Hormonal control of programmed cell death/apoptosis

Wieland Kiess and Brian Gallaher

Children’s Hospital, University of Leipzig, Oststr. 21–25, D-04103 Leipzig, Germany and
Research Centre for Developmental Medicine and Biology, University of Auckland, School of Medicine, Auckland, Private Bag 92019, New Zealand

(Correspondence should be addressed to W Kiess)
(B G is now at the Children’s Hospital, University of Leipzig, Oststr. 21–25, D-04103 Leipzig, Germany)

Abstract
Apoptosis or programmed cell death is a physiological form of cell death that occurs in embryonic development and during involution of organs. It is characterized by distinct biochemical and morphological changes such as DNA fragmentation, plasma membrane blebbing and cell volume shrinkage. Many hormones, cytokines and growth factors are known to act as general and/or tissue-specific survival factors preventing the onset of apoptosis. In addition, many hormones and growth factors are also capable of inducing or facilitating programmed cell death under physiological or pathological conditions, or both. Steroid hormones are potent regulators of apoptosis in steroid-dependent cell types and tissues such as the mammary gland, the prostate, the ovary and the testis. Growth factors such as epidermal growth factor, nerve growth factor, platelet-derived growth factor (PDGF) and insulin-like growth factor-1 act as survival factors and inhibit apoptosis in a number of cell types such as haematopoietic cells, preovulatory follicles, the mammary gland, phaeochromocytoma cells and neurones. Conversely, apoptosis modulates the functioning and the functional integrity of many endocrine glands and of many cells that are capable of synthesizing and secreting hormones. In addition, exaggeration of the primarily natural process of apoptosis has a key role in the pathogenesis of diseases involving endocrine tissues. Most importantly, in autoimmune diseases such as autoimmune thyroid disease and type 1 diabetes mellitus, new data suggest that the immune system itself may not carry the final act of organ injury: rather, the target cells (i.e. thyrocytes and β cells of the islets) commit suicide through apoptosis. The understanding of how hormones influence programmed cell death and, conversely, of how apoptosis affects endocrine glands, is central to further design strategies to prevent and treat diseases that affect endocrine tissues. This short review summarizes the available evidence showing where and how hormones control apoptosis and where and how programmed cell death exerts modulating effects upon hormonally active tissues.

European Journal of Endocrinology 138 482–491

Defining apoptosis/programmed cell death
There are two major types of cell death, namely apoptosis and necrosis (1–9). Both apoptosis and necrosis involve a sequence of consecutive biochemical and morphological events ultimately leading to cell death (3, 4, 6). Necrosis is characterized by rupture of the cell membrane and leakage of cell plasma. It very often causes an acute inflammatory response and pathological tissue reaction involving groups of adjoining cells (1). In contrast, apoptosis or programmed cell death is a physiological form of cell death (8). Typically, cells from multicellular organisms self-destruct when they are no longer needed or have become damaged (1–9). To survive, all cells from multicellular animals depend upon the constant repression of this suicide programme by signals from other cells. Apoptosis usually involves scattered individual cells in a tissue. It occurs in embryonic development (10–16) and also during involution of organs (17–24). It is characterized by distinct biochemical and morphological changes such as DNA fragmentation, plasma membrane blebbing and cell volume shrinkage. Many hormones, cytokines and growth factors are known to act as general or tissue-specific survival factors preventing the onset of apoptosis; conversely, many hormonal factors are known to induce or enhance apoptotic processes (Table 1).

Ultrastructural changes in apoptosis
Early apoptosis is characterized by compaction and segregation of chromatin in sharply circumscribed masses. There is convolution of the nuclear outline,
condensation of the cytoplasm with preservation of the integrity of organelles, and convolution of the cell surface (1, 3, 4, 6). In the next phase, the nucleus fragments and the cytoplasm condenses, with extensive protrusion of the cell surface. The separation of the surface protuberances produces membrane-bounded apoptotic bodies of various sizes and composition. These bodies are phagocytosed by nearby cells and degraded by lysosomal enzymes (3, 4, 6, 9). In summary, the consecutive and ordered appearance of condensed chromatin, budding of the nucleus and subsequent nuclear fragmentation is characteristic of apoptosis. In parallel, overall condensation also occurs in the cytoplasm. Extensive protrusion/blebbing of the cell surface follows, especially when thymocytes and lymphocytes become apoptotic (1, 3, 4, 6). In lymphocytes and other cell types, membrane-bounded apoptotic bodies appear, but cytoplasmic organelles remain intact. Whereas apoptotic bodies are often recognized by light microscopy, transmission electron microscopy or scanning electron microscopy have to be used to visualize the specific ultrastructural changes typical of programmed cell death (6, 9).

### Incidence of apoptosis in health and disease

Apoptosis is a unique feature of multicellular organisms that enables continuous renewal of tissues by cell division while maintaining the steady-state level of the various histological compartments. Programmed cell death exists only rarely in prokaryotes or protozoa that proliferate and expand perpetually under optimal conditions; however, it has been described in a few unicellular organisms (1). This is consistent with the assumption that apoptosis has emerged during evolution as a series of steps providing a selective advantage to the best adapted offspring by preventing flawed offspring from competing for resources (1). Programmed cell death is a constitutive feature during the normal development of mammals (14, 15). Cell deletion in regressing interdigital webs and during the development of the gut mucosa and of the retina are well studied examples of apoptotic cell death during the development of mammals (14). In amphibia, apoptosis is responsible for the involution of larval organs during metamorphosis. Steady-state kinetics are maintained in most healthy adult mammalian tissues by apoptosis occurring at a low rate that complements mitosis. In fact, the traditional emphasis placed on cell proliferation as the dominant parameter in cell population control is being tempered by the realization that cell deletion and cell death are also of cardinal importance (3). Importantly, normal involution of endocrine-dependent tissues induced by changes in blood concentrations of trophic hormones is mediated by apoptosis, as are other normal involutinal processes such as ovarian follicular atresia (22–24).

Pathological atrophy of endocrine-dependent organs after pathological withdrawal of trophic hormonal stimulation is accompanied by a massive wave of apoptosis. This occurrence has been observed in the prostate after castration (25, 26) and in the adrenal cortex after suppression of secretion of adrenocorticotrophic hormone (ACTH) by administration of glucocorticoid (27). Various forms of cancer therapy, such as a variety of cancer-chemotherapeutic agents and moderate doses of radiation, induce or enhance extensive apoptosis in rapidly proliferating cell populations (5, 28). Apoptosis also occurs in many types of viral infection. T lymphocytes are known to induce apoptosis, as are natural killer and killer cells (29, 30). Apoptosis induced by immune cells may be involved in oncogenesis and autoimmune diseases such as autoimmune thyroid disease and diabetes mellitus (3, 4, 9).

### Biochemical and molecular mechanisms

The process of programmed cell death involves an epigenetic reprogramming of the cell that results in an energy-dependent cascade of biochemical changes. These changes eventually lead to morphological changes within the cell, resulting in cell death and elimination. Changes in intracellular and, most importantly, intranuclear Ca\(^{2+}\) concentrations are likely to be involved in activating cleavage of DNA by nucleases during programmed cell death (31). In fact, the double-stranded linker DNA between nucleosomes is cleaved at regular inter-nucleosomal sites through the action of such Ca\(^{2+}\)-Mg\(^{2+}\)-sensitive neutral endonucleases (32). Zinc is a potent inhibitor of such enzymes (6). Most apoptotic cells require synthesis of RNA and proteins (8, 9). Delay or abrogation of apoptosis by inhibition of macromolecular synthesis is well known. The dying cells express large amounts of mRNA for several enzymes. In addition, several degradative

---

### Table 1 Involvement of hormones, cytokines and growth factors in apoptosis/programmed cell death.

<table>
<thead>
<tr>
<th>Known inhibitors of apoptosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
</tr>
<tr>
<td>Oestradiol</td>
</tr>
<tr>
<td>Progesterone</td>
</tr>
<tr>
<td>Growth factors (EGF, IGF-I, NGF, PDGF)</td>
</tr>
<tr>
<td>Interleukins</td>
</tr>
<tr>
<td>Growth hormone</td>
</tr>
<tr>
<td>Prolactin</td>
</tr>
<tr>
<td>Gonadotrophins</td>
</tr>
<tr>
<td>Potential inducers of programmed cell death</td>
</tr>
<tr>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Progesterone</td>
</tr>
<tr>
<td>Thyroid hormones</td>
</tr>
<tr>
<td>Growth factor (IGF-I, EGF, PDGF, NGF)</td>
</tr>
<tr>
<td>Transforming growth factor-β</td>
</tr>
<tr>
<td>Tumour necrosis factor</td>
</tr>
<tr>
<td>Fas ligand</td>
</tr>
</tbody>
</table>

---

---
enzymes become activated. Regulatory proteins maintain control over the apoptotic cascade (3).

**Genes associated with programmed cell death**

Genes responsible for the morphological and biochemical processes that fragment and phagocytose the dying cell without evoking an immune response have been identified: among these are classic components of signalling pathways (Table 2). Others, such as fos, myc, hsp 70 and p53, seem to be of particular biological significance (Table 3) (11, 12, 33, 34). Often, such genes are recruited from other cellular functions, such as mitosis and differentiation. It is important to note that genes displaying a prolonged increase in the mRNA steady-state concentrations, such as p53, are most probably expressed in the surviving cells, whereas other genes might only be expressed by cells destined to die (9).

p53 mutations are frequent in some types of cancer, for example breast cancer. Whereas wild-type p53 inhibits cell growth in vitro, p53 is believed not to affect the induction of programmed cell death directly in many cells (35, 36). Rather, mutations in the p53 gene can result in immortalization of cells and inhibition of apoptosis in transformed cells. A protein called p21WAFl/CIP1 has been shown to be a critical downstream effector of p53 and a potent inhibitor of cyclin-dependent kinases (37).

**Signal transduction in programmed cell death**

Apoptotic cell death can be triggered by calcium overload. Moreover, increases in cytoplasmic or nuclear ionized calcium (or both) have been implicated in all phases of apoptosis (Table 2). An increase in intracellular calcium pools very often precedes, and even can induce, internucleosomal DNA cleavage in the nucleus. Conversely, calcium chelators inhibit apoptosis. In general, Ca^{2+} signals are required for a number of cellular processes, including the activation of nuclear events such as gene transcription and cell cycle events. Intranuclear Ca^{2+} fluctuations are believed to affect chromatin organization, induce gene expression and activate cleavage of nuclear DNA by nucleases during apoptosis (31).

Increases in intracellular concentrations of cyclic AMP (cAMP) influence differentiation and luteinization of granulosa cells. Forskolin, a potent activator of adenylate cyclase, stimulated cell death in primary granulosa cells. Moreover, in such cells, blocking of the cellular phosphodiesterase activity in forskolin-stimulated cells by isobutylmethylxanthine, which maintains high concentrations of intracellular cAMP, led to further enhancement of cell death.

The glucocorticoid-induced apoptotic cell death in immature thymocytes is augmented by protein synthesis inhibitors, inhibitors of protein kinase C and heat-shock proteins (45). These data suggest that protein kinase C isoforms and heat-shock protein pathways...
have an important role in the signalling cascade of hormone-induced apoptotic cell death (Table 2).

The ligand-activated oestrogen receptor induces apoptosis in an erythroid cell line by binding to and inhibiting GATA-1, an erythroid transcription factor essential for survival and maturation of erythroid precursor cells. GATA-1 inhibition is reflected in the down-regulation of presumptive GATA-1 target genes (46). These data show that apoptosis can be regulated at the transcriptional level and directly involves the hormonal control of transcription factor expression.

Many enzymes that are involved in the regulation of growth and development, such as tyrosine kinases (47) and phosphatases, also modulate the progression towards cell death. In addition and most importantly, a family of proteases, also known as interleukin-1 converting enzymes, have a key role in apoptotic processes (1, 2, 6, 40, 48, 49).

**Regulation of apoptosis**

Regulation of apoptosis is mediated by many factors and on many levels of cell metabolism and cell biology. Viral infection, metabolic derangements such as sudden changes in glucose concentrations, heat, irradiation, toxins and drugs, all are capable of influencing the transition of a given cell to programmed cell death. In addition, the multiplicity of hormonal factors such as cytokines, steroids and peptide hormones or their withdrawal (as demonstrated in Fig. 1) are all involved in steering cells between death and proliferation (17, 50–55).

**Role of growth factors/cytokines in apoptosis**

Whereas it is well known that both epidermal growth factor (EGF) and the insulin-like growth factor (IGF)/insulin family stimulate the growth of many cell types by activating their respective tyrosine kinase receptors, it has also become apparent that both classes of growth factors and their receptors are capable of preventing apoptosis in many cells and cell types (Fig. 2) (47, 56–58). In human colorectal carcinoma cells, an anti-EGF receptor antibody induces apoptosis, whereas insulin delayed apoptotic DNA fragmentation. Signal transduction pathways shared by EGF and IGFs/insulin are thus believed to be involved in regulating apoptosis triggered...
by blockade of the EGF receptor. A number of genes, particularly c-Myc, are believed to have key roles in apoptosis triggered by growth factor withdrawal (35). C-Myc might have the potential to induce either cell death or proliferation; in the latter case, growth factors prevent the cell from proceeding on the death pathway, and will thus favour proliferation. Alternatively, cell cycle arrest, which normally occurs as a consequence of growth factor withdrawal, is overridden by c-Myc in such a way that the cell inappropriately continues to die by apoptosis (9, 36).

Some neurones are dependent on nerve- or target-derived neurotrophic factors. Absence of such factors or interruption of the continuous supply of neurotrophic factors such as NGF, eventually leads to the induction of apoptotic cell death and loss of neurones (59). Both axonal elongation and neuronal survival are maintained through the availability of growth factors and seem to be essential for peripheral nerve regeneration after injury (60).

In immature thymocytes and mature T cells, interleukins, such as IL-2 and IL-4, inhibit dexamethasone-induced apoptosis, whereas high doses of IL-2 are able to induce apoptosis both in thymocytes and in peripheral T cells (30, 45). A number of different growth factors and cytokines are involved in the regulation of apoptosis in the epidermis and in the regressing hair follicle (61).

The mechanisms by which growth factors modulate apoptosis might relate to their ability to influence the entry of a cell into the cell cycle: in fact, when tumour cells are forced out of the cell cycle into the quiescent state (G0) they become insensitive to programmed cell death. Growth factors prevent transit from G1 to G0 and thus increase the lytic susceptibility of a tumour cell. In summary, the susceptibility of a cell to the induction of cell death is believed to be a consequence of simultaneously activated growth stimulatory and growth inhibitory signalling pathways (55).

Role of steroid hormones in apoptosis
Steroid hormones have a major role in the regulation of growth, development, homeostasis and programmed cell death (17, 62). Together with other hormones and growth factors, steroids regulate both induction and inhibition of cell death, along with many other cellular functions, and the cellular composition of organs throughout the body (22, 63).

Glucocorticoids induce apoptotic cell death in immature thymocytes and mature T cells through an active process, characterized by extensive DNA fragmentation (51). This process requires macromolecule synthesis and is inhibited by interleukins IL-2 and -4 (30, 45). Interestingly, it has become evident that adrenal steroids act on the brain: glucocorticoids are taken up and retained by the hippocampus. Glucocorticoid receptors have a role in containing programmed cell death in the hippocampus and determine the rate of neurogenesis (60, 62). Low levels of adrenal steroids are also believed to enable development of cell death in the dentate gyrus. Thus glucocorticoids could also regulate apoptosis in the central nervous system (62, 64).

In cultured MCF-7 human breast cancer cells, tumour necrosis factor (TNF)-α exerted a dose-dependent inhibition of cell growth. Although an earlier cytostatic effect was apparent, nuclear shrinkage and cytolyis of the cells suggest that growth inhibition is mediated via an increase in programmed cell death in vitro. 17β-Oestradiol sensitized the cells to both the cytostatic and the cytolytic effects of TNF-α. Chun et al. (21) have suggested that sex steroids have an important role in the regulation of apoptotic cell death in the ovary: whereas oestrogens inhibit ovarian granulosa cell apoptosis, androgens seem to enhance ovarian DNA fragmentation. These conclusions were drawn from experiments in hypophysectomized rats treated with diethylstilboestrol, oestradiol, oestradiol benzoate or testosterone. In vitro, 17β-oestradiol protected neurones from oxidative-stress-induced cell death. This effect was oestrogen receptor dependent (19).

Quantitative light and electron microscopic data indicate that antiprogestins initiate terminal differentiation, which eventually leads to apoptotic cell death in breast cancer cells. In contrast, progesterone is a potent inhibitor of programmed cell death in such cells (65).

Extensive programmed cell death is initiated at the onset of amphibian metamorphosis, resulting in 100% of cells dying in some larval tissues. All cell death during metamorphosis is under hormonal control: thyroid hormone is able to initiate apoptosis and to lead to tail regression in amphibian development (16). Bernal & Nunez (20) have suggested that thyroid hormone also has a role in oligodendrogial and neuronal differentiation and cell death.

Role of peptide hormones in programmed cell death
Whereas, as noted above, thyroid hormone is able to initiate the extensive programmed cell death that occurs at the onset of amphibian metamorphosis, prolactin (PRL), when given exogenously, prevents both natural and thyroxine-induced metamorphosis (16). In addition, lactogenic hormones such as PRL, human growth hormone and human placental lactogen inhibit dexamethasone-induced cytolyis of Nb2 lymphoma cells. The effect of PRL has been shown to be a direct inhibition of dexamethasone-induced DNA fragmentation, indicative of programmed cell death. Thus PRL has the capacity to protect the cell against glucocorticoid-receptor-mediated induction of apoptosis (52). A similar anti-apoptotic effect of PRL has been shown in Burkitt lymphoma cells.

Mullerian inhibiting substance (MIS) is a differentiating and antiproliferative peptide. It is tightly regulated
Hormonal control of programmed cell death/apoptosis

Hormonal control of apoptotic cell death in the prostate

In hormone target tissues, such as the prostate, apoptosis can be induced by ablation of the appropriate hormone. In fact, the epithelial cells of the prostate undergo apoptosis after castration (9). Both in normal and in neoplastic prostatic cells, androgens serve as cell-type-specific endogenous regulators of programmed cell death. Androgens simultaneously influence DNA synthesis and induce the synthesis of substances with mitogenic effects in prostate cells. They counterbalance these agonistic effects on proliferation with an antagonistic effect on programmed cell death. Conversely, oestrogens exert direct and indirect opposing effects on cell death in the prostate (26).

Gonadectomy leads to apoptotic cell death in the mouse reproductive tract (44, 68). After the apoptotic events, down-regulation of Bcl-2 and new expression of Fas were observed. Using Fas-lacking mice, it was demonstrated that the regression of the male reproductive tract is triggered by Fas-mediated apoptosis. Suzuki et al. (44) concluded from their experiments that, in the mouse prostate, the apoptotic death signal involves a number of steps, the first and most important of which was down-regulation of Bcl-2.

Hormonal control of apoptosis in the ovary

It is now established that atresia of ovarian follicles in mammals is initiated by apoptotic cell death of the granulosa cells in response to hormonal deprivation (9, 14, 17, 21, 69). Only a small proportion of follicles escape programmed cell death. Growth factors and oestrogens have been identified as follicle survival factors; androgens and gonadotrophin releasing hormone potentiate apoptosis of the follicle (14).

Granulosa cells are the main producers of the female sex steroid hormones that are responsible for the cyclicity in ovarian function. Programmed cell death in the ovary has a crucial role in limiting the number of follicles that can ovulate and thus prevents the development of more embryos than can successfully complete pregnancy (17). In vivo studies on the hormonal regulation of follicle atresia have been difficult because of the presence of heterogeneous population of follicles in the ovary. However, using serum-free cultures of preovulatory follicles, Chun et al. (21) were able to study the regulation of apoptosis by gonadotrophins, IGF-I and IGF-binding protein (IGFBP)-3. A spontaneous increase in apoptotic DNA...
fragmentation occurred after 24 h of culture in the absence of hormones, whereas hCG or FSH suppressed follicular apoptosis in a dose-dependent manner by as much as 60–62%. Treatment of follicles with IGF-I or insulin also inhibited follicular atresia, whereas IGFBP-3 reversed the inhibitory effect of both hCG and IGF-I on apoptosis. It was concluded that endogenously produced IGF-I in part mediates the effect of gonadotrophins to inhibit follicular apoptosis (21). In addition, these studies by Chun et al. have suggested that sex steroids have an important role in the regulation of apoptotic cell death in the ovary. It is believed that oestrogens inhibit and androgens enhance endonuclease activity in ovarian granulosa cells.

**Hormonal control of apoptotic cell death in the mammary gland**

Interaction of the retinoic acid receptor type of receptors and an array of lactogenic and mammogenic hormones such as EGF and hydrocortisone seems to be of utmost importance for mammary gland development (38).

Growth of the normal mammary gland involves proliferation, differentiation, programmed cell death and remodelling of the basement membrane throughout the cyclic ovarian stimulation of the menstrual cycle and during the pregnancy and lactation cycle. The regulation of these processes involves a concerted action of both oestrogen and progesterone.

Regression of the lactating mammary gland is induced by the decreasing prolactin and glucocorticoid hormone concentrations associated with weaning (9). The hormone dependency of breast cancer has been recognized for nearly a century. Cyclical patterns of cell division and cell death are observed also in normal breast tissue; the influence on disease progression of cyclical hormonal concentrations among premenopausal women is now being elucidated. Withdrawal of lactogenic hormones triggers a programme of epithelial cell death that is characterized by decreased gene expression for the milk protein casein, and increased expression of apoptosis-associated genes such as transforming growth factor-β (18).

**Hormonal control of apoptotic cell death in the uterus**

Discontinuation of oestrogen stimulation results in apoptotic cell death in the uterine epithelium of neonatal mice, but not in the stroma (54). In addition, oestrogen, progesterone, dihydrotestosterone and dexamethasone all inhibit programmed cell death of uterine epithelium when administered to female newborn mice for 4 days from the day of birth (54). Endometria of rhesus monkeys treated with RU486, an antiprogestin, had significantly more epithelial cell death by apoptosis, increased stromal compaction and less proliferating stromal cells than had endometria from animals treated with oestradiol (68). It was concluded that, in the primate endometrium, progesterone and oestradiol have proliferative or anti-apoptotic effects, or both (68). However, after prolonged exposure of the endometrial stroma to progesterone, apoptosis occurs in this tissue, and may contribute to breakthrough bleeding.

Molecular mechanisms controlling cell death during blastocyst implantation and decidualization have been studied recently. In fact, progesterone and oestrogen control endometrial differentiation and apoptosis by controlling Bcl-2 gene family expression. Expression of Bcl-2 decreased after hormone treatment and decidualization, whereas Bax protein increased during decidualization. In summary, the balance between Bax and Bcl-2 expression is altered during stromal cell differentiation. Increased expression of Bax precedes nucleosomal DNA fragmentation and apoptosis. These processes are believed to play a significant part in placental development (39).

**Hormones and apoptosis in disease states**

As has been briefly outlined above, the ‘decision’ of a cell to undergo programmed cell death can be influenced by a wide variety of regulatory stimuli, including many hormones. Recent evidence suggests that alterations in cell survival contribute to the pathogenesis of a number of human diseases, including cancer, viral infections, autoimmune diseases, neurodegenerative disorders, and acquired immunodeficiency syndrome (AIDS). Treatments designed to regulate the time frame during or extent to which a cell undergoes apoptosis may have the potential to change the natural progression of some of these diseases (3, 8, 28, 70).

Recent experimental evidence suggests that apoptosis has an important role in regulation of tumour growth and tumour response to cancer therapy. Apoptosis develops rapidly after cytotoxic treatments and is dose dependent. The apoptotic response correlated well with the antitumour efficacy of radiation or chemotherapy, or a combination thereof, which makes it a candidate predictor of tumour treatment response (5). Tumours vary in their apoptotic response to cytotoxic drugs and irradiation. In addition to this intertumour heterogeneity, there is also a significant intratumour heterogeneity in induction of apoptosis, consistent with the idea that the propensity for apoptosis is genetically and hormonally regulated. Within the prostate, for example, androgens are capable of both stimulating proliferation and inhibiting the rate of the glandular epithelial cell death (25). An imbalance in programmed cell death is believed to occur during prostatic cancer progression (25). Regulating apoptosis might therefore be an effective and natural way to improve antitumour therapy; therapeutic gain would be achieved by increasing the apoptotic response of cancerous tissues, or by inhibiting the apoptotic response of normal tissues (5).
In polycystic renal disease, normal renal tissue is lost in association with progressive deterioration of renal function. Apoptotic DNA fragmentation was detected in polycystic kidneys, and even more often in polycystic kidneys from patients with renal failure, whereas no apoptotic DNA fragmentation was present in kidneys from patients without renal disease.

Most importantly, in autoimmune diseases such as autoimmune thyroid disease and type 1 diabetes mellitus, new data suggest that the immune system itself may not carry out the final act of organ injury; rather, the target cells (i.e. thyrocytes and β cells of the islets) commit suicide through apoptosis (71). To date, no autoimmune diseases in humans have been directly linked to genes involved in the control of apoptosis; however, investigations into the role of apoptosis in the development of autoimmune diseases such as type 1 diabetes are now beginning to be undertaken. Alterations in the susceptibility of lymphocytes to death by apoptosis in vitro have been reported in autoimmune disease. In addition, increased apoptotic rates in islets of Langerhans have been demonstrated in the pancreas of diabetic subjects.

Autoimmune diseases are characterized by the proliferative expansion of lymphocytes reactive to self antigens. It has been shown that repetitive treatment with antigen can result in the selective death of antigen-reactive lymphocytes in vivo. Specific deletion of lymphocytes by repetitive treatment with a disease-associated autoantigen has been shown to be effective in the treatment of experimental autoimmune disease.

Such treatments may prove effective in human autoimmune disease such as type 1 diabetes and Grave’s disease if the specific antigens involved in the autoimmune reaction are to be identified. The primary location of apoptotic cells in rheumatoid arthritis synovial tissue is at the level of the synovial lining. Local invasiveness and tissue destruction in rheumatoid arthritis seem to be controlled by proto-oncogenes, c-jun, c-fos and c-myc. From the findings of ovarian studies, it is apparent that oestrogens generally prevent and androgens induce apoptosis. In fact, the expression of c-myc in primary cultures of synovial macrophages treated with oestrogens is increased (51). Further studies of the influence of gonadal steroids on synovocyte apoptosis and proto-oncogene expression could offer new perspectives on the pathogenesis and therapy of synovitis in rheumatoid arthritis and other rheumatic diseases (51).

As in amphibian morphogenesis, apoptosis is a key component of developmental processes in mammalian tissues. Failure to induce cell death might hence lead to failure of organogenesis and to organ malformations. MIS, for example, is important for sexual differentiation. Failure of MIS to induce localized programmed cell death may be associated with tumourigenesis, infertility and, most importantly, with sexual ambiguity (13). An exaggerated programmed cell death during embryonal development may cause developmental abnormalities.

Certain viruses can inhibit apoptosis, and metabolic stress or damage of cell structures can induce apoptosis. Therefore, not only viral infections, but also drugs and chemical and physical injuries during embryogenesis may interfere with balanced programmed cell death and thus induce malformations. Drugs and therapy designs directed to modulate the apoptotic process will offer new approaches to the prevention of congenital malformations (14).

Conclusions

This review has aimed to summarize some of the available evidence showing where and how hormones control apoptosis and where and how programmed cell death exerts modulating effects upon hormonally active tissues. The understanding of how hormones influence programmed cell death and, conversely, of how apoptosis affects endocrine glands, is central to further design strategies to prevent and treat diseases that affect endocrine tissues.

Acknowledgements

This work was partly supported by grants from the Alexander von Humboldt Foundation, Bonn, Germany (to B G), the Deutsche Krebshilfe, Bonn, Germany (to W K) and BIOMED 2 program, Brussels (W K).

References

13 Catlin EA, MacLaughlin DT & Donahoe PK. Mullerian inhibiting


Received 23 December 1997
Accepted 5 February 1998