Autoimmunity, 1989, Vol. 2, pp. 177–189
Reprints available directly from the publisher
Photocopying permitted by license only

REVIEW

IMMUNE HORMONES (CYTOKINES); PATHOGENIC ROLE IN AUTOIMMUNE RHEUMATIC AND ENDOCRINE DISEASES

KLAUS BENDTZEN

Laboratory of Medical Immunology, 7544, Rigshospitalet University Hospital, Copenhagen, Denmark

KEY WORDS: Review, HLA and disease, cytokines, interleukins, interferons, tumor necrosis factors, rheumatoid arthritis, insulin-dependent diabetes mellitus, autoimmune thyroid diseases.

There is increasing clinical and experimental evidence that many autoimmune diseases develop as a result of abnormalities in the T lymphocyte-mediated immunity. These diseases include systemic rheumatic diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus, and, possibly, some nonsystemic rheumatic diseases such as osteoarthritis and gout. Included also are the organspecific endocrine diseases, insulin-dependent diabetes mellitus (IDDM), Graves' disease, Hashimoto's thyroiditis and, possibly, idiopathic Addison's disease, idiopathic hypopituitarism and pernicious anemia. Disorders of T cell-mediated immunity may also contribute to the development of multiple sclerosis, coeliac disease, active chronic hepatitis, and some fibrotic skin-, liver- and lung diseases.

T cell-mediated immune reactions are initiated and controlled by proteins and glycoproteins produced by the T- and B lymphocytes (lymphokines) as well as other cells involved in these reactions[1]. The mediators are collectively termed cytokines. They are hormones of the immune system acting at extremely low concentrations (10^{-10} to 10^{-14} M) via specific receptors on target cells. Most cytokines act regionally, i.e. in the vicinity of the production site, but some of the mediators modulate the functions of cells at distant locations via blood and lymph circulation. Table 1 summarizes the biological properties of the best characterized human cytokines.

This review will briefly discuss the involvement of cytokines, particularly those originating from monocytes/macrophages (Mϕ), in the processes leading to RA, IDDM and other autoimmune diseases.

Correspondence: K. Bendtzen, MD, Lab. Med. Immunol. 7544, Rigshospitalet University Hospital, 20 Tagensvej, DK-2200 Copenhagen N, Denmark.

Table 1 Properties of human cytokines

Acronym	Principal sources	mw (kD)	Major function(s)
IL-1α/β (= LAF)	monocyte/macrophage NK cell B cell dendritic cell Langerhans' cell (skin) keratinocyte endothelial cell astrocyte synovial cell smooth muscle cell	17.5	activate: T-, B- and NK cells, endothelial cells, hepatocytes chondrocytes, osteoclasts, fibroblasts nerve cells (induce fever and slow-wave sleep) thyrocytes, pancreatic β-cells (low conc) suppress: thyrocytes, pancreatic β-cells (medium conc)
TNF-α	monocyte/macrophage keratinocyte T cell	17	activates: neutrophils, eosinophils, endothelial cells chondrocytes, osteoclasts, fibroblasts nerve cells (induce fever)
TNF-β	T cell	17	same as TNF-α
IL-2 (= TCGF)	T cell	15	necessary for T cell growth promotes B cell growth and differentiation activates Mϕ
IL-4 (= BSF-1) (= BCGF-I)	T cell	12–30	promotes B- and T cell growth activates mast cells
IL-5 (= TRF) (= BCGF-II)	T cell	35–60	promotes: B cell differentiation eosinophilocyte functions
IL-6 (= IFN-β2) (= BSF-2) (= HPGF) (= BCDF)	monocyte/macrophage fibroblast endothelial cell T cell myxoma cells carcinomas	24	promotes: antiviral activity (weak) B cell growth, differentiation and Ig secretion growth of factor-dependent hybridomas/ plasmacytomas hepatocyte production of acute-phase proteins pituitary functions several effects similar to IL-1?
BGDF	T cell	> 60	promotes B-cell growth and differentiation
IFN-α	leukocytes	20	activates: NK cells B cells + other cells
IFN-γ	T cell	17–26	activates: monocytes/macrophages, fibroblasts B cell differentiation + other cells (induction of MHC class II antigens) general growth-inhibitory functions antiviral activity

Abbreviations:
IL: interleukin; LAF: lymphocyte-activating factor; NK: natural killer (cell); TNF: tumor necrosis factor; TCGF: T cell growth factor; BSF: B cell-stimulatory factor; BCGF: B cell growth factor; TRF: T cell replacing factor; IFN: interferon; HPGF: hybridoma/plasmacytoma growth factor; BCDF: B cell differentiation factor; BGDF: B cell growth and differentiation factor.

EVIDENCE FOR THE INVOLVEMENT OF T CELL-MEDIATED IMMUNE REACTIONS IN AUTOIMMUNE RHEUMATOID AND ENDOCRINE DISEASES

I shall first consider some of the clinical evidence for a pathogenic role of cellular immunity in RA and IDDM, both diseases serving here as models for ceratin autoimmune rheumatoid and endocrine diseases.

In this regard, one must realize that disorders of cellular or humoral immunity observed during the course of a disease may be the result rather than the cause of the disease. This may for instance underly the glucose intolerance seen in up to 75% of patients suffering from cystic fibrosis[2]. In this disease, there is no evidence of a primary autoimmune dysfunction. However, the immune abnormalities may still contribute to the disease processes and thus play a pathogenetic role. With respect to the organ specific autoimmune diseases, one is also confronted with the fact that the cellular immune irregularities are usually disclosed by the use of cells from the circulation rather than cells from the target organ. Finally, clinically relevant interpretations of the findings are difficult, because the patients are often treated with potent immunomodulating drugs at the time of investigation.

RA

The inflammatory processes in RA include production of synovial fluid, activation and proliferation of cells in the synovial membrane, destruction of articular cartilage and bone, and repair processes resulting in fibrosis, ectopic calcification and metaplastic bone formation. Polymorphonuclear leukocytes (PMN) and Mϕ play a critical role in all these processes[3-5]. Immunocompetent cells are also involved, and in severe cases the inflamed synovial tissue may resemble a lymphoid organ with germinal centers of B lymphocytes surrounded by T lymphocytes. Generally, a relatively large proportion of the infiltrating T cells bear membrane markers characteristic for activated cells, and such cells are often found in the blood as well (reviewed in[3]). The presence of plasma cells and immune complexes in the synovial tissue and the frequent finding of autoantibodies, particularly anti Fc-IgG rheumatoid factors, and hypergammaglobulinemia also suggests that antibody-mediated reactions are involved in the disease processes. However, these humoral reactions may reflect that the cellular infiltrate in the synovial tissue is dominated by activated cells of the helper phenotype, and these cells may trigger B cells to produce antibodies in an uncontrolled manner.

Many investigators believe that in RA, the host responds to an exogenous antigen, or an endogenous antigen rendered immunogenic in an aberrant manner, to generate an inappropriate cellular as well as humoral immune response.

IDDM

The most impressive evidence for the role of T lymphocytes in autoimmune diseases comes from transplant studies[6]. When monozygotic twins with IDDM received a segmental pancreas graft from the nondiabetic sibling, the initially almost normal β-cell function was lost within a few months, apparently as a result of a T cell-mediated immune reaction[6]. This reaction was not part of an allograft rejection,

because the twins were genetically identical, and autoantibodies did not appear to contribute to the cell damage. Also, the exocrine tissue and the non-β-cells of the islets were not affected. Thus, the immune system, probably the T cells, retain the capacity to selectively destroy the islet β-cells even after previous elimination of these cells.

The temporal association of IDDM with other autoimmune diseases such as idiopathic Addison's disease and Hashimoto's thyroiditis[7], supports an autoimmune pathogenesis of IDDM and, possibly, other endocrine diseases.

The pathogenetic importance of T cell functions is supported by the fact that ciclosporin, a T cell-selective immunosuppressive drug, is effective in inducing and maintaining remission in patients with different autoimmune diseases, including RA and newly diagnosed IDDM[8].

Immunogenetic studies

Another piece of evidence that T cell-mediated immune reactions may be pathogenetically involved in autoimmune diseases is the contribution to the development of these diseases by genes in the major histocompatibility complex (MHC) particularly in the MHC class II region, in man the HLA-D region[9]. For instance, the HLA allele DR4 is positively associated with RA, and DR3 and DR4 are positively associated with IDDM. HLA-DR3 is also associated with the development of Graves' disease, atrophic thyroiditis, idiopathic Addison's disease, coeliac disease, active chronic hepatitis and myasthenia gravis. Interestingly, DR2 is positively associated with multiple sclerosis, but the same antigen tends to protect against IDDM. HLA-DR5 is found more frequently than expected in patients with Hashimoto's thyroiditis.

MHC class II molecules are normally expressed on Mϕ and on B lymphocytes, but aberrant expression of these antigens has been observed on thyroid cell membranes in Graves' disease, Hashimoto's thyroiditis and on islet β-cells in IDDM[10–12]. Recently, *in vitro* experiments have shown that interferon-γ (IFN-γ), produced by T lymphocytes, is a potent inducer of MHC class II antigens on various cells including endothelial and epithelial cells normally devoid of these molecules[13]. For example, IFN-γ induces normal thyroid follicular cells (thyrocytes) to express MHC class II antigens[14]. Interestingly, the Mϕ- and T cell hormones tumor necrosis factor (TNF-α) and lymphotoxin (= tumor necrosis factor-β (TNF-β) though ineffective by themselves synergize with IFN-γ in the induction of MHC class II molecules in several *in vitro* test systems, including human islet cells[12]. IFN-γ by itself induces MHC class II antigens only on insulin-containing cells in islets from prediabetic BB rats[15], and this cytokine also increases MHC class I (HLA-A, -B and -C) expression on human β-cells[10].

Pathogenetic role of MHC class II molecules?

Because of the critical role of these molecules in the presentation of antigens to T lymphocytes (Figure 1), it may be speculated that aberrant expression of MHC class II molecules facilitates presentation of otherwise 'forbidden antigens' to autoreactive T lymphocytes contributing to tissue damage as a result of a T cell-mediated attack. This, however, may not be the only explanation because expression of MHC class II molecules *in vivo* also depends upon the presence of Mϕ[14], most likely because of their crucial role in the activation of T cells[1,16,17]. Mϕ are indeed the first to infiltrate the pancreatic islets in the spontaneously diabetic BB rat, and a blockade of Mϕ function

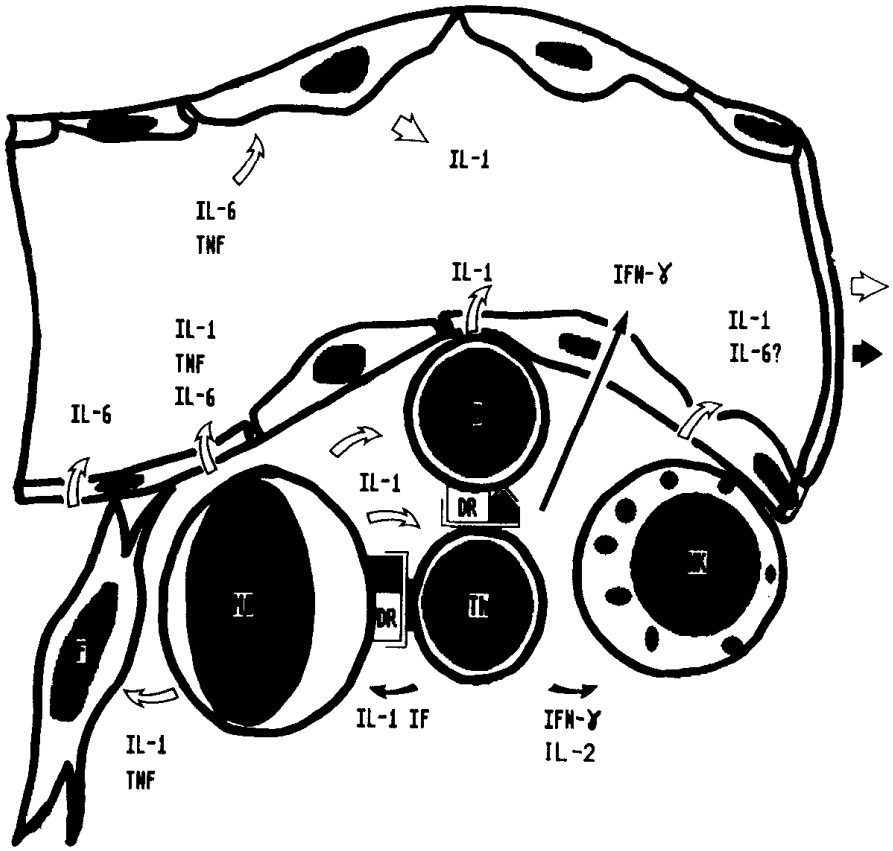

Figure 1 Role of MHC class II molecules and IL-1 in antigen presentation to T- and B lymphocytes. Production of IL-1, IL-6, TNF-α, TNF-β and IFN-γ by the cells involved in the initial triggering of the immune system may initiate and perpetuate damage to bystander cells if closely surrounded by activated MØ and lymphocytes (model 1), or if the cells are situated downstreams to the inflammatory reaction (model 2).

in prediabetic BB rats prevents the development of the disease[18]. Natural killer (NK) cells and even B lymphocytes may also be important in this regard, probably because both cell types produce the T cell-activating cytokine, interleukin 1 (IL-1)[16].

CYTOKINES

IL-1, tumor necrosis factor (TNF), interferon-γ (IFN-γ) and interleukin 6 (IL-6) are members of a growing family of polypeptide mediators that includes interferons and some hemopoietic growth factors (Table 1)[1,17]. These cytokines orchestrate the complex processes of inflammation, immune reactions and hemopoiesis. The cytokines mentioned above are produced during immunoinflammatory reactions but also during conditions of 'stress', and they fulfil important roles in the generation of fever and the acute-phase reaction, and in the cachexia resulting from chronic infectious and neoplastic diseases[16,19]. The peptides are also considered important in the development of a number of autoimmune diseases, including RA and other immunoinflammatory disorders of bone and connective tissues, and IDDM and autoimmune thyroid diseases (see below).

IL-1

IL-1 is a small group of peptides of mw 17.5 kD primarily produced by activated Mϕ and NK cells, but also by other cell types, including B lymphocytes and endothelial cells (Table 1)[1, 16]. IL-1 is necessary for the induction of activated T lymphocytes, and IL-1 is almost certainly produced by Mϕ and/or NK cells and B lymphocytes infiltrating endocrine tissues during autoimmune diseases. So far, two distinct members have been characterized, IL-1α and IL-1β (see[16]).

TNF-α and TNF-β

TNF-α is produced primarily by Mϕ, but appropriately stimulated T lymphocytes also elaborate this cytokine. TNF-α has been identified as the mediator of the cytotoxic activity in serum of mice infected with mycobacteria and subsequently injected with *E. coli* endotoxin[19]. Certain tumor cells are highly susceptible to the toxic activity of TNF *in vitro* and *in vivo*, whereas normal cells usually survive treatment with the hormone. TNF-α, or a TNF-α-like cytokine(s), appears to be involved in the defence against parasitic diseases such as malaria.

TNF-α is genetically and structurally closely related to a T lymphocyte-derived cytokine, TNF-β, also referred to as lymphotoxin[16]. Both species of TNF are of mw 17 kD, but TNF-β in particular tends to aggregate to higher molecular weight forms.

The TNFs induce endothelial cell proliferation and production of IL-1, and they synergize with IFN-γ in the induction of MHC class I and II molecules in a number of cell types.

IFN-γ

IFN-γ is produced primarily by T lymphocytes challenged by recall antigens or nonspecific polyclonal activators[1,13,17]. It is one of at least three species of interferons. The structure of the human IFN-γ gene is known[20] and confirms its difference from the other interferons, IFN-α, IFN-β_1 and IFN-β_2 see below). IFN-γ is pH 2 labile, and tends to aggregate into dimers of variously glycosylated proteins[13,17]. IFN-γ has antiviral and certain cell-suppressive activities, but its immunoregulatory functions may be the most important ones (immune interferon). In this regard the Mϕ-activating property of IFN-γ is particularly interesting[13,17].

IL-6 (= interferon β_2; = B cell-stimulating factor 2)

Human fibroblasts induced by various stimuli produce several mRNA's encoding IFN-like activities including classical IFN-β, now referred to as IFN-β_1. A structurally different 21–26 kD molecule with antiviral activity produced by fibroblasts under similar circumstances is termed IFN-β_2[21]. This molecule is now known to be identical with a B cell-stimulating factor termed BSF-2[22] and a factor capable of promoting the growth of hybridomas and plasmacytomas[23,24] (Table 1).

In the context of this review, it is interesting that IL-1 and TNF-α induce the production of IL-6 in fibroblasts and endothelial cells[24]. To date, IL-1 is indeed the most potent inducer of IL-6, suggesting that IL-6 may function as a second mediator of some of the effects ascribed to IL-1 and/or TNF. This is emphasized by recent findings that IL-6 is a potent activator of the same hepatocyte and pituitary functions which are induced by IL-1[25].

PATHOGENETIC INVOLVEMENT OF IL-1 AND TNF IN RA, IDDM AND AUTOIMMUNE THYROID DISEASES?

RA

In rheumatoid inflammatory reactions cells entering the joint and periarticular tissues from the blood interact with cells and constituents of the connective tissue. Many of these processes occur at or near the vascular wall. Mϕ play an essential role in the expression of symptoms of rheumatic diseases[3,5], and Mϕ products are almost certainly involved in these processes. The Mϕ products include eicosanoids and proteolytic enzymes which degrade articular tissue components such as collagen, elastin and proteoglycans. In addition, peptides are produced which increase vascular permeability and attract other cells. This not only contributes to the acute symptoms of swelling, pain and stiffness but also to the destructive processes causing the chronic symptoms.

IL-1 and TNF, and possibly IL-6, have many biological effects which qualify them as potentially important mediators in rheumatic diseases (Tables 1 and 2). The most relevant actions of IL-1 — usually observed in *in vitro* experiments — could be their stimulatory effects on T- and B cells, Mϕ (e.g. MHC class II antigen expression and production of eicosanoids), chondrocytes (production of collagen type II), fibroblasts (production of collagen types I and II and eicosanoids), and osteoclasts (bone resorption). TNF-α share many of these effects with IL-1.

Table 2 Functions of IL-1 and TNF[a] which may be pathogenetically relevant in autoimmune diseases

Activation *in vitro* of:
– T- and B lymphocytes[b]
– NK cells[b]
– monocytes (thromboxane production)[b]
– neutrophils (adherence, degranulation, thromboxane and superoxide production)
– endothelial cells (production of IL-1, PGI_2, procoagulant-, leukocyte adhesion-, and class I MHC molecules)
– chondrocytes (production of collagenase, plasminogen, PGE_2, and decrease of cartilage proteoglycan)
– osteoclasts (via osteoblasts?)
– fibroblasts (growth, production of PGE_2 and collagenase)
– hepatocytes (acute-phase-protein in production, and decreased production of albumin)[b]
Cytostatic/cytotoxic in vitro to
– pancreatic islet β-cells (activates at low concentration)[b]
– thyrocytes (activates at low concentration)[b]
Induction *in vivo* of:
– fever (hypothalamus)
– slow-wave sleep[b]
– anorexia
– acute-phase-protein synthesis[b]
– reduction in blood Zn^{2+}, Fe^{2+} and albumin, and elevation in blood Cu^{2+}[b]
– reduction in hepatocyte p450 enzyme activity[b]
– wasting (muscle protein- and fat degradation)
– ACTH and cortisone release[b]
– leukocytosis (immature neutrophils)
– increased insulin release[b]

[a] Many, if not all, effects ascribed to TNF-α may also be produced by TNF-β.
[b] Ascribed to IL-1 only.

Abbreviations:
MHC: major histocompatibility complex; ACTH: adrenocorticotropic hormone; PG: prostaglandin.

Several potential cellular sources of IL-1 are present in the arthritic joint, including Mϕ, B lymphocytes and vascular endothelial cells (see Table 1). The demonstration of IL-1 in synovial fluids from rheumatoid and osteoarthritic joints further suggests that IL-1 in particular may play an important role in the pathogenesis of arthritis[5,26]. An unbalanced reaction between immunocompetent cells and accessory cells such as Mϕ, NK cells and PMN might continually induce the production of IL-1 and other proinflammatory substances, for example eicosanoids derived from both the cyclooxygenase and the lipoxygenase pathways. This would contribute to the chronic nature of diseases such as RA. It is interesting that IFN-γ and IFN-α both inhibit several of the above mentioned actions of IL-1. These effects of the interferons may well explain recent clinical findings of a benefical effect of IFN-γ (see[27]).

The arthritogenic activity of IL-1 is most clearly seen from *in vivo* animal experiments using recombinant IL-1 (rIL-1). Thus, human rIL-1β induces Mϕ and PMN accumulation at 24 h after injection[28]. This is associated with depletion of proteoglycan from the articular cartilage and an increase in the glycosaminoglycan content of the joint fluid. Similar signs of cartilage damage by IL-1 are seen in joints of rabbits previously depleted of PMN and Mϕ by systemic administration of nitrogen mustard, indicating that IL-1 itself is capable of stimulating resident cells of the joint, such as the chondrocytes, to cause proteoglycan depletion[29].

IDDM and autoimmune thyroid diseases

Recently, the predominant species of human IL-1, IL-1β, has been shown to be a potent suppressor of insulin production *in vitro*, possibly as a result of a direct and selective cytotoxic effect on pancreatic islet β-cells[30–32]. IL-1α also reduces insulin production, but it is 10 × less potent than IL-1β[33]. Furthermore, it should be noted that IL-1β is produced by activated Mϕ at much larger quantities than IL-1α[16,30]. The effect of IL-1β is augmented by TNF-α[33], further incriminating the Mϕ as at least one type of cell that might be responsible for the processes leading to IDDM.

Similar effects have been obtained when testing IL-1β on human thyroid cells removed during surgery of paraadenomatous glands[34,35]. The secretion of thyroglobulin and cAMP is markedly suppressed even by low concentrations of recombinant IL-1β (15 pg/ml = 10^{-12} M). Again, the effect is augmented by TNF and, in addition, by IFN-γ. The thyrocytes are not killed by IL-1β, but their ability to form follicles and accumulate glycogen in response to thyroid stimulating hormone is suppressed[35]. Interestingly, a stimulatory effect on thyroglobulin production is consistently observed at very low concentrations of IL-1β (1.5–150 fg/ml = 10^{-16}–10^{14} M)[34,35]. Similar results have been obtained with regard to the effect of IL-1β on insulin production by rat pancreatic β-cells[30,36].

Role of IL-6?

The possible role of IL-6 in the processes leading to RA and autoimmune endocrine diseases is as yet unclear. However, recent studies indicate that a number of functions ascribed to IL-1 may in fact be mediated by IL-6 (Table 1). One of the possibilities that has to be considered is that IL-1 induces the production of IL-6 in different cell types, including endothelial cells and fibroblasts (see Figure 2), bone cells, and even pancreatic islet and thyroid cells. IL-6 has already been shown to be produced by

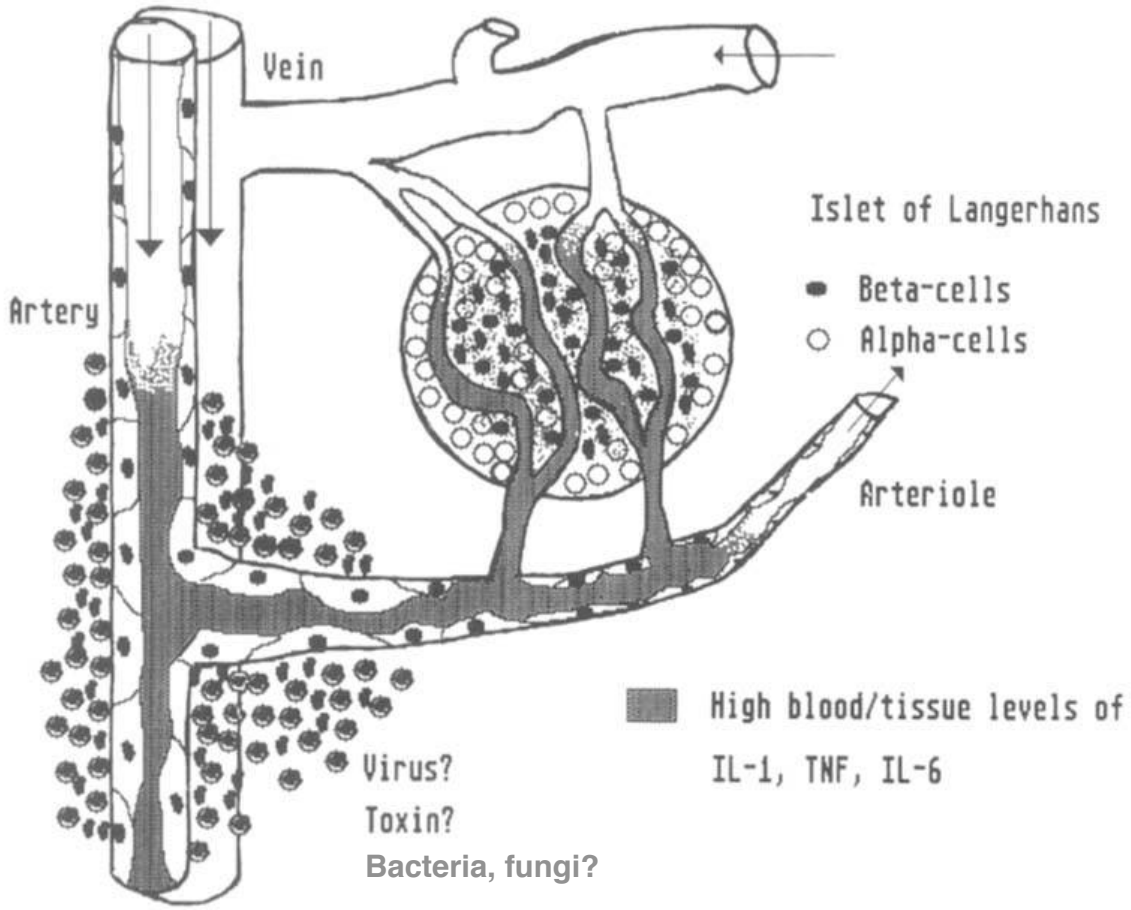

Figure 2 Model to explain how an inflammatory process, topographically unassociated with a pancreatic islet, may inititate β-cell damage — selectively, but in an immunologically unspecific manner (modified from[37]). Infiltrating mononuclear cells, primarily MØ and NK cells, as well as endothelial cells are potent producers of IL-1β. TNF-α and TNF-β augment this production and potentiate the damaging effect of IL-1β on β-cells. IL-6, produced by MNC and by endothelial cells and fibroblasts, may contribute to this effect. IFN-γ and IL-1β increase vascular permeability aiding the accumulation of cytokines within the islet. The inflammatory processes may not involve the entire pancreatic gland, and the amount of IL-1β and the TNFs may not always be sufficient to cause permanent damage to the β-cells. Furthermore, only a few β-cells may be damaged during each inflammatory incident, and a certain degree of regeneration of functional β-cells would be expected. The disease process may therefore proceed stepwise and take months or years to complete. IFN-γ, reinforced by TNF-α and IL-1β, may induce MHC class II molecules on the β-cells, and TNF-α also synergizes with IFN-γ to increase the expression of MHC class I molecules on these cells. Expression of certain MHC class II haplotypes may confer 'immunogenic' functions upon the β-cells hereby initiating an autoimmune attack on these cells.

endothelial cells and fibroblasts in response to IL-1 and TNF-α, and the production is greatly enhanced by IFN-γ[24].

The above findings and considerations indicate a central role of Mϕ and, perhaps, NK cells and their products IL-1, TNF-α and IL-6 in a number of autoimmune diseases. Even endothelial cells, fibroblasts and other cells in the connective tissue could be involved through their production of cytokines such as IL-1 and IL-6. Moreover, low concentrations of IL-1 may accumulate in endocrine tissues by diffusion from the blood during conditions of stress, and this cytokine may therefore

fulfil an important beneficial function by potentiating the secretion of insulin and thyroid and pituitary hormones under these circumstances.

MODELS TO EXPLAIN THE INVOLVEMENT OF CYTOKINES IN THE DEVELOPMENT OF RA AND IDDM[37]

Model 1

In the first model, the *initial* reaction specifically affects the target cells in the synovial and bone tissues or in the endocrine gland(s).

The damage to the cells is initiated for instance by virus or toxins that specifically affect the target cells. This causes the release of antigenic material(s) which may attract Mϕ and PMN. The phagocytic cells take up antigen and release chemotactic factors for T and B lymphocytes and, possibly, NK cells. The Mϕ, or perhaps the MHC class II-positive target cells themselves, then present the antigen(s) to specifically reactive T lymphocytes in a process where IL-1, TNFs, IFN-γ and IL-6 are released by the interacting cells (Figure 1). The effect of IL-1β, potentiated by TNF-α and IFN-γ, results in further damage to the cells. Eventually, autoantibodies and immune complexes may contribute to the destructive processes.

The specificity in this model is governed by the specifically reactive T lymphocytes and to a certain extent by the specificity of the initial infectious or toxic damage inflicted upon the target cells.

Model 2

Another model may also account for the *initial* processes leading to autoimmune diseases. In this model, the immunoinflammatory reactions that trigger the disease processes are not directly related to the target tissues.

The initial toxic, inflammatory or infectious reaction takes place in the vicinity of the target cells which eventually as 'innocent bystanders' become the victims of the immunological attack. A model for the initiation of β-cell damage in IDDM is depicted in Figure 2. A perivascular process and/or vasculitis in the afferent arteriole trigger the production of TNF and, possibly, IL-1β, IFN-γ and IL-6. The ability of TNF and IL-6 to induce IL-1β in endothelial cells contribute to the accumulation of high local concentrations of IL-1β in the central region of the islets dominated by β-cells. IL-1β primarily or exclusively damages the β-cells, and this eventually triggers an autoimmune reaction specifically aimed at the β-cells. Thus, the initial β-cell unspecific reaction eventually becomes immunologically specific, and autoreactive T cells and autoantibodies may, as in the first model, assist in destroying the β-cells.

This model predicts that there may be several 'etiological factors' involved in the course of events leading to IDDM, even in the same individual. The model also explains the finding of MHC class II proteins on vascular endothelium in prediabetic BB rats preceeding infiltration of the islets by mononuclear cells[15,37], and in recent-onset IDDM, even in capillaries in or around islets without mononuclear cell invasion[10].

The magnitude of the T cell-mediated attack in both models would be expected to depend upon the MHC class II types of the individual, and this therefore might account for the MHC association of many autoimmune disorders. However, it has recently been shown that the TNF-α genes, as well as the TNF-β genes, are located

on chromosome 6 in the MHC class III region between the HLA-DR and HLA-B regions[39]. If therefore the TNF genes are polymorphic, the disease-associated HLA haplotypes may be linked to allele(s) for the TNF's coding for prolonged and/or pronounced secretion of TNF. Transcription of the TNF genes might also be governed by HLA types in such a way that specific HLA alleles promote and other alleles suppress the expression of the TNF genes.

Recent findings do suggest that normal human beings vary considerably with regard to the ability of their blood Mϕ to secrete *in vitro* TNF-α in response to *E. coli* endotoxin with or without IFN-γ. Interestingly, HLA-DR2 positive individuals dominate the low-responder group[40].

CONCLUSION

There is strong evidence for a role of T lymphocytes, Mϕ, NK cells and, possibly, B lymphocytes in the pathogenesis of RA, IDDM and other autoimmune endocrine diseases. The peptide hormones (cytokines) produced by these cells, particularly IL-1β, TNF-α and IFN-γ, are potent modulators of bone and synovial tissue cells as well as pancreatic islet β-cells and thyrocytes. The genes for TNF-α, and TNF-β, are topographically associated with the MHC genes, in man the HLA-DR and -B genes, and certain HLA alleles seem to govern the elaboration in *vitro* of TNF-α. IL-6 has many properties in common with IL-1 and TNF, and it may be involved in certain autoimmune disease processes as well.

It seems highly relevant to investigate the possible role of these cells and their mediators in other known or subjected autoimmune diseases such as gout, osteoarthritis, idiopatic Addison's disease, pernicious anemia, coeliac disease, active chronic hepatitis and certain fibrotic skin-, liver- and lung diseases. One or several cytokines may also affect the function of oligodendrocytes and hence play a role in the pathogenesis of multiple sclerosis.

Treatment to prevent the production and/or function of IL-1, TNF, IFN-γ and IL-6 may prevent the development, or ameliorate the symptoms, of many autoimmune diseases.

Acknowledgements

This work was supported by the Willumsen Foundation and the Danish Medical Research Council.

References

1. Bendtzen K. Lymphokines in inflammation. Inflammation Basic Mechanisms Tissue Injuring Principles and Clinical Models (Venge P & Lindbom A eds) 1985; Almqvist & Wiksell International. Stockholm: 187–217
2. Wilkin TJ, Stutchfield P, Smith CS, Heaf DP. Autoimmunity, diabetes, and cystic fibrosis. *Lancet* 1987; **ii**: 157
3. Padula SJ, Clark RB, Korn JH. Cell-mediated immunity in rheumatic disease. *Human Pathol* 1986; **17**: 254–263
4. Bunning RAD, Richardson HJ, Crawford A, Skjødt H, Hughes D, Evans DB, Gowen M, Dobson PRM, Brown BL, Russell RGG. The effect of interleukin-1 on connective tissue metabolism and its relevance to arthritis. *Agents Actions* 1986; **18**: 131–153
5. Pujol JP, Loyaū G. Interleukin-1 and osteoarthritis. *Life Sci* 1987; **41**: 1187–1198

6. Sibley RK, Sutherland DER, Goetz F, Michael AF. Recurrent diabetes mellitus in the pancreas iso- and allograft. A light and electron microscopic and immunohistochemical analysis of four cases. *Lab Invest* 1985; **53**: 132–144
7. Rossini AA, Mordes JP, Like AA. Immunology of insulin-dependent diabetes mellitus. *Ann Rev Immunol* 1985; **3**: 289–320
8. Schindler R, ed. Ciclosporin in autoimmune diseases. Springer-Verlag 1985; Berlin.
9. Svejgaard A, Platz P, Ryder LP. HLA and disease susceptibility: Clinical implications. *Clin Immunol Allergol* 1984; **4**: 567–580
10 Bottazzo GF, Dean BM, McNally JM, MacKay EH, Swift GF, Gamble DR. In situ characterization of autoimmune phenomena and expression of HLA molecules in the pancreas in diabetic insulitis. *N Engl J Med* 1985; **313**: 353–360
11. Hanafusa T, Chiovato L, Doniach D, Pujol-Borrell R, Russell RCG, Bottazzo GF. Aberrant expression of HLA-DR antigen on thyrocytes in Graves' disease: relevance for autoimmunity. *Lancet* 1983; **2**: 1111–1115
12. Pujol-Borrell R, Todd I, Doshi M, Bottazzo GF, Sutton R, Gray D, Adolf GR, Feldmann M. HLA class II induction in human islet cells by interferon-γ plus tumour necrosis factor or lymphotoxin. *Nature* 1987; **326**: 304–306
13. Trinchieri G, Perussia B. Immune interferon: a pleiotrophic lymphokine with multiple effects. *Immunol* Today 1985; **6** 131–136
14. Iwatani Y, Gerstein HC, Iitaka M, Row VV, Volpe R. Thyrocyte HLA-DR expression and interferon-production in autoimmune thyroid disease. *J Clin Endocrinol Metab* 1986; **63**: 695–708
15. Baird JD, Bone AJ, Walker R, Cooke A. MHC antigen expression in the pancreas. *Nature* 1987; **329**: 493–494
16. Bendtzen K. Interleukin 1 and tumor necrosis factor: Prototypes of macrophage hormones. Highlights on Endocrinology (Christiansen C & Riis BJ eds) 1987; Proc. 1st. Eur. Congr. Endocrinol. Copenhagen: 291–300
17. Bendtzen K. Non-immunologlobulin peptide mediators of immune responses. Highlights on Endocrinology (Christiansen C & Riis BJ eds) 1987; Proc. 1st. Eur. Congr. Endocrinol. Copenhagen: 301–308
18. Oschilewski U, Kiesel U, Kolb H. Administration of silica prevents diabetes in BB-rats. *Diabetes* 1985; **34**: 197–199
19. Beutler B, Cerami A. Cachectin and tumour necrosis factor as two sides of the same biological coin. *Nature* 1986; **320**: 584–588
20. Gray PW, Goeddel DV. Structure of the human immune interferon gene. *Nature* 1982; **298**: 859–863
21. Zilberstein A, Ruggieri R, Korn JH, Revel M. Structure and expression of cDNA and genes for human interferon-β2, a distinct species inducible by growth-stimulatory cytokines. *EMBO J* 1986; **5**: 2529–2537
22. Hirano, T, Yasukawa, K, Harada H, Taga T, Watanabe Y, Matsuda T, Kashiwamura S, Nakajima K, Koyama K, Iwamatsu A, Tsunasawa S, Sakiyama F, Matsui H, Takahara Y, Taniguchi T, Kishimoto T. Complementary DNA for a novel human interleukin (BSF-2) that induces B lymphocytes to produce immunoglobulin. *Nature* 1986; **324**: 73–76
23. Aarden L, Lansdorp P, De Groot E. A growth factor for B cell hybridomas produced by human monocytes. *Lymphokines* 1985; **10**: 175–185
24. Van Damme J,Opdenakker G, Simpson RJ, Rubira MR, Cayphas S, Vink A, Billiau A, Van Snick J. Identification of the human 26-kD protein, interferon β2 (IFN-β2), as a B cell hybridoma/plasmacytoma growth factor induced by interleukin 1 and tumor necrosis factor. *J Exp Med* 1987; **165**: 914–919
25. Gauldie J. Interferon β2 is identical to HSF and regulates the full acute phase protein response in liver cells. Symposium IV; International Workshop on Monokines and Other Non-Lymphocytic Cytokines. Hilton Head Island. SC. USA. Dec 6–10, 1987.
26. Bendtzen K, Petersen J, Halkjaer-Kristensen J, Ingemann-Hansen T. Interleukin-1-like activities in synovial fluids of patients with rheumatoid arthritis and traumatic synovitis. *Rheumatol Int* 1985; **5**: 79–82
27. Browning J. Interferons and rheumatoid arthritis: insight into interferon biology? *Immunol Today* 1987; **8**: 372–374
28. Pettipher ER, Higgs GA, Henderson B. Interleukin 1 induces leukocyte infiltration and cartilage proteoglycan degradation in the synovial joint. *Proc Natl Acad Sci USA* 1986; **83**: 8749–8753
29. Pettipher ER, Henderson B, Higgs GA, Moncada S. Arthritogenic activity of interleukin 1 in leucopaenic rabbits. Congress of the Int Assoc Biol Stand — Cytokines 1987. London, UK.
30. Bendtzen K, Mandrup-Poulsen T, Nerup J, Nielsen JH, Dinarello CA, Svenson M. Human pI 7 interleukin 1 is cytotoxic for pancreatic islets of Langerhans. *Science* 1986; **232**: 1545–1547

31. Mandrup-Poulsen T, Egeberg J, Nerup J, Bendtzen K, Nielsen JH, Dinarello CA. Ultrastructural studies of time-course and cellular specificity of interleukin-1 mediated islet cytotoxicity. *Acta Pathol Microbiol Immunol Scand Sect C* 1987; **95**: 55–63
32. Eizirik DL, Strandell E, Bendtzen K, Sandler S. Functional characteristics of rat pancreatic islets maintained in culture following exposure to human interleukin 1. Diabetes 1988; in press.
33. Mandrup-Poulsen T, Bendtzen K, Dinarello CA, Nerup J. Human tumor necrosis factor potentiates human interleukin-1 mediated rat pancreatic β-cell cytotoxicity. *J. Immunol* 1987; **139**: 4077–4082
34. Rasmussen ÅK, Bech K, Feldt-Rasmussen U, Poulsen S, Siersbæk-Nielsen K, Friis T, Bendtzen K. The influence of interleukin-1 on the function of in vitro cultured human thyroid cells in monolayers. *Acta Endocrinol* 1987; Suppl. **281**: 93–95
35. Bendtzen K, Rasmussen ÅK, Bech K, Feldt-Rasmussen U, Egebjerg J. Cytokines in autoimmunity. *Immunol Today* 1987; **8**: 203–204
36. Spinas GA, Mandrup-Poulsen T, Mølvig, J, Bæk L, Bendtzen K, Dinarello CA, Nerup J. Low concentrations of interleukin-1 stimulate and high concentrations inhibit insulin release from isolated rat islets of Langerhans. *Acta Endocrinol* 1986; **113**: 551–558
37. Bendtzen K, Rasmussen ÅK, Bech K, Feldt-Rasmussen U, Buschard K. Pathogenic role of interleukin 1 and tumor necrosis factor in autoimmune endocrine diseases. *Clin Immunol Newslett* 1988; **9**: 72–74.
38. Dean BM, Walker R, Bone AJ, Baird JD, Cooke A. Pre-diabetes in the spontaneously diabetic BB/E rat: lymphocyte subpopulations in the pancreatic infiltrate and expression of rat MHC class II molecules in endocrine cells. *Diabetologia* 1985; **28**: 464–466
39. Nedwin, GE, Naylor S, Sakaguchi AY, Smith D, Jarrett-Nedwin J, Pennica D, Goeddel DV, Gray PW. Human lymphotoxin and tumor necrosis factor genes: structure, homology and chromosomal localisation. *Nucl Acids Res* 1985; **13**: 6361–6373
40. Bendtzen K, Morling N, Fomsgaard A, Svejgaard A, Svenson M. Effect of HLA-D and -B region genes and interferon-γ on the *in vitro* production of tumor necrosis factor and interleukin-1. (in press)