In type 1 diabetes, an immune-mediated process leads to the destruction of pancreatic β-cells. In the last decade, considerable progress has been made in understanding the cellular and biochemical pathogenic processes of the disease. However, more needs to be learned about the immune mechanisms leading to the development of autoreactive immune cells and the molecular mechanisms of β-cell death. The study of apoptosis of autoreactive lymphocytes as well as apoptosis of β-cells may give answers to many still unsolved questions. This review focuses on the possible role of apoptosis both in the regulation of immune mechanisms involved in the pathogenesis of type 1 diabetes and as a way for β-cells to die. The advancement in the knowledge of the possible role of apoptosis and its regulation in the pathogenesis of type 1 diabetes may provide new therapeutic tools for the prevention of the disease. Diabetes 47:1537-1543, 1998

There are two conceptually different ways through which eukaryotic cells can die: one is death by necrosis caused by ischemic, chemical, physical, or thermal cell injury; the other is by apoptosis, a type of programmed cell death, which is required for the normal maintenance of development and homeostasis in a cell system, an organ, or an individual as a whole (1). The machinery required for apoptosis is present in all mammalian cells (2). The interest in apoptosis has accelerated tremendously in the past few years (3). Recent evidence indicates that alterations in cell survival contribute to the pathogenesis of a variety of diseases such as cancer, neurodegenerative disorders, viral infections, and autoimmune diseases, including IDDM (4). A direct linkage between genes involved in the control of apoptosis and human autoimmune diseases is yet to be demonstrated. However, this is a field in which investigations are just beginning. Understanding the molecular mechanisms and the genetic control of apoptosis and how the apoptotic process can be modulated have obvious implications for the understanding of the pathogenesis of these diseases and the future design of new therapeutic strategies.

APOPTOSIS: AN OVERVIEW

Apoptosis plays a central role in the regulation of development and homeostasis in metazoan animals (2). The term “apoptosis” (Greek: leaf-fall) is often used synonymously with programmed cell death, the latter being a more functional definition. Apoptosis refers to the morphological features of programmed cell death, which is characterized by shrinkage, nuclear condensation, membrane blebbing, and membrane changes that eventually lead to phagocytosis of the affected cell. As opposed to what is seen in necrosis, apoptotic cells do not swell and burst, but undergo phagocytosis before the intracellular content leaks, thereby avoiding to evoke an immune response (5) (Table 1). An unresolved question is how the apoptotic program is regulated so that only selected cells die. Apoptosis is controlled by many different signals that converge toward a common apoptotic program (2). Triggering of apoptosis may take place in different stages of the apoptotic cascade, depending on the initiating stimulus (6). The pathways that lead to activation of apoptosis vary among different cells, but the final pathway leading to cell death seems to be common. Therefore, when studying apoptosis, it is important to discern between processes that are cell-specific and those that are death-specific (7). The signals inducing apoptosis are varied and even the same signals can induce differentiation and proliferation, depending on conditions and cell type (3). The following signaling pathways have been implied in apoptosis: the Fas system (also known as APO-1 or CD95), protein tyrosine kinases, serine/threonine kinases, the Ras signaling pathway, protein kinase C, calcium signaling pathways, ceramide, cAMP, and free radicals (Fig. 1).

There are two gene families that are particularly important in the control of apoptosis: the genes encoding the interleukin-1β-converting enzyme (ICE) family of cysteine proteases (now known as caspases), and those related to the protooncogene bel-2 (3). Proteolytic activity is involved in many apoptotic systems, the ICE family being of special importance, since it seems to be central in Fas-mediated and tumor necrosis factor (TNF)-induced apoptosis. Proteolysis is probably a common event in the apoptotic process, with different proteases involved and several proteins having been shown to be the subject of proteolytic activity (Table 2). The bel-2 family of proteins are important modulators of apoptosis (Table 3). New evidence suggests that Bel-2 protein has two
TABLE 1
Main differential features of apoptosis and necrosis

<table>
<thead>
<tr>
<th>Apoptosis</th>
<th>Necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous (programmed cell death)</td>
<td>Injury-induced (accidental cell death)</td>
</tr>
<tr>
<td>Chromatin becomes fragmented and condensed along the nuclear envelope. Finally, formation of one large or several (oligonucleosomal) fragments.</td>
<td>Only slight morphological changes in the nucleus.</td>
</tr>
<tr>
<td>Loss of cell junctions and cell detachment from neighboring cells. Cell surface ruffling and blebbing (zeiosis). Cell membrane keeps the capacity to maintain osmotic gradients.</td>
<td>Major damage in cell membrane with loss of its control of selective permeability.</td>
</tr>
<tr>
<td>Organelles and cell shrink</td>
<td>Early mitochondrial changes in shape and function, with swelling of cytoplasm and organelles. Organelle dissolution and rupture.</td>
</tr>
<tr>
<td>Budding off of membrane-bound apoptotic bodies, containing the organelles and nuclear fragments. Stimulation of phagocytosis by nearby cells (professional or nonprofessional phagocytes). No spilling of intracellular contents. Therefore, no inflammatory response is induced.</td>
<td>Cell swelling and rupture, with leakage of cell contents into surrounding tissue space. This induces an inflammatory response and the initiation of tissue repair process.</td>
</tr>
</tbody>
</table>

different functions: 1) as an ion channel protein and 2) as an adaptor/docking protein through its binding to several other proteins. However, the precise way in which these proteins modulate apoptosis is unclear and conflicting theories have been proposed (3). Further, the gene product of bcl-2 does not prevent apoptosis under all circumstances (e.g., does not protect target cells from apoptosis induced by cytotoxic T-cells [8]). Finally, genes involved in cell differentiation and proliferation are also important in modulating the apoptotic process (e.g., the protooncogene c-myc, the tumor suppressor p53, and the apoptosis suppressor gene A20). Both c-myc and p53 are implicated in the induction of apoptosis under certain conditions, whereas A20 is a cytokine-induced primary response gene involved in the inhibition of the apoptotic process (3).

**APOPTOSIS IN THE REGULATION OF IMMUNE MECHANISMS INVOLVED IN THE PATHOGENESIS OF IDDM**

**Apoptosis and the immune repertoire.** Apoptosis plays an important role in determining the quantitative and qualitative composition of the immune system. In IDDM, tolerance to the pancreatic b-cells is lost and immunological effector mechanisms are then directed against this cell type (9). For the purpose of this study, we will focus mainly on the role of programmed cell death in the selection of T- but not of B-cells. During the process of precursor T-cell receptor gene recombination, it is estimated that only -10% of T-cells will succeed in expressing both a and b chains of the T-cell receptor (5). The others die by apoptosis. Once a complete T-cell receptor is expressed on the cell surface, there are three alternatives awaiting the T-cell in the thymus: negative selection, positive selection, or no selection. If T-cell receptors bind with high affinity to self-antigens presented by the thymic antigen-presenting cells, the cell is eliminated by apoptosis to avoid autoimmunity. Failure or resistance of these cells to undergo

**FIG. 1. Schematic representation of the apoptotic cascade. The cell is able to integrate the information received from intracellular as well as extracellular milieu. Different death signals may activate one or more signal transduction pathways, which probably may converge in one or few final death pathways. Components of the different signaling pathways may interact with each other producing regulatory steps in which inhibition or potentiation of the process may take place. Further, triggering of apoptosis may take place at different points of the cascade, depending on the initiating stimulus.**

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the apoptotic process results in the delivery of autoreactive
T-cells to the periphery. Cells with no affinity for histocompat-
ibility antigens are also useless to the immune system and
die by apoptosis, in a process that is probably triggered
by endogenous glucocorticoids (10). Those T-cells expressing
T-cell receptors that recognize a foreign peptide, cross-
reactive with a self-peptide, will undergo further maturation
and will finally express either CD4 or CD8 (positive selection).

One of the central signaling pathways of apoptosis in the
immune system is the Fas system. Fas is a 45-kDa surface
receptor belonging to the TNF/nerve growth factor receptor
family, which on binding by Fas ligand (FasL), transduces the
signal for programmed cell death (10,11). Fas has been sug-
gested to play an essential role in tissue development and
homeostasis (12). In the immune system the Fas and FasL are
essentially involved in downregulation of immune reactions
and in T-cell-mediated cytotoxicity (13). The FasL is almost
exclusively expressed by activated CD4+ and CD8+ T-cells
(13). Although both T-helper (Th)1 and Th2 cells express the
Fas ligand, Th1 cells are capable of lysing other target cells
more readily than Th2 by a Fas-mediated mechanism
(14,15). Thus, mature T-cells in the periphery may undergo
an additional selection process known as peripheral clonal
deletion, in which those T-cells interacting with self-antigens
expressed in the periphery are eliminated (16). Further,
to ensure that the organism can downregulate activated lymph-
cytes, there must be a process of elimination of lympho-
cytes after they have been activated by antigen (17). Where-
as the negative and positive selections, which take
place in the thymus, do not seem to involve a Fas-mediated
mechanism, the Fas system is implicated in both the clonal
deletion of autoreactive T-cells in peripheral lymphoid
organs and the elimination of activated T-cells (13). Therefore,
the Fas system is central in the regulation of peripheral
immune responses.

Fas is constitutively expressed by mature T-cells, but
expression is enhanced upon activation by antigen, thus ren-
dering T-cells more sensitive to FasL-mediated apoptosis
(18). If the Fas-FasL system is defective, activated lympho-
cytes may accumulate (19). Thus, if these cells are not effi-
ciently eliminated, the occurrence of autoimmune disease is
enhanced as has been shown in murine experimental models:
the lpr and gld mutations in mice lead to a loss of function of
Fas and FasL, respectively, which cause activated lympho-
cytes to accumulate leading to the appearance of autoim-
mune diseases (13,20).

Apoptosis and autoimmunity. Recent data suggest that
defective regulation of apoptosis in lymphoid cells may be a
factor that contributes to the pathogenetic mechanism of
autoimmune diseases (21). In the murine nonobese diabetic
(NOD) model of IDDM, the development of autoimmunity has
also been suggested to be influenced by mechanisms con-
trolling programmed cell death of lymphocytes (22,23). Acti-
ivated T-cells from NOD mice showed a markedly increased
resistance to induction of apoptosis after deprivation of
interleukin (IL)-2 when compared to other strains (24). The
gene encoding resistance to apoptosis was mapped to the
middle region of chromosome 1 in which the antiapoptotic
protooncogene bcl-2 is located. Through F2 intercross stud-
ies, the Idd6 susceptibility locus in the distal region of chro-
mosome 6 of NOD mice was strongly associated with
increased resistance to apoptosis (25). Immature T-cells
from NOD mice possessed an increased resistance to in vivo
dexamethasone-induced apoptosis (23), and lymphocytes
from NOD mice were more resistant to cyclophosphamide-
induced apoptosis than other mouse strains (26), which
again imply that defective apoptotic pathways may be
involved in the disease pathogenesis. The resistance of T-cells
to apoptosis in NOD mice has recently been found to be
associated to upregulation of the antiapoptotic Bcl-x protein
in T-cells (27). These findings in the NOD mouse may induce
a new search for diabetes-susceptibility genes in human
IDDM. Fas expression on NOD mouse T-cell subsets has not
been reported, to the best of our knowledge.

Recently, it was shown that B- and T-cells from subjects
with IDDM and those at risk for the disease are highly defec-
tive in the surface expression of Fas (28). This led the
authors to hypothesize that loss of tolerance in IDDM may be
partly explained by a defective expression of Fas.

A ROLE FOR APOPTOSIS IN THE DESTRUCTION
OF B-CELLS
Two schools of thought. Whether β-cell death in IDDM is
deferred to apoptosis or necrosis or a combination of both has not
been clarified. There are two main schools of thought regard-
The mechanisms of β-cell destruction in IDDM. According to one model, β-cells are destroyed by cytotoxic T-cells using perforin or granzymes as effector molecules. Perforin causes lysis of the target cell, whereas granzymes A and B mainly cause apoptosis (29). Another model (30, 31) (Fig. 2), hypothesizes that β-cell antigen-specific T-helper cells, activated to transcribe cytokine genes, induce the build-up of a specific and nonspecific mononuclear cell infiltrate and activates endothelial cells, which express adhesion molecules and liberate inflammatory mediators. Recruited macrophages are stimulated by interferon (IFN)-γ to produce IL-1β and TNF-α, which in synergy with IFN-γ lead to β-cell toxicity via β-cell–specific induction of iNOS and apoptosis-activating pathways. Further, the model implies that IL-1 leads to β-cell Fas expression, rendering the β-cells susceptible to lysis by Th1 and cytotoxic T-cells expressing Fas L.

**Nitric oxide and β-cell apoptosis: can NO be the answer?** Several pathways have been suggested to be responsible for nitric oxide (NO)-mediated β-cell death (Fig. 2). Among these, NO inactivates Krebs cycle aconitase by nitrosylation of Fe-S groups thereby preventing glucose oxidation and ATP generation, leading to cell death by necrosis (32). Further, NO has been shown to damage cellular DNA through the induction of DNA strand breaks (33, 34). DNA single-strand breakage and necrotic cell death were observed after exposure of rat islets to sodium nitroprusside or activated macrophages (34). DNA strand breaks may cause β-cell necrosis by itself or by the activation of DNA repair mechanisms (including the induction of the enzyme poly(ADP ribose) polymerase), which can cause β-cell death through depletion of cellular nicotinamide adenine dinucleotide (35). However, evidence is accumulating suggesting a third pathway by which the β-cell may undergo apoptosis through the exposure to certain cytokines (30). It is known that cytokine-mediated NO synthesis may cause apoptosis in macrophages and fibroblasts (36). Pancreatic β-cells have been shown to be susceptible to apoptotic death (i.e., apoptosis is involved in the normal reduction in the β-cell mass post partum [37] or in dynamic changes in islets in the posttransplantation period [38]). Apoptosis in β-cells can be induced through several pathways, such as protein kinase C inhibition (39), guanine triphosphate binding protein activation (40), and streptozotocin (41, 42). Also, IL-1β alone (43, 44) or in combination with TNF-α/IFN-γ (45) induces apoptosis in transformed or normal islet β-cells. Further, DNA fragmentation, which is characteristic of apoptotic cell death, has been observed as an early event in IL-1β–induced islet β-cell destruction (46). The combination of IL-1β, TNF-α, and IFN-γ induces oligonucleosomal DNA fragmentation typical of apoptosis in rat islets (46). A recent study has shown that IL-1β induces an increase in the ceramide content of RINm5F cells, and ceramide has been shown to be implicated in the induction of apoptosis (47). After being released by the hydrolysis of membrane sphingolipids (mainly sphingomyelin), ceramide acts as a signaling molecule by activating stress-activated protein kinases and phospholipase A2 leading to formation of prostaglandin E2. Moreover, the involvement of the ceramide-dependent signaling system in the regulation of programmed cell death by cytokines, such as TNF-α has been demonstrated (48). Additionally, the other transcriptional factors c-jun and c-fos, which are also implied in the signaling cascade leading to apoptosis, are induced by IL-1 in rat islets of Langerhans and RINm5F cells (49). In mouse pancreatic β-cell lines (βTC1 and NIT-1), the combination of three cytokines (IL-1β, TNF-α, and IFN-γ) was able to induce apoptotic cell death (50). Interestingly, this study also showed that overexpression of bel-2 in βTC1 cells partially protected them from cytokine-induced death. More recently, it has been shown that a combination of cytokines (50 U/ml IL-1β + 1,000 U/ml TNF-α + 1,000 U/ml IFN-γ) is able to induce DNA strand breaks as well as an increase in apoptotic cells in human islets, with no signs of additional necrosis (51). These results suggest that apoptosis may be responsible for cytokine-induced cell death.

NO production seems to be an important signal for β-cell apoptosis. Thus, it has been shown that RINm5F cells undergo DNA fragmentation, nuclear condensation, and apoptotic formation in response to IL-1β (52). These events were preceded by NO production, and inhibition of iNOS prevented apoptotic cell death. The same group described that both chemical NO donors and IL-1β–induced endogenously delivered NO caused the expression of the apoptosis-linked tumor suppressor gene p53 in this cell line while it was absent in untreated cells (53). These findings indicate that the protein p53, which is an apoptosis inducer, as mentioned above, may be involved in the process of NO-induced apoptosis. Further studies demonstrated that both exogenous NO (released by streptozotocin) and IL-1β–induced NO was associated with typical apoptotic changes in isolated rat islets and in the tumor-derived β-cell line HIT (54). Also, the use of NO donor S-nitrosoglutathione produced apoptosis in HIT-T15 cells, an effect that was reproduced by cGMP analogs, suggesting that apoptotic cell death induced by NO is secondary to rise in cGMP levels, thus involving activation of cGMP-dependent protein kinase (55). A significant increase in the percentage of apoptotic cells in rat islets was seen after in vitro exposure to IL-1β (44). Further, these authors were able to correlate the degree of NO production with the ability of IL-1β to induce programmed cell death and to reduce apoptosis by inhibiting NO production.
However, some observations suggest that NO production is neither necessary nor sufficient for the mediation of cytokine-induced β-cell destruction. Thus, a previous study failed to observe DNA fragmentation, mitochondrial damage, or cell destruction in RIN cells in spite of IL-1β-induced NO production (56). Neither the reduction of DNA and insulin content in human islet single cell cultures (57), nor the cytokine-induced reduction of insulin content and secretion of human islets (58) could be prevented by the inhibition of cytokine-inducible NO synthase. Further, nicotinamide, which is effective in preventing cytokine-induced β-cell destruction, did not completely block NO production in rodent islet cultures (59,60). Moreover, isolated human islets are more resistant to the suppressive effects of IL-1β and NO than isolated rodent islets (61). Cytokine-induced apoptosis in human islets is probably independent of NO generation (51). In vivo, inhibition of iNOS causes only a delay but not protection against diabetes development (62–64). Therefore, additional mediators of cytokine-induced β-cell death may be necessary, such as the facilitation of other apoptosis-inducing pathways, which include the mitogen-activated protein (MAP) kinase cascade and the Fas/FasL system (65) (Fig. 2).

**Apoptosis and Fas expression by β-cells.** Recently, IL-1β–induced Fas expression in thyrocytes was found to be the mechanism responsible for thyrocyte apoptosis in Hashimoto’s thyroiditis (66). Interestingly, in purified human β-cells, only IL-1β (50–100 U/ml) of several different cytokines was able to induce the expression of Fas after 24 h (67). Further, induction of Fas in β-cells by infiltrating T-cells produces β-cell apoptosis, which is a predominant mechanism of this T-cell–mediated destruction of insulin-producing cells (11). Therefore, data provided by these studies point to Fas-mediated apoptosis as a central pathway leading to β-cell destruction in IDDM.

**In vivo detection of apoptosis in IDDM pathogenesis.** Evidence for a role of apoptosis in β-cell destruction in animal models of IDDM is accumulating. However, the removal of apoptotic cells is so efficient that it may prove extremely difficult to demonstrate in vivo. This efficient engulfment of apoptotic cells is usually carried out by the monocyte-phagocyte system, although normal epithelial cells, vascular endothelium, or tumor cells can also do so (68). In addition, the progression of the apoptotic process is so fast that it makes it difficult to observe, and more importantly to quantify (69). For example, in the young mouse thymus, in which more than one third of the cells die each day, it is almost impossible to find an apoptotic cell in an average tissue section (5). Furthermore, the rapid clearance of dead cells may be an additional difficulty in the study of apoptosis in animal IDDM models such as the NOD mouse (70).

Despite these methodological difficulties, a recent study in the well-known multiple low-dose streptozotocin model of IDDM was able to demonstrate that apoptosis of mouse β-cells was identified as the mode of death of these cells (71). These authors suggested that in other models of IDDM, or even in human IDDM, apoptosis may require careful and extensive histological studies because the rate at which β-cell destruction takes place is much slower than that in the low-dose streptozotocin model.

In BDC2.5/NOD.scid mice, an accelerated model of diabetes, which produce CD4+ T-cells bearing a transgenic T-cell receptor but are devoid of CD8+ T-cells, histological and immunochemical analysis of pancreases showed clear evidence of apoptosis of pancreatic β-cells, without any evidence of β-cell necrosis in infiltrated islets (70). Further, a strong correlation between the degree of insulitis and β-cell apoptosis was demonstrated. From the kinetics of apoptosis calculated by these authors, it is not surprising that apoptosis was not observed before in nontransgenic NOD mice. Interestingly, a thorough histological and immunochemical study was able to confirm that apoptosis is the main mode of death of pancreatic β-cells in the NOD mouse (72). An outstanding finding of this study is that the initiation of the apoptotic process precedes the light microscopic lymphocytic infiltration of the islets, thus suggesting that initial β-cell death is mediated by resident macrophages and their products, mainly cytokines, in accordance with the second model described above.

**Autoantibodies and β-cell apoptosis?** Although the autoimmune β-cell destruction in IDDM is not antibody-mediated, apoptosis has been shown to occur in normal pancreatic β-cells and RINm5F cells after exposure to serum from patients with IDDM, an effect that was found to be IgM-mediated (73). As this effect of diabetic sera was prevented by addition of a blocker of calcium channels, the authors hypothesize that an IgM-mediated increase in calcium influx may be part of the autoimmune damage of β-cells. However, the interpretation of this finding and the contribution to the pathogenesis of IDDM remains to be clarified.

**FUTURE STUDIES**

From the data reviewed above it is clear that the process of apoptosis as a central mechanism of β-cell death in IDDM deserves further study. The area of apoptosis research is one of the most fertile current fields in cell biology, and in-depth insight into modulation of the molecular mechanisms of apoptosis has been reached. Preventive intervention may be aimed at the level of immune cells and/or the level of the target cell. Methods that induce selective apoptosis of the immune cell as a target may be considered. Future strategies may explore methods to induce selective apoptosis of autoreactive cells that mediate the destruction of β-cells. As for other autoimmune diseases (4), it has been shown that repetitive treatment with antigen, such as insulin in IDDM, can result in selective death of reactive lymphocytes in vivo. However, the exact mechanism by which such treatment induces apoptosis is unclear, though priming of cell death through a Fas-mediated mechanism has been suggested (74).

The advancement in the knowledge of apoptosis of β-cells is likely to progress quickly in the near future. If apoptosis is the main common mode by which β-cells die in response to immune attack by cytokines and/or T-cells in IDDM, it may be possible to develop novel strategies to prevent this mode of β-cell death, thereby preventing or delaying the onset of the disease.

It has been clearly established that protection from programmed cell death may be exerted at four different levels: interception of an apoptosis-inducing stimulus; functional antagonism of an otherwise apoptosis-inducing trigger; interference with signal transduction cascades, or blockade of catabolic enzymes participating in cellular suicide (75). These levels of intervention may apply in the design of strategies of prevention of β-cell death. Moreover, the existence of processes that may involve apoptosis at different levels of the pathogenic process of IDDM offers possibilities in the pre-
apoptosis of the disease. Treatments that increase the apoptotic threshold of pancreatic β-cells may be beneficial. For example, some methods can include the blockade of the binding of death ligands (e.g., TNF and FasL). Strategies may be directed to increase resistance to apoptotic stimuli by enhancing the expression of Bcl-2. Insulin may have potential therapeutic applications in the prevention of IDDM (currently under clinical evaluation) due to its potential immune modulating effect and its capacity to induce β-cell rest. It should be investigated if insulin, because of its growth factor–like effect, has antiapoptotic effects on β-cells, further contributing to its efficacy in preventing the disease (76).

Cell specificity of therapeutic approaches is critical since IDDM, as most autoimmune diseases, is not characterized by a generalized increase in the susceptibility or resistance to apoptosis. The potential harm of using a therapy that enhances the survival of cells at the expense of increasing the risk of other autoimmune disorders or enhancing tumor progression through the prevention of apoptotic cell death should be pointed out (4). However, even central elements of the apoptotic process may be pharmacologically manipulated in a cell-specific fashion. The manipulation of bcl-2, p53, or c-myc may change the susceptibility of cells to programmed cell death (75). Tissues can significantly vary the expression of certain members of the bcl-2 or ICE families. Moreover, specific inhibitors of individual members of the ICE family exist. Therefore, systemic modulation of bcl-2 or ICE may not be as toxic as might have been expected. There is a large array of factors that may be potentially useful in the induction or inhibition of programmed cell death in lymphocytes and other target cells (75). Although in its infancy, a potential new therapeutic field is open for the study of preventive tools in IDDM.

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