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Apoptosis and Autoimmune Disorders

Reginald Halaby

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1. Introduction

Apoptosis, or programmed cell death, comes from a Greek term meaning "the falling off of the leaves." Apoptosis is also known as cell suicide and is a mechanism that is present in most eukaryotic cells to regulate cell numbers. It can be considered as the opposite of mitosis. Apoptosis is a normal part of development and is required during development, creation of the central nervous system, degeneration of the tadpole tail during metamorphosis, and the loss of certain appendages during the larval to pupal metamorphosis in holometabolous insects.

Apoptosis is a major aspect of development and homeostasis. Apoptosis contributes to the sculpting of developing structures in vertebrate and invertebrate embryos. Deletion of interdigital webs in developing limbs (Hammar & Mottet, 1971), development of the fetal intestinal mucosa (Harmon et al., 1984), and retinal development (Penfold & Provis, 1986) all involve apoptosis. Apoptosis serves as a major mechanism for the regulation of cell numbers. For example, in the visual system of developing vertebrates, apoptosis preferentially eliminates neurons that form improper connections (Cowan et al., 1984). In the mammalian embryonic central nervous system, over 1/3 of newly formed cells die (Oppenheim et al., 1982) and during development of *Caenorhabditis elegans* 131 of the 1090 somatic cells die (Ellis & Horvitz, 1986). Some cells seem to die because they have no apparent function, such as the Mullerian duct in male embryos (Price et al., 1977). Apoptosis can serve as a defense mechanism to remove unwanted and potentially dangerous cells, such as self-reactive lymphocytes (Smith et al., 1989).

During development, the survival of lymphocytes is mediated by both active signaling and passive processes that regulate survival. These processes are extremely selective resulting in the elimination of the majority of developing lymphocytes (Owen & Jenkinson, 1992). Both T- and B-lymphocytes undergo developmental stages and appear to share many regulatory mechanisms. For example, the early survival of lymphocyte precursors is mediated primarily by cytokines, which both regulate the numbers of progenitors and play critical

roles in initiating the rearrangement of the antigen receptor genes (Baird et al., 1999). Developing lymphocytes must create unique antigen receptors by rearrangement to generate the incredible diversity characteristic of an adaptive immune response (Jung et al., 2006). A consequence of the stochastic nature of this process is that only 1/3 of rearrangements are joined appropriately and give rise to a functional antigen receptor (Jung et al., 2006). Although several mechanisms (use of alternative antigen receptor gene loci and receptor editing) exist to allow further opportunities for successful rearrangement, the majority of lymphocytes fail to generate functional antigen receptors and are thus eliminated by programmed cell death (Berg & Kang, 2001; Nemazee, 2006).

2. Apoptosis and disease

The suppression of apoptosis increases the susceptibility of an individual to malignancy whereas uncontrolled apoptosis is associated with degenerative diseases. These include acquired immunodeficiency syndrome (AIDS; Ameison & Capron, 1991), cancer (Ling et al., 1993), Parkinson's disease (Walkinshaw & Waters, 1995), and Alzheimer's disease (Landfield et al., 1992). Abnormally elevated levels of apoptosis have been found in the lymph nodes of HIV-infected persons (Muro-Cacho et al., 1995). Indeed a clearer understanding of the regulation of apoptosis may result in better therapies.

In this chapter, we will examine how inappropriate or excessive apoptosis can lead to autoimmune disorders, such as type I diabetes, autoimmune thyroid disease, rheumatoid arthritis, lupus and others. Furthermore, we present data demonstrating that apoptosis-related treatments can be effective against various autoimmune disorders.

3. Type I Diabetes

Type I diabetes (T1D; also known as insulin-dependent or juvenile-onset diabetes) results from a presumed T-cell attack on the insulin-secreting β-cells of the pancreas. Controlled apoptotic cell death contributes to normal T-cell selection and education. Among the regulatory T-cells that actively suppress effector T-cells, the $FOXP3^+CD4^+CD25^{high}$ T-cells (T_{regs}) represent one of the best characterized sub-populations. There is accumulating evidence of a deficiency in either the frequency or function of T_{regs} in various human autoimmune diseases (Bacchetta et al., 2007), as well as in the pathogenesis of T1D (Brusko et al., 2005; Putnam et al., 2005). An increase in T_{reg} apoptosis was found to correlate with a decline in suppressive potential of these cells. The fact that both hyperglycemic T1D subjects and normoglycemic *at-risk* subjects showed this phenomenon suggests that T_{reg} apoptosis is more a precursor to, rather than a consequence of diabetes (Jailwala et al., 2009). Although T_{reg} apoptosis is likely to be one of the peripheral imbalances in T1D, there is very little known about the pathways and genes that make T_{regs} sensitive to apoptosis during the period right after the onset of disease. Understanding the mechanism by which cytokine deprivation in T1D induces expression of apoptotic genes should identify potential targets for novel treatments.

Therefore, interruption of normal T-cell selection can result in the generation of autoreactive cells (Takuma & Faustman, 2003). However, the mechanisms by which most candidate genes predispose to type 1 diabetes remain unclear. A recent study reports that *PTPN2*, a candidate gene for type 1 diabetes, modulates β-cell apoptosis after exposure to type I and II interferons (IFNs), cytokines that contribute to β-cell loss in early type 1 diabetes (Santin et al., 2011). The *PTPN2* gene encodes a phosphatase that is ubiquitously expressed (Doody et al., 2009). This phosphatase is induced by IFNγ and a synthetic dsRNA, polyinosinic-polycitidilic acid (PIC), in β-cells and exacerbates IFNγ- and PIC-induced β-cell apoptosis by modulating STAT1 activation (Coli et al., 2010; Moore et al., 2009). However, the mechanisms connecting this candidate gene to actual β-cell death remain unclear. Inhibition of *PTPN2* sensitizes pancreatic β-cells to apoptosis induced by both type I and II IFNs (Santin et al, 2011).

4. Autoimmune Thyroid Diseases

The Fas and TRAIL pathways are present and functional in the thyroid, and there is evidence suggesting their involvement in autoimmune diseases of the thyroid (Bretz et al., 1999; Kawakami et al 2000). Giordano et al. (1997) reported the constitutive expression of FasL (Fas ligand) on normal and Hashimoto's thyroiditis (HT) thyrocytes using immunohistochemistry, flow cytometry, and RT-PCR. The percentage of FasL-positive thyrocytes in Graves' thyroid was less than in normal thyroids (Sera et al., 2000). In contrast, another study was unable to detect FasL in thyrocytes (Xerri et al., 1997).

Although it is widely accepted that thyrocytes express the death receptor Fas, little is known about how this expression is modulated. It has been demonstrated that there is increased expression of Fas in the thyrocytes of patients with Hashimoto's thyroiditis (Hammond et al., 1997). Fas was also upregulated in the thyrocytes of patients with Graves' disease (Sera et al., 2000). The thyroid gland of Graves' disease patients contains TUNEL-positive thyrocytes and PCNA-positive thyrocytes, together with monocuclear cell infiltration (Sera et al., 2000). These data suggest that apoptosis and proliferation of thyrocytes may be abnormally accelerated, however, the proliferation of thyrocytes may outweigh their apoptosis, resulting in hyperplasia. IL-1β-treated thyrocytes become sensitive to apoptosis by anti-Fas IgM and activated T cells (Eguchi, 2001). Moreover, IL-1β-stimulated thyrocytes show reduced cytotoxic activity toward activated T cells. These results indicate that the IL-1β produced in the thyroid gland of Graves' disease patients might act on the thyroctyes to reduce their resistance to Fas-mediated apoptosis and lose their cytotoxic activity against activated T-cells, thus abolishing the immune-privilege status of the thyroid (Eguchi, 2001). This may provide an explanation for the accumulation of activated T cells in the of Graves' disease patients.

TSH receptor (TSHR) antibodies may be stimulating, blocking, or neutral in their functional influences and are found in patients with autoimmune thyroid disease, especially Graves' disease (Morshed et al., 2010). Although neutral TSHR antibodies failed to generate cAMP via Gαs effectors, they initiated unique molecular signaling, possibly via recruitment of

multiple G proteins (Laugwitz et al., 1996; Büch et al., 2008), and thus influenced multiple downstream signal transduction cascades including PKC/MAPK, mTOR/S6K, NF-κB, certain cytokines, and oxidative stress signaling and ultimately caused rat thyroid cell apoptosis on chronic exposure. These findings suggest that oxidative stress may play a significant role in such antibody-induced thyrocyte death and thus exacerbate the chronic inflammatory process via antigen-driven mechanisms seen in autoimmune thyroid disease.

Bcl-2 is mitochondiral protein that inhibits apoptosis (Park & Hockenbery, 1996). Increased serum Bcl-2 may be linked to accelerated apoptosis and was observed in patients with malignancies (Tas et al., 2006). In euthyroid Hashimoto's thyroiditis patients compared with controls and euthyroid Graves' disease, increased serum Bcl-2 has been reported (Myśliwiec et al., 2006). In a recent study, a tendency towards higher Bcl-2 in Hashimoto's thyroiditis patients was found (Jiskra et al., 2009). Jiskra et al. (2009) further showed that there was no difference in serum Bcl-2 between hyperthyroid Graves' disease and when the euthyroid state was achieved.

5. Systemic Lupus Erythematosus

A common feature of autoimmune diseases such as systemic lupus erythematosus (SLE), systemic sclerosis, and mixed connective tissue disease is the breakdown of tolerance of self antigens, a consequence of which is the production of antibodies reactive with multiple self proteins (von Mühlen & Tan, 1995). In patients with SLE, increased numbers of apoptotic lymphocytes and macrophages have been observed (Emlen et al., 1994). Other proteins have been implicated to play a contributing role in the pathogenesis of SLE. Protein phosphatase 2A (PP2A) is an abundant and ubiquitously expressed, highly conserved enzyme (Janssens et al., 2008). It regulates a variety of cellular processes, including cell cycle progression and cell division, cell death, cytoskeleton dynamics, and signaling pathways (Janssens & Goris, 2001; Sontag, 2001). PP2A is composed of a scaffold subunit (A), a catalytic subunit (C), and a regulatory (B) subunit. A recent study showed that the subunit Bβ is involved in the regulation of programmed cell death triggered by IL-2 deficiency and identified a subset of patients with SLE in which altered regulation of PP2A Bβ is associated with resistance to IL-2 deprivation-induced apoptosis (Crispín et al., 2011). Apoptosis is an essential phenomenon that modulates the duration of immune responses and maintains the diversity of the lymphoid armamentarium. The importance of this process is well known, and the deficiency of central molecules involved in lymphocyte apoptosis causes lymphoproliferative and autoimmune diseases in mice and humans (Turbyville & Rao, 2010; Cohen, 2006). Apoptosis induced by IL-2 deprivation is triggered by intrinsic cellular signals (Lenardo et al., 1999). The balance between anti- and pro-apoptotic Bcl-2 family proteins determines the maintenance of the mitochondrial membrane potential. In the presence of IL-2, Bad is phosphorylated and sequestered in the cytoplasm by 14-3-3 proteins (Zha et al., 1996; Pastorino et al., 1999). Bim, another pro-apoptotic molecule, is absent, and levels of anti-apoptotic Bcl-2 and Bcl-x are high. During IL-2 deprivation, Bad becomes dephosphorylated, dissociates from 14-3-3, and translocates to the mitochondrial membrane

where it binds to Bcl-2 and Bcl-x and neutralizes their anti-apoptotic capacity (Zha et al., 1996; Yang et al., 1995). This process results in the loss of the mitochondrial membrane potential and leads to apoptosis. The regulation of T-cell death following activation is known to be altered in patients with SLE (Gergely et al., 2002; Xu et al., 2004). Recent results indicate that the kinetics of apoptosis following IL-2 deprivation is affected in a fraction of patients with SLE (Crispín et al., 2011). Importantly, induction of PP2A Bβ upon IL-2 withdrawal was suboptimal or completely absent in these patients, which confirms the importance of PP2A Bβ as a molecule induced in cytokine withdrawal apoptosis and suggests that its faulty expression may underlie the observed phenotype. Mitochondrial hyperpolarization (MHP) could also contribute to the apoptosis resistance observed in SLE patients upon IL-2 deprivation (Gergely et al., 2002; Fernandez et al., 2006).

6. Apoptosis in rheumatoid arthritis

Fas and FasL both exist in membrane (mFas, mFasL) and soluble (sFas, sFasL) forms, but only engagement of mFas leads to the activation of caspase-8 via the Fas-associated death domain protein (FADD; Okamoto et al., 2000). Activated caspase-8 may lead to apoptosis via at least two well-described pathways: direct activation of caspase-3; and alteration of mitochondrial transmembrane potentials via Bcl-2 homology 3 (BH3)-interacting death-domain agonist (BID), leading to the cytoplasmic translocation of cytochrome c, which leads to activation of caspase-9, which in turn activates caspase-3 (Peng, 2006). Both pathways are regulated at the level of caspase-8 activation by the endogenous inhibitor FADD-like IL-1β-converting enzyme (FLICE)-inhibitory protein (FLIP), which may also be recruited by FADD. Interestingly, FLIP may also participate in an alternate signalling pathway, recruiting tumour necrosis factor-associated factor (TRAF) 1, TRAF2, the MAP kinase kinase kinase Raf1 and receptor-interacting protein (RIP) to activate extracellular signal-regulated kinase (ERK) and nuclear factor κB (NF-κB) pathways, leading to proliferation and/or inflammation (Peng, 2006).

Apoptotic cells are uncommonly observed in rheumatoid arthritis (RA) tissues *in vivo*, but synoviocytes, synovial T cells and macrophages have often been observed to express high levels of Fas and/or FasL, and are highly susceptible to Fas/FasL-induced apoptosis *in vitro*. This contrasts with osteoarthritis, in which such abnormalities in Fas/FasL expression and susceptibility to Fas-induced apoptosis are generally not observed (Firestein et al., 1995; Nakajima et al., 1995). The discrepancy between an absence of apoptotic cells *in situ* and enhanced susceptibility to Fas-induced apoptosis *in vitro* probably reflects multiple anti-apoptotic processes and/or phenomena in the rheumatoid synovium (Peng, 2006). For instance, increased intrasynovial and/or serum sFas appears to compete with mFas and prevent apoptosis of synoviocytes (Hasunuma et al., 1997). Also, in some studies, invading T cells have been found to be defective in FasL expression, which may account for ineffective clearance of activated (Fas-expressing) cells (Cantwell et al., 1997). In addition, synoviocyte- and/or stromal cell-derived cytokines [including transforming growth factor (TGF) β1 (Kawakami et al., 1996), basic fibroblast growth factor, TNF-α ,and interleukin-1

(Kobayashi et al., 2000a; Tsuboi et al., 1996)] protect RA synoviocytes from Fas-induced apoptosis, and such factors may account for the ability of RA T cells to be protected from apoptosis via their close interactions with fibroblast-like synoviocytes (Salmon et al., 1997). Furthermore, rheumatoid synovial fluid contains high levels of nitric oxide, which inhibits caspase-3 (Migita et al., 2001), as well as stromelysin-1 (matrix metalloproteinase-3), which can cleave mFasL to produce sFasL, which can compete with death-inducing mFasL (Matsuno et al., 2001). Thus, multiple pathways, both intra- and extracellular, impair Fas-induced apoptosis in RA joints. Still, whether these phenomena actually underlie the disease etiology or simply result from the initial inflammatory pathways of RA itself remains undetermined.

7. Sjogren's Syndrome

Sjogren's syndrome (SS) is an autoimmune disorder that affects multiple exocrine glands, particular those that produce moisture to coat exposed epithelia such as the oral and ocular surfaces. The role of apoptosis in loss of glandular tissue in SS is less clear (Wang et al., 2006). Environmental and genetic factors appear to contribute to the etiology of SS, although the evidence is relatively premature (Bolstad & Jonsson, 2002; Yamamoto, 2003). T-cell-mediated cytotoxicity (Manganelli & Fietta, 2003; Hayashi et al., 2004) and autoantibodies are important in loss of gland function. There is also a failure to remove autoimmune T-cells at the level of thymic selection, resistance of T-cells within the gland to undergo apoptosis, aberrant expression of increased levels of cell adhesion molecules on glandular epithelial cells (facilitating infiltration of autoimmune lymphocytes to glands), up regulation of human leukocyte antigen (HLA)-DR, and polyclonal activation of B-lymphocytes (Rehman, 2003). Glandular epithelial cells contribute to the autoimmune process by secreting pro-inflammatory cytokines. Specifically, pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β and 6 (Roescher et al., 2010) and (Muraki et al., 2004) in the exocrine glands in response to immune-mediated inflammation, are found over-expressed in the SS patients. IL-6, a potent inflammatory cytokine, is involved in acute phase reactions and both B and T-cell responses and the formation of germinal center-like structure (Roescher et al., 2010). It was found to be consistently high in saliva and serum and in the salivary glands of SS patients, not in subjects with xerostomia (dry mouth) only (Roescher et al., 2009). Furthermore, IL-1β is an effective inducer of other inflammatory cytokines such as IL-6, IL-8, TNF-α, and granulocyte-macrophage colony-stimulating factor (Fibbe et al., 1989; Chrousos, 1995). Dry-eye disease is accompanied by an increase in the proinflammatory forms of IL-1 (IL-1 α and mature IL-1 β) and a decrease in the biologically inactive precursor IL-1 β in tear fluid of SS patients (Solomon et al., 2001).

Several studies have analyzed the role of the Fas/FasL system in salivary gland lesions of patients with SS. Bolstad et al. (2003) demonstrated a substantial increase in the salivary gland tissue expression of the negative regulator molecules PD-1 and CTLA-4 and the apoptotic signal molecules Fas and FasL in SS patients compared with controls, suggesting the involvement of the Fas/FasL system in the apoptosis of ductal and acinar epithelial cells.

Abu-Helu et al. (2001) showed that salivary gland epithelial cell lines (SGEC) constitutively expressed more membranous Fas and intracellular FasL than controls, while Shibata et al. (2002) detected Fas/FasL expression in ductal and acinar cells of SS patients but not in controls. Other studies have suggested that Fas may accelerate the apoptotic death of peripheral CD4 T cells in SS patients (Zeher et al., 1999; Ohashi et al., 1996). However, Ohlsson et al. (2001) found Fas-induced epithelial cell apoptosis to be a rare event, with a frequency of less than 1% in salivary glands from 18 SS patients.

Loss of p53 activity allows the survival and proliferation of cells that should otherwise be eliminated. In primary SS, the expression of p53 and p21 was analyzed in salivary glands from 10 patients and 10 controls (Mariette et al., 2002). The p53 antigen was detected in the ductal cells of nine SS patients and only one control, and the p21 antigen in eight patients and two controls. Both antigens were located in the ductal cells of SS patients, but not in acinar cells. The expression of p53 and p21 in the ductal cells located around lymphoid infiltrates may represent a defense mechanism allowing DNA repair and thus preventing apoptosis, while the lack of over-expression of p53 and p21 in acinar cells could be one of the mechanisms responsible for acinar destruction by apoptosis in SS salivary glands.

Kong et al. (1997) demonstrated in SS that the expression of Bcl-2 makes them resistant to apoptotic cell death. Nakamura et al. (2000a) showed that Bcl-2 and Bcl-x were preferentially expressed in infiltrating mononuclear cells rather than in the acinar and ductal epithelial cells from salivary glands of 17 SS patients, while Ohlsson et al. (2002) detected Bcl-2 (but rarely Bax) in the infiltrating lymphocytes of salivary glands from SS patients. However, Abu-Helu et al. (2001) found that SGEC cell lines constitutively expressed antiapoptotic proteins, such as Bcl-2 and cFLIP, that might protect them from both spontaneous and anti-Fas mAb-mediated apoptosis. Kamachi et al. (2002) found an inhibitory effect of IFN-γ in Bcl-2 expression, which was enhanced by coadministration of TNFα, leading to an increase in the apoptosis of salivary gland cells. It seems that apoptosis of the epithelial acinar and ductal cells may depend on the imbalance between up-regulated death-promoters (Fas and Bax) and down-regulated apoptosis-suppressor signals (Bcl-2).

A stronger expression of activated caspase-3 and cleaved PARP in the acinar and ductal cells of salivary glands was found in 13/15 (87%) SS patients, while staining for activated caspase-9 was negative. Nakamura et al. (2000b) analyzed the role of the X chromosome-linked inhibitor of apoptosis (XIAP), a member of the IAP family that inhibits the activation of caspases, and found a strong expression in the acinar and ductal epithelial cells of SS patients but not in those of controls. Because caspase-3 and caspase-7 are effector enzymes, XIAP might protect salivary epithelial cells from apoptotic death in SS (Nakamura et al., 2000b). Hayashi et al. (2003) suggested that treatment with caspase inhibitors might prevent the development of the inflammatory process in salivary glands, and Inoue et al. (2001) found that caspase-inhibiting agents could inhibit the cleavage of α-fodrin. Increased caspase cascade activity may be involved in the progression of autoantigen proteolysis and tissue destruction in primary SS. The presence of activated caspase-3 in salivary glands indicates that excessive apoptosis may contribute to epithelial destruction in primary SS.

From the studies above, it can be concluded that the extrinsic apoptotic pathway as well as the intrinsic apoptotic pathway are involved in the pathogenesis of SS. FasL and its receptor, Fas, are essential in the homeostasis of the peripheral immune system. It can be considered that a defect in activation-induced cell death of effector T cells may result in the development of autoimmune exocrinopathy in Sjogren syndrome (Hayashi et al., 2004). Conversely, the increased rate of apoptosis of in epithelial cells in SS may result from either the imbalance between the down-regulated apoptosis-inhibitor Bcl-2 and the up-regulated apoptosis-inducer Bax, via the intrinsic pathway (Manganelli P & Fietta, 2003).

8. Apoptosis-related therapies for autoimmune disorders

Injection of high doses of soluble peptides leads to a state of T-cell unresponsiveness (referred to as anergy) owing to a block in T-cell proliferation and/or IL-2 production, or results in activation-induced cell death (AICD) after T-cell re-stimulation with the cognate peptide (Burstein et al., 1992; Critchfield et al., 1994). It is thought that tolerance induced by soluble peptides may be useful for antigen-specific immunotherapy for the treatment of human autoimmune diseases. Non-obese diabetic (NOD) mice spontaneously develop type 1 diabetes, which is characterized by T-cell-mediated inflammation of the pancreatic islets (insulitis) and the eventual destruction of the insulin-producing β-cells7. Prevention of type 1 diabetes in NOD mice can be achieved by inducing specific T-cell tolerance to pancreatic β-cell autoantigens prior to the total destruction of all the islet β-cells (Miller et al., 2007).

One of the more promising methods to induce tolerance for the prevention and treatment of autoimmune diseases, and the prevention of transplant rejection, is intravenous treatment with antigen-coupled, ethylene carbodiimide (ECDI)-fixed splenocytes (referred to here as antigen coupled cells). Treatment with antigen-coupled cells can induce anergy *in vitro* and peripheral tolerance *in vivo* (Miller et al., 1979; Sriram et al., 1983). The induction of tolerance by antigen-coupled cell treatment has also been shown to be an effective therapy in other disease models, including experimental autoimmune thyroiditis (Braley-Mullen et al., 1980) and in the NOD mouse model of diabetes (Fife et al., 2006). Unlike soluble-peptide therapy, in which (depending on the disease-inducing autoantigen) the tolerizing antigen can induce an anaphylactic response that results in the death of treated mice, antigen-coupled-cell therapy does not induce an allergic response, regardless of the antigen used, and appears to be well tolerated at all stages of disease (Smith et al., 2005; Pedotti et al., 2001).

Zauli et al. (2010) showed that recombinant human tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) ameliorated the severity of streptozotocin (STZ)-induced type 1 diabetes in a mouse model. Specifically, exogenous recombinant TRAIL, co-injected with STZ, significantly reduced the levels of islet damage with respect to animals injected with STZ alone (Zauli et al., 2010). Of note, treatment with recombinant TRAIL does not impair the viability of pancreatic islets, even when overexpressed (Dirice et al., 2009).

Thyroid arterial embolization was shown to effectively enhance the positive expression of pro-apoptotic genes of Fas, FasL, Bax, Bcl-2 and P53 in Grave's disease (GD) thyroid, thus

promoting apoptosis of GD thyroid and restoring the thyroid size and function to normal conditions (Zhao et al., 2009). Furthermore, T lymphocytes from GD patients treated with thyroid hormones accompany reduction of Bcl-2 protein expression, production of reactive oxygen species, and reduction of mitochondrial delta psi, resulting in apoptotic lymphocyte death (Mihara et al., 1999). In a study of patients with Hashimoto's thyroiditis treated with Simvastatin, it was shown that CD4+ cells and B lymphocytes increased while CD8+ cells, natural killer cells, and activated T lymphocytes decreased significantly (Gullu et al., 2005). This effect is probably mediated via lymphocyte apoptosis as demonstrated with in vitro experiments and is not confined to Simvastatin since Mevastatin, Pravastatin and Cerivastatin also induced apoptosis in lymphocytes (Gullu et al., 2005). Thyroid cells can be sensitized to die via apoptosis by a unique combination of interferon-gamma and IL-1beta cytokines. Interferon-gamma/IL-1beta pretreatment sensitizes human thyroid cells to Fas-mediated apoptosis in a complex manner that overcomes the blockade of initiator caspases through increased expression of cell surface Fas receptor, increases in proapoptotic molecules that result in mitochondrial activation, and late caspase cleavage (Mezosi et al., 2005).

Lupus-prone (NZB x NZW)F1 mice spontaneously develop elevated titers of anti-DNA Abs that contain T cell determinants in their V(H) regions. It has been shown that tolerization with an artificial peptide based on these T cell determinants (pConsensus (pCons)) can block production of anti-DNA Abs and prolong survival of the mice (Singh et al., 1995). These data indicate that clinical suppression of autoimmunity after administration of pCons depends in part on the generation of CD8+ Ti cells that suppress secretion of anti-DNA Ig using mechanisms that include Foxp3, TGFβ, and resistance to apoptosis (Hahn et al., 2005). It is postulated that in the CD8+ Ti cells, secretion of TGFβ, expression of *Foxp3*, and reduced apoptosis may likely be linked (Hahn et al., 2005).

The above studies strongly suggest that modulation of the Fas pathway may serve as attractive therapeutic targets. Many current RA therapies are in fact known to induce apoptosis in synovial cells, such as methotrexate and TNF-directed therapies, and appear to do so at least in part via Fas, at least in some pathogenic cell populations, such as T cells and/or synovial macrophages (Oshima et al., 2000; Genestier et al., 1998; Catrina et al., 2005). Thus, approaches targeted more specifically against Fas/FasL may be of benefit.

More direct evidence includes one study demonstrating the ability of anti-sense oligonucleotides against FLIP to sensitize RA synoviocytes strongly to Fas-induced apoptosis (Palao et al., 2005). Furthermore, in a model in which severe combined immunodeficient (*scid*) mice are engrafted with RA synovium, treatment with an apoptosis-inducing anti-Fas antibody, as well as gene therapy with FasL or FADD, induces apoptosis in both synoviocytes and mononuclear cell populations, diminishing cellular infiltrates (Okamoto et al., 1998; Kobayashi et al., 2000b; Matsuno et al., 2002). Thus, if apoptotic strategies are to be used therapeutically in inflammatory arthritis, current evidence altogether strongly supports activation of the apoptotic Fas pathway as a primary objective, at least in RA.

A recent study evaluated whether cholinergic autoantibodies contained in IgG purified from Sjogren sera could trigger apoptosis of A253 cell line (Reina et al., 2012). The use of A253 cell lines has revealed that salivary gland epithelial cells are particularly susceptible to Fas-mediated as well as Fas-independent apoptotic death after stimulation with IFN-γ, probably via the downregulation of the apoptosis inhibitor protein c-FLIP (Abu-Helu et al., 2001). Reina et al. (2012) demonstrated that anti-cholinergic autoantibodies in IgG purified from primary SS patient's sera mediates apoptosis of the A253 cell line in an inositol phosphate, caspase-3 and metalloproteinase-3 dependent manner.

9. Summary

The research reviewed in this chapter clearly demonstrates that there is a delicate balance between death and survival signals in the pathogenesis of autoimmune disorders. The apoptotic pathways involved may be disease-specific or shared in common. Although the precise mechanisms by which apoptosis modulates autoimmune disorders in not fully understood, deciphering the role played by apoptosis in these disorders will lead to improved treatment modalities for patients.

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Acknowledgement

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