF-α, tumor necrosis factor α.

Leptin in inflammation and autoimmunity

Susceptibility to autoimmune reactions is greater for females than males for diseases such as Sjogren's syndrome, systemic lupus erythematosus (SLE), autoimmune thyroid disease, rheumatoid arthritis (RA) and multiple sclerosis [36]. The reasons for this sexual dimorphism are unclear, but might include factors such as sex-related differences in immune responsiveness, hormonal effects and sex-linked genetic factors. In rodents, after immunization, females have more vigorous T-cell and antibody responses than males, produce higher levels of Th1 cytokines (because of the presence of estrogens) than males and show consistent *in vitro* secretion of IFN-γ and IL-1 [36]. Conversely, androgens and testosterone promote the production of IL-4 and IL-5, and a switch to protective Th2 responses [36]. Serum levels of leptin show marked sexual dimorphism also, being higher in females than males [8]. Leptin treatment affects directly the course of relapsing–remitting EAE induced by proteolipid protein peptide ($PLP_{139–151}$) in susceptible SJL female mice and resistant males [15]. Indeed, before or after disease onset, the administration of leptin to female SJL mice worsens the disease significantly, with a concomitant increase in the $PLP_{139–151}$-specific DTH response. Similarly, this same treatment renders male SJL mice susceptible to disease, with the appearance of $PLP_{139–151}$-specific DTH reactivity and a switch from a Th2 to Th1 pattern of cytokine release. All of these observations suggest the involvement of leptin in the gender-related differences in susceptibility to autoimmune diseases. Further support for this idea comes from studies of leptin-deficient *ob/ob* mice, which are naturally resistant to EAE, after immunization with myelin oligodendrocyte glycoprotein peptide ($MOG_{35–55}$) [14] or the adoptive

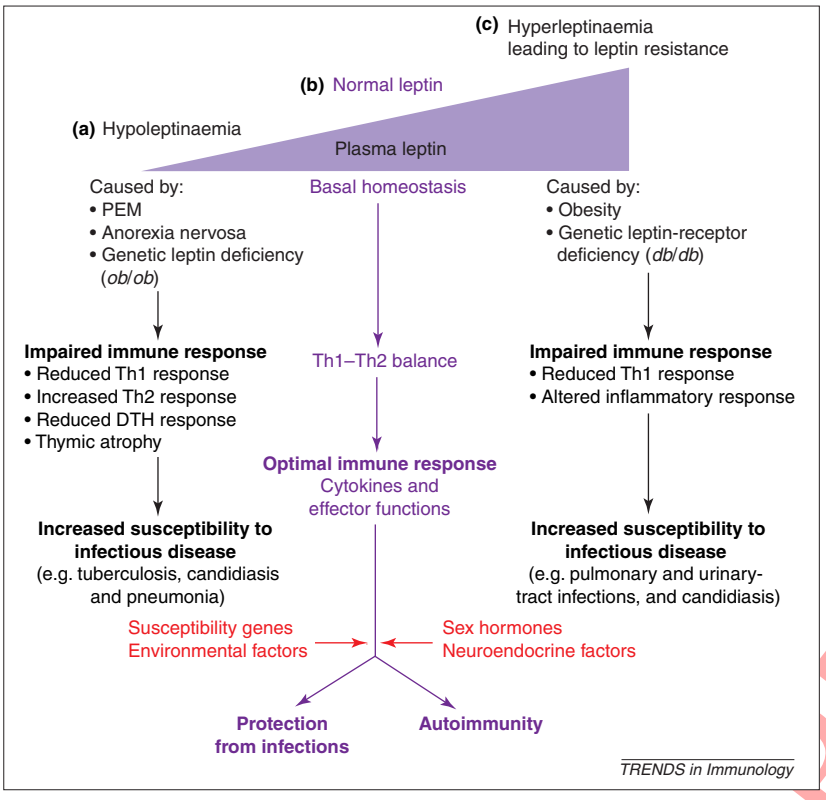

Fig. 3. Model of the actions of leptin in balancing susceptibility to infection and autoimmunity. (a) Reduction of the level of circulating leptin [e.g. owing to protein-energy malnutrition (PEM), anorexia nervosa or genetic leptin deficiency (*ob*/*ob*)] results in reduced immunocompetence in humans and mice and increased susceptibility to infection. (b) In normal conditions, leptin contributes to protection from infectious agents, on the one hand, but also, to loss of tolerance and autoimmunity, on the other hand. (c) Conditions of hyperleptinaemia [e.g. obesity or genetic leptin-receptor deficiency (*db*/*db*)] that lead to leptin resistance result in reduced immunocompetence and an increased frequency of infection, similar to the effects of malnutrition. Abbreviations: DTH, delayed-type hypersensitivity; Th, T helper.

transfer of pathogenic T cells that induce EAE in wild-type control mice. Chronic leptin replacement rendered these mice susceptible to both actively and passively acquired disease, and wild-type animals developed a disease with increased mortality and neurological symptoms.

Finally, other reports from the literature have demonstrated the involvement of leptin in other inflammatory and autoimmune diseases, such as T-cell-mediated damage to pancreatic β-cells, carragenan-induced paw edema and pleurisy, experimental arthritis, and experimental colitis and hepatitis [16–19,23]. Some of these conditions are associated with the production of IL-18, TNF-α and IFN-γ, which is impaired in *ob*/*ob* mice but restored completely by leptin administration [14,23]. Taken together, these findings support the hypothesis that leptin and nutritional status play a crucial role in determining susceptibility to autoimmune disease.

Fewer infections, more autoimmunity: the leptin hypothesis

During the past century, in the industrialized world, the incidence of infections has diminished greatly because of improved hygienic conditions, better nutrition, vaccination and the use of antibiotics [2]. Interestingly, in the affluent and more-developed societies, epidemiological studies have revealed a concomitant increase in the incidence of autoimmune diseases, whereas these diseases have become less common in the less-developed countries [4,5,37]. Thus, susceptibility to infection and autoimmunity appear to be inversely related. Several factors, other than nutrition, might contribute to this relationship also, such as the environment, genetic background and exposure to specific pathogens. Nevertheless, changes in diet and calorie intake and subsequently, serum leptin concentration should be taken into account to explain the complex network connecting nutritional status and susceptibility to autoimmune and infectious diseases. Animal studies provide support for this concept. In some murine models of SLE, IDDM and EAE, the induction and progression of disease can be prevented by starvation and/or reduced calorie intake, or by administering nutrients, such as polyunsaturated fatty acids, able to reduce the inflammatory response [34,35,38–40]. In humans, a similar observation has been reported by Bruining *et al.* [37], who described an increased incidence of IDDM at younger ages in affluent countries, where affluence is associated with increased postnatal growth and abundant nutrition. More specifically, children that developed diabetes had a greater gain in body-mass index (BMI) in the first year of life

'…nutritional deficiency might protect individuals from autoimmunity…but predispose to infections…'

compared with healthy siblings and the early presence of autoantibodies specific for IA-2 (pancreatic islet tyrosine phosphatase) [37]. Leptin, with its pleiotropic functions, including the promotion of Th1 responses, reduction of the apoptotic rate of thymocytes, reversal of acute-starvation-induced immunosuppression and induction of expression of adhesion molecules [e.g. ICAM-1 and CD49b (integrin α_2)] [7,10,11], is a good candidate for contributing to the pathogenesis and maintenance of autoimmunity in genetically predisposed individuals. Conversely, malnutrition and nutritional deficiency might protect individuals from autoimmunity by lowering circulating leptin concentrations, but predispose to infections, such as candidiasis, tuberculosis, pneumonia, and bacterial and viral diarrhea [2] (Fig. 3). Last but not least, the most common form of human obesity, characterized by hyperleptinaemia causing central and peripheral leptin resistance [8], is associated with an increased frequency of infection [41]. In this context, leptin-receptor desensitization is perceived by T cells as a

condition of leptin deficiency, leading to immune dysfunction in a similar manner to malnutrition and genetic leptin deficiency (Fig. 3).

New leptin-based therapeutic strategies?

The recently discovered connection between leptin and immune function suggests several therapeutic possibilities. For example, the administration of leptin antagonists could be used to reduce leptin concentrations in conditions characterized by enhanced T-cell immunity, such as autoimmunity and inflammation, whereas leptin administration could be used to stimulate the immune system during immunosuppression and infections associated with leptin deficiency. Interestingly, leptin levels can be targeted easily by reducing food intake or administering specific nutrients, such as polyunsaturated fatty acids, or zinc-free diets [7,33,39]. Although food deprivation in adults has been effective for the treatment of RA [42], it is not easily applicable to children during growth. Nevertheless, this approach, alone or together with the coadministration of soluble, recombinant leptin receptor, could be suggested for the treatment of certain autoimmune diseases.

Another approach could be the use of drugs that reduce the concentration of serum leptin. Drugs that are able to activate the peroxisome proliferator-activated receptor γ could be good candidates [43,44], because this transcription factor, once activated by its endogenous ligand (15-deoxy-$\Delta^{12,14}$-prostaglandin-J_2), represses expression of the *obese* gene [43,45].

Additional immunotherapeutic uses of leptin could include the treatment of immunodeficiencies and infectious diseases and possibly, its use as an adjuvant for vaccination protocols.

Until now, the only clinical use of leptin has been for a few cases of genetically leptin-deficient individuals and in obese nonleptin-deficient patients to reduce food intake [46]. This treatment restored some of the impaired neuroendocrine functions, such as the control of food intake and energy expenditure, and also restored reproductive function in genetically leptin-deficient individuals [47]. No studies are available yet on the effects of leptin replacement on the immune function of leptin-deficient humans. Until now, the only evidence available is that in these individuals, the dramatic reduction of leptin levels predisposes to death from infectious diseases in early childhood [13]. Indeed, an increased frequency of death from infectious diseases has been observed in leptin-deficient children compared with normal-weight siblings of the same generation in a Turkish family, where environment and access to nutrients were identical [13].

Conclusions

Since its discovery in 1994, leptin has attracted increasing interest in the scientific community on account of its remarkably pleiotropic functions. Many related aspects remain to be investigated. However, current information on leptin function and regulation already suggests novel possibilities, using as yet unexploited leptin-based therapeutic tools, for the treatment of both infection and autoimmune disease.

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Defining the dynamics of self-assembled Fas-receptor activation

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Fas–Fas-ligand, the most well investigated apoptotic signaling system, plays a pivotal role in several human diseases. Its signaling through multiple pathways; multiple, complex regulatory points; and recently described tendency to undergo ligand-independent self-assembly warrant a comprehensive understanding of its physiologically well controlled function. In this review, we attempt to develop such a perspective on the regulation of Fas signaling. The multistep Fas regulation model presented here should be helpful in devising effective interventions for conditions resulting from the dysregulation of Fas.

The importance of cell death to life has now been well recognized, not only in pathological conditions but also, in normal embryogenesis, development, homeostasis and immunity. Imbalanced regulation of apoptotic cell death has been implicated in several human diseases, including tissue degenerative disorders, autoimmune phenomena, AIDS and cancer [1,2]. The past decade has seen tremendous interest in the phenomenon of apoptosis and provided several insights into its mechanistic bases. For example, a new category of the tumor necrosis factor α receptor (TNFR) superfamily has been recognized as a group of death receptors. An homologous intracellular domain, called the death domain (DD), characterizes this special group, which includes TNFRI (p55), Fas (CD95) and receptors for TNF-related apoptosis-inducing ligand (TRAIL) [e.g. death receptor 4 (DR4) and DR5] [3]. The DD seems to be the seat of the intracellular death trigger in the majority of cases. Of all the death receptors, the most extensively investigated receptor is Fas (CD95). The varying experimental designs of different investigators – using primarily *in vitro* systems with several, different cell lines established in individual laboratories – have yielded divergent and frequently debatable results. Apparently, the activation of Fas by its specific ligand (FasL) can signal cell death by more than one mechanism in the same cell; the relative

'…the direct activation of the caspase cascade…and the mitochondrion-mediated pathway are the predominant…arms of Fas signaling.'

contribution and importance of each mechanism might differ in individual cell types [4–6]. The complexities of Fas signaling and its potential detrimental consequences necessitate stringent regulation. Although several control points have been identified, so far no unifying theme of regulation has

 1471-4906/02/$ – see front matter PII: S1471-4906(02)02192-0